Turkish Journal of Ophthalmology

www.oftalmoloji.org

E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

Original Articles

Review

Case Reports

November
December 2019
49 Volume
Issue 6

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: December 2019
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

Osman Şevki ARSLAN,
İstanbul University Cerrahpaşa Faculty of Medicine, Department of Opthalmology, İstanbul, 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, Arzu Sevdasız
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: +90 212 801 44 36/37 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

Research Articles

Review

Case Reports

INDEX

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

2019 Issue 6 at a Glance:

This issue of our journal includes six original articles, one review, and four case reports that we believe will interest you.

Amblyopia is characterized by decreased visual acuity resulting from interrupted conduction between the retina and visual cortex during development of the visual system, with no apparent organic pathology. Relative afferent pupil defect may be observed in unilateral amblyopia. It has been suggested that weak fixation and light stimuli hitting extrafoveal areas of the retina may lead to changes in pupillary reflexes. Bitirgen et al. evaluated pupillary light reflexes in 14 anisometropic patients and 37 strabismic patients using dynamic pupillometry (MonPack One, France) and showed that the pupils of amblyopic eyes contracted later in response to light, remained contracted for a shorter time, and dilated faster (See pages 310-314).

Diabetic macular edema (DME) is the most common cause of visual loss in diabetic retinopathy (DR), and the 25-year cumulative incidence of DME in type 1 DM is reported to be approximately 29%. Yalçın et al. defined cystoid macular degeneration (CMD) in DME as the presence of cysts larger than 450 µm in horizontal diameter and 300 µm in vertical diameter that are located within 1000 µm of the foveal center and accompanied by macular ischemia, outer retinal damage, loss of foveal contour, and diffuse or mixed edema (See pages 315-322).

A study by Özdemir et al. evaluating the effectiveness and long-term outcomes of intravitreal dexamethasone implants in the treatment of DME in vitrectomized eyes demonstrated improved vision and a decrease in central retinal thickness. Although the benefits of treatment lasted for at least 6 months in most patients, maximum effect was observed in the first 3 months. Two of the 17 patients had intraocular pressure elevation over 25 mmHg and were treated with antiglaucomatous drugs (See pages 323-327).

Full-thickness macular hole (MH) is an anatomical defect involving the complete disruption of all neural retinal layers in the fovea, from the internal limiting membrane (ILM) to the retinal pigment epithelium, and has an annual incidence of 7.4 per 100,000. Karaçorlu et al. compared the outcomes of idiopathic MH operations performed with 23-G pars plana vitrectomy (PPV) under air versus standard PPV and found that PPV under air was superior in terms of parameters such as vitreous visualization, effective vitrectomy time, and total operative time. In the PPV under air group, retinal touch and sudden hypotony both occurred in 10% of the eyes, while 1 of 2 pseudophakic eyes had air escape into the anterior chamber and 1 had fogging of the intraocular lens. Microperimetry examination showed no retinal or optic nerve damage (See pages 328-333).

Keilani et al. present the clinical outcomes of patients with complicated retinal detachment associated with proliferative vitreoretinopathy in the lower quadrant who underwent pars plana vitrectomy followed by silicone oil-RMN3 (Oxane® HD) or silicone oil-perfluorohexyloctane (Densiron® 68). They report that the Densiron 68 group had higher anatomic success rates, no recurrence, and better visual acuity. There were no differences between the two groups in terms of intraocular pressure, emulsification, or intraocular inflammation (See pages 329-341).

Koçak et al. evaluated the effectiveness and safety of demarcation laser photocoagulation to prevent progression of subclinical retinal detachment (SCRD) to clinical retinal detachment. Of the 21 eyes of 20 patients that underwent 360° laser photocoagulation and were followed for at least 6 months, progression to clinical retinal detachment occurred in only 4 eyes, all of which had refractive errors greater than -3.0 diopters and multiple retinal tears in the upper quadrant. The authors emphasized that in patients with SCRD, demarcation laser photocoagulation should be considered as a primary treatment option to avoid potential complications of intraocular surgery (See pages 342-346).

Primary congenital glaucoma (PCG) can be sporadic or have a familial inheritance pattern and its prevalence varies from 1:2500 to 1:1000. Given the long life expectancy of pediatric patients and the potential for PCG to be progressive and result in blindness, the diagnosis, follow-up, and treatment of this disease are crucial. In this issue, Mocan, Mehta, and Aref review current developments regarding the genetics and surgical management of PCG. Their review includes a detailed explanation of genetic loci (GLC3A, B, C, and D) associated with the disease and protein structures that are important in the development of the trabecular network and Schlemm's canal,

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

EDITORIAL

as well as a discussion of traditional surgical treatments and recent advances (See pages 347-355).

In the first case report of this issue, Baş and Gündüz describe how they treated both eyes of a patient with pediatric acute toxic epidermal necrolysis at bedside by using symblepharon rings for sutureless fixation of large (4x4 cm) amniotic membrane grafts. Bilateral epithelialization was achieved in 8 weeks, with no symblepharon, scar formation, or limbal stem cell deficiency observed in long-term follow-up (See pages 356-360).

Ocular tuberculosis is a rare form of extrapulmonary tuberculosis, with a prevalence of 0.2–18% depending on geographic region. In the second case report, Yaghoubi et al. present an Iranian patient with endophthalmitis in one eye, retinal vasculitis in the other eye, and infective endocarditis detected in systemic examination. PCR analysis of vitreous and pericardial fluid revealed Mycobacterium tuberculosis, and treatment was initiated with isoniazid, ethambutol, pyrazinamide, and rifampin. However, treatment was discontinued when the patient developed hepatitis. The patient was eventually treated with a combination of isoniazid/ethambutol with short-term systemic corticosteroids and exhibited significant visual improvement and no recurrence during 3 years of follow-up (See pages 361-363).

Vasoproliferative retinal tumors (VPRTs) are rare, benign tumoral lesions of unclear pathogenesis that appear as a raised, yellowish-pink vascularized mass on the surface of the retina. They are frequently located in the pre-equatorial or equatorial region of the inferior retina, especially in the 5–7 o'clock segment. In the third case report of this issue, Özalp et al. present their management of uveitis and secondary glaucoma after cryotherapy in a patient with multiple sclerosis and VPRT (See pages 364-366).

Finally, Değirmenci et al. describe a 70-year-old woman who was using leflunomide and systemic corticosteroids for rheumatoid arthritis and had decreased vision in her right eye and bilateral macular edema and choroidal folds. Based on optical coherence tomography findings of intraretinal and subretinal fluid accumulation in the right eye and intraretinal fluid accumulation in the left eye, she was diagnosed as having central serous chorioretinopathy-like maculopathy and the corticosteroid therapy was discontinued. Her maculopathy was completely resolved after 8 months of follow-up (See pages 367-369).

We hope you read the articles featured in our final issue of the year with interest and pleasure.

Respectfully on behalf of the Editorial Board,

Banu Bozkurt, MD

DOI: 10.4274/tjo.galenos.2019.32748
Turk J Ophthalmol 2019;49:310-314

Original Article

Evaluation of Pupillary Light Reflex in Amblyopic Eyes Using Dynamic Pupillometry

Gülfidan Bitirgen*, Mohammed Daraghma**, Ahmet Özkağnıcı*

*Necmettin Erbakan University Meram Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
**Reyhanlı Sevgi Hospital, Clinic of Ophthalmology, Hatay, Turkey

Abstract

Objectives: To evaluate the pupillary light reflex responses in patients with unilateral strabismic and anisometropic amblyopia using dynamic pupillometry.

Materials and Methods: A total of 102 eyes of 51 patients with unilateral amblyopia were included in this cross-sectional study. Of the 51 patients, 37 (72.5%) had strabismic amblyopia and 14 (27.5%) had anisometropic amblyopia. All patients underwent complete ophthalmological examination, and pupillary light reflex responses were measured using a computerized dynamic pupillometry system (MonPack One; Metrovision, France). Initial pupil diameter; the amplitude, latency, duration, and velocity of pupil contraction; and the latency, duration, and velocity of pupil dilation were recorded. Results obtained from the patients' amblyopic and normal fellow eyes were compared using paired-samples t-test and Wilcoxon signed rank test.

Results: The mean age of the patients was 11.9±6.0 years. Amblyopic eyes had longer contraction latency (p=0.009), shorter contraction duration (p=0.002), and higher dilation velocity (p=0.033) compared to fellow eyes, while other parameters did not show significant differences. In subgroup analysis, eyes with strabismic amblyopia had longer contraction latency (p=0.006) and shorter contraction duration (p=0.017), while eyes with anisometropic amblyopia had shorter contraction duration (p=0.030) when compared with fellow eyes.

Conclusion: In this study, the objective records obtained by dynamic pupillometry showed that pupillary light reflex responses are affected in amblyopic eyes. This finding may shed light on unclear aspects of the pathophysiology of amblyopia.

Keywords: Amblyopia, anisometropia, dynamic pupillometry, pupillary light reflex, strabismus

Introduction

Amblyopia is characterized by decreased visual acuity resulting from interrupted communication between the retina and visual cortex during development of the visual system, with no apparent organic pathology. Deprivation, strabismus, and refractive errors early in life lead to the loss of central visual functions such as visual acuity, contrast sensitivity, and visual field.[1] With a reported prevalence of 2-4% in the population, amblyopia is the leading cause of preventable vision loss.[2,3,4]

Numerous studies have been conducted on the tissues affected in amblyopic eyes. Histopathological and clinical studies have revealed changes in the retina, optic nerve, lateral geniculate nucleus, and visual cortex in amblyopic eyes.[5,6,7] Several studies have also examined the relationship between amblyopia and the pupillary light reflex, and reported changes in pupil diameter and the pupillary reflex in amblyopia.[8,9,10,11,12] In addition, relative afferent pupillary defect in patients with unilateral amblyopia has been reported at rates ranging from 9% to 81.8%.[8,9,10] It has been suggested that weak fixation and the

Address for Correspondence: Gülfidan Bitirgen MD, Necmettin Erbakan University Meram Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
Phone:+90 536 362 85 25 E-mail: gbitirgen@yahoo.com **ORCID-ID**: orcid.org/0000-0002-0509-5649
Received: 21.02.2019 **Accepted:** 04.07.2019

Cite this article as: Bitirgen G, Daraghma M, Özkağnıcı A. Evaluation of Pupillary Light Reflex in Amblyopic Eyes Using Dynamic Pupillometry. Turk J Ophthalmol. 2019;49:310-314

projection of light stimuli extrafoveal retinal areas in amblyopic eyes may cause changes in pupillary reflexes.[10,11]

Minute pupillary changes may be undetectable in routine ophthalmologic examination. The introduction of automated infrared pupillometry devices has allowed the objective and quantitative measurement of pupil diameter and kinetic reflexes to light stimuli. Dynamic pupillometry has been widely used in recent years, especially for the evaluation of autonomic dysfunctions.[13,14,15] Previous studies investigating pupillary changes in amblyopic patients have utilized methods such as neutral density filters, video pupillography, and wavefront analyzers. However, few studies have reported the results of dynamic infrared pupillometry. The aim of this study was to evaluate pupillary light reflex responses recorded with dynamic pupillometry in patients with unilateral strabismic and anisometropic amblyopia.

Materials and Methods

The study included 102 eyes of 51 patients with amblyopia in one eye and no visual impairment in the fellow eye. Patients with visual acuity between 20/400 and 20/32 in the amblyopic eye or with at least two lines of difference between eyes and with visual acuity of 20/20 or better in the fellow eye were included in the study. Visual acuity was measured with a standard Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Anisometropia was defined as a spherical equivalent difference of at least 1.5 diopters between the eyes. Patients with deprivation amblyopia or organic eye disease, history of previous intraocular surgery, visual acuity worse than 20/400, and those who were unable to fixate or cooperate were excluded from the study. The study was approved by the Clinical Research Ethics Committee of the Necmettin Erbakan University (2018/1135). Informed consent forms were obtained from all patients in the study or their legal guardians.

Each patient underwent detailed ophthalmologic examination including visual acuity measurement, cycloplegic refraction examination, strabismus examination, slit-lamp anterior segment examination, and dilated fundus examination. Pupillary light reflex responses were evaluated with dynamic pupillometry (MonPackOne®; Metrovision, France). The device is equipped with infrared illumination (880 nm) and a high-resolution infrared sensor that allows measurement of pupil parameters in complete darkness. Pupillary responses were elicited with white light stimulus in a completely dark environment (light intensity: 100 cd/m^2, on/off duration: 200/3300 ms) and recorded with measurement sensitivity of 0.1 mm. The patient was allowed 5 minutes for dark adaptation and the measurements of both eyes were performed monocularly. Initial pupil diameter; the amplitude, latency, duration, and velocity of pupil contraction; and the latency, duration, and velocity of pupil dilation were measured from the patients' amblyopic and healthy eyes and compared (Figure 1).

Statistical Analyses

SPSS version 17.0 software package was used for statistical analyses of the data (SPSS for Windows, Chicago, USA). The Shapiro–Wilk test was used to evaluate conformity of quantitative data to normal distribution. When comparing data obtained from the amblyopic eyes and healthy eyes of the patients, a paired-samples t-test was used for normally distributed data, and Wilcoxon signed rank test was used for non-normally distributed data. Pearson and Spearman correlation tests were used to analyze correlation between pupillary responses and depth of amblyopia. Differences with p values less than 0.05 were considered statistically significant.

Results

Thirty-seven (72.5%) patients in the study had strabismic amblyopia and 14 (27.5%) had hypermetropic anisometropic amblyopia. Of the patients with strabismic amblyopia, 29 (78.4%) had esotropia and 8 (21.6%) had exotropia. The mean age of the patients was 11.9±6.0 years. Snellen visual acuity in the amblyopic eyes ranged from 20/400 to 20/32 (mean 0.56±0.30 logMAR). Visual acuity was 20/20 or better in all fellow eyes.

Compared to the healthy fellow eyes, amblyopic eyes exhibited longer pupil contraction latency (median 205.0 vs. 246.0 ms, respectively; p=0.009), shorter contraction duration (median 613.0 vs. 562.0 ms, respectively; p=0.002), and higher dilation velocity (median 2.18 vs. 2.23 mm/s, respectively; p=0.033). There were no significant differences in other parameters between the two eyes (Table 1). Subgroup analysis showed that in patients with strabismic amblyopia, amblyopic eyes had longer contraction latency (median 252.0 vs. 193.0 ms; p=0.006) and shorter contraction duration (median 566.0 vs. 613.0 ms; p=0.017) compared to the healthy eyes, with no significant differences in terms of other parameters (Table 2). In patients with anisometropic amblyopia, contraction duration was shorter in amblyopic eyes compared to healthy eyes (median 550.0 vs. 613.0 ms, respectively; p=0.030), with no significant differences in the other parameters (Table 3).

Correlation analyses did not reveal any significant relationship between the visual acuity and pupillary light reflex parameters of amblyopic eyes.

Discussion

Although amblyopia is defined as a decrease in visual acuity without structural damage to the eye and visual pathways, cell shrinkage has been demonstrated in the parvocellular layers of the lateral geniculate nucleus.[5,16] Changes in the macula, peripapillary retinal nerve fiber layer, and choroidal thickness have also been reported in optical coherence tomography studies.[17,18,19] Longer latencies and lower amplitudes in visual-evoked potential (VEP) and markedly reduced responses in pattern electroretinography have been documented in electrophysiological tests of amblyopic eyes.[20,21]

Considering the possibility that retinal ganglion cells and anterior visual pathways may be affected in amblyopic eyes, studies have also been conducted to evaluate pupillary light reflexes. Measurements with neutral density filters have revealed relative afferent pupillary defect in amblyopic eyes.[9,10] Portnoy et al.[10] demonstrated the presence of afferent pupillary defect in 45 of 55 amblyopic patients using this method and suggested that this defect may be due to poor fixation ability and incomplete

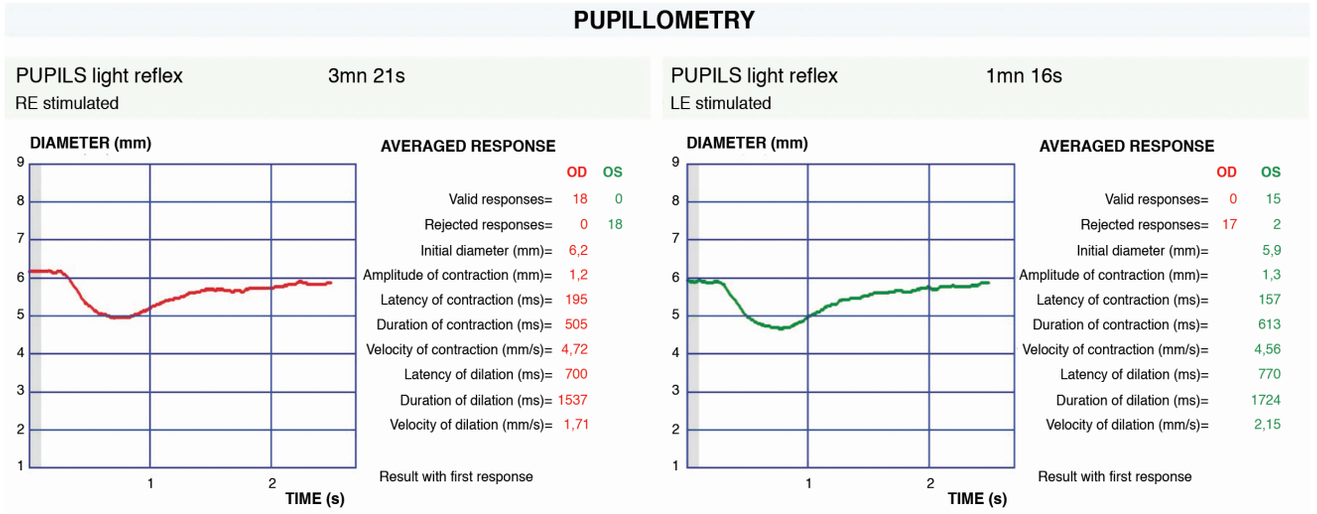


Figure 1. Pupillary light reflex responses recorded by dynamic pupillometry in a patient with strabismic amblyopia in the right eye

Table 1. Pupillary light reflex responses of the patients' amblyopic eyes and normal fellow eyes

	Amblyopic eye (n=51)	Normal eye (n=51)	p
Initial pupil diameter (mm)	6.16±0.55	6.22±0.63	0.204[a]
Contraction amplitude (mm)	1.55±0.36	1.52±0.32	0.571[a]
Contraction latency (ms)	246.0 (174.0-282.0)	205.0 (128.0-273.0)	**0.009**[b]
Contraction duration (ms)	562.0 (511.0-641.0)	613.0 (578.0-701.0)	**0.002**[b]
Contraction velocity (mm/s)	5.32±1.18	5.10±1.16	0.122[a]
Dilation latency (ms)	831.0 (766.0-866.0)	805.0 (768.0-867.0)	0.584[b]
Dilation duration (ms)	1573.0 (1502.0-1669.0)	1631.0 (1535.0-1696.0)	0.515[b]
Dilation velocity (mm/s)	2.23 (1.85-2.69)	2.18 (1.84-2.55)	**0.033**[b]

*Data are expressed as mean ± standard deviation for normally distributed parameters and median (1st-3rd quartiles) for nonnormally distributed parameters.
[a]Paired samples t test [b]Wilcoxon signed rank test

Table 2. Pupillary light reflex responses in patients with strabismic amblyopia

	Amblyopic eye (n=37)	Normal eye (n=37)	p
Initial pupil diameter (mm)	6.14±0.61	6.19±0.69	0.472[a]
Contraction amplitude (mm)	1.53±0.36	1.51±0.33	0.660[a]
Contraction latency (ms)	252.0 (178.0-279.0)	193.0 (124.0-264.5)	**0.006**[b]
Contraction duration (ms)	566.0 (511.5-644.0)	613.0 (567.0-707.0)	**0.017**[b]
Contraction velocity (mm/s)	5.27±1.23	5.05±1.17	0.239[a]
Dilation latency (ms)	833.0 (766.5-867.0)	804.0 (766.5-853.5)	0.731[b]
Dilation duration (ms)	1571.0 (1469.0-1668.0)	1628.0 (1470.5-1699.0)	0.645[b]
Dilation velocity (mm/s)	2.16 (1.83-2.67)	2.14 (1.79-2.51)	0.051[b]

*Data are expressed as mean ± standard deviation for normally distributed parameters and median (1st-3rd quartiles) for nonnormally distributed parameters.
[a]Paired samples t test [b]Wilcoxon signed rank test

Table 3. Pupillary light reflex responses in patients with anisometropic amblyopia			
	Amblyopic eye (n=14)	**Normal eye (n=14)**	**p**
Initial pupil diameter (mm)	6.19±0.38	6.30±0.46	0.112[a]
Contraction amplitude (mm)	1.60±0.38	1.57±0.30	0.727[a]
Contraction latency (ms)	235.0 (144.0-286.0)	241.0 (130.0-281.8)	0.637[b]
Contraction duration (ms)	550.0 (494.3-650.5)	613.0 (590.3-680.0)	**0.030**[b]
Contraction velocity (mm/s)	5.46±1.07	5.22±1.16	0.271[a]
Dilation latency (ms)	800.5 (734.5-865.3)	828.5 (790.0-868.3)	0.593[b]
Dilation duration (ms)	1586.5 (1506.0-1678.8)	1635.0 (1541.8-1695.0)	0.638[b]
Dilation velocity (mm/s)	2.37 (1.97-2.88)	2.35 (2.05-2.76)	0.551[b]

*Data are expressed as mean ± standard deviation for normally distributed parameters and median (1st-3rd quartiles) for nonnormally distributed parameters.
[a]Paired samples t test [b]Wilcoxon signed rank test

development of the foveal ganglion cells in amblyopic eyes. In a study based on infrared pupillography, patients with strabismic and anisometropic amblyopia exhibited prolonged pupil contraction latency in the direct light reflex response, but no prolonged latencies were observed in indirect responses.[22] The authors therefore proposed that afferent fibers were responsible for prolonged latency and that there was no pathology in the pupillomotor efferent system. In the same study, examination of 8 amblyopic patients who improved with treatment revealed no prolongation of pupil contraction latency, suggesting that latency prolongation may be a reversible phenomenon that can resolve with amblyopia treatment. In a study evaluating the multifocal VEP test results of amblyopic patients, it has been reported that VEP latency was longer and amplitude was lower in amblyopic eyes.[20] Our findings that amblyopic eyes had prolonged pupil contraction latency, or in other words, showed a longer delay between light stimulus and pupil contraction compared to healthy fellow eyes supports the view that afferent transmission is slowed in amblyopia.

Dynamic pupillometry enables the objective and reliable recording of pupillary light reflex responses and independent evaluation of several parameters that reflect pupil movements. In their study of the dynamic pupillometry responses of patients with hypermetropic anisometropic amblyopia, Yetkin et al.[23] reported that the pupil contraction amplitude of amblyopic patients was lower compared to that of healthy subjects, while no difference was detected in other parameters. In the present study, we observed longer pupil contraction latency, shorter contraction duration, and greater dilation velocity in patients' amblyopic eyes compared to their healthy fellow eyes, with no significant differences in terms of initial pupil diameter or other parameters. Yuksel et al.[24] evaluated the anterior segment parameters and pupil diameters of patients with hypermetropic anisometropic amblyopia using the Pentacam device and reported no difference in pupil diameter between amblyopic eyes and normal eyes. In their study evaluating the pupil diameters of patients with anisometropic amblyopia under mesopic conditions using an ocular wavefront analyzer, Kocamış et al.[12] reported smaller pupil diameter in amblyopic eyes. It is known that differences in refractive error can also affect pupil diameter. Another study using a wavefront analyzer on non-amblyopic patients showed that refractive error was correlated with the mesopic pupillary diameter, with larger pupil diameters in myopic patients.[25] In that study, initial pupil diameters did not differ significantly between amblyopic and healthy eyes both in patients with strabismic amblyopia and those with hypermetropic anisometropic amblyopia. In our study, initial pupil diameter measurements were obtained by the dynamic pupillometry device under scotopic conditions. Inconsistent results reported in the literature on this issue may be attributable to differences in the lighting conditions under which measurements are made and the sensitivities of the devices used. In addition, the limited number of patients with anisometropic amblyopia in our study, which is one of its limitations, may have contributed to the lack of statistical significance.

Portnoy et al.[10] reported that there was no correlation between the degree of relative afferent pupil defect detected in amblyopic eyes and the type or depth of amblyopia. Other studies evaluating the correlation between visual acuity level and pupil diameter and light reflexes in amblyopic eyes also failed to reveal a significant relationship.[12,22] Similarly, none of the pupillary light reflex parameters examined in the present study showed significant correlation with depth of amblyopia in our patients.

One of the limitations of this study is that its cross-sectional design precludes an evaluation of whether pupillary light reflex responses changed in patients whose visual acuity in the amblyopic eye improved with treatment. The small number of patients with anisometropic amblyopia and the absence of patients with myopic anisometropia are other limitations of the study.

Conclusion

In this study, the pupils of amblyopic eyes were found to contract later in response to light, remain contracted for a shorter time, and dilate faster. These findings may not only facilitate early diagnosis of amblyopia, but may also shed light on the unexplained mechanisms involved in its pathophysiology. Long-

term studies of amblyopic patients will also allow investigation into whether improved visual acuity after treatment is associated with changes in pupil responses.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of the Necmettin Erbakan University (2018/1135).

Informed Consent: Informed consent was obtained from all patients in the study or their legal guardians.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Gülfidan Bitirgen, Mohammed Daraghma, Design: Gülfidan Bitirgen, Ahmet Özkağnıcı, Data Collection or Processing: Gülfidan Bitirgen, Mohammed Daraghma, Analysis or Interpretation: Gülfidan Bitirgen, Ahmet Özkağnıcı, Literature Search: Gülfidan Bitirgen, Mohammed Daraghma, Writing: Gülfidan Bitirgen, Ahmet Özkağnıcı

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. Greenstein VC, Eggers H, Hood DC. Multifocal VEP and automated perimetry abnormalities in strabismic amblyopes. J AAPOS. 2008;12:11-17.
2. Simmers AJ, Bex PJ, Hess RF. Perceived blur in amblyopia. Invest Ophthalmol Vis Sci. 2003;44:1395-1400.
3. Polat SA, Akyol N. The prevalance of amblyopia and allergic eye disease in second year primary school students. Turkiye Klinikleri J Med Sci. 2003;23:213-219.
4. Williams C, Harrad RA, Harvey I, Sparrow JM. Screening for amblyopia in preschool children: results of a population-based, randomised controlled trial. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Ophthalmic Epidemiol. 2001;8:279-295.
5. von Noorden GK, Crawford ML. The lateral geniculate nucleus in human strabismic amblyopia. Invest Ophthalmol Vis Sci. 1992;33:2729-2732.
6. Yen MY, Cheng CY, Wang AG. Retinal nerve fiber layer thickness in unilateral amblyopia. Invest Ophthalmol Vis Sci. 2004;45:2224-2230.
7. Gümüstas S, Altintas Ö, Anik Y, Kaya A, Altintas L, Inan N, Ali D. Anterior visual pathways in amblyopia: quantitative assessment with diffusion tensor imaging. J Pediatr Ophthalmol Strabismus. 2013;50:369-374.
8. Greenwald MJ, Folk ER. Afferent pupillary defects in amblyopia. J Pediatr Ophthalmol Strabismus. 1983;20:63-67.
9. Firth AY. Pupillary responses in amblyopia. Br J Ophthalmol. 1990;74:676-680.
10. Portnoy JZ, Thompson HS, Lennarson L, Corbett JJ. Pupillary defects in amblyopia. Am J Ophthalmol. 1983;96:609-614.
11. Thompson HS. Afferent pupillary defects. Pupillary findings associated with defects of the afferent arm of the pupillary light reflex arc. Am J Ophthalmol. 1966;62:860-873.
12. Kocamış Sİ, Çakmak HB, Çağıl N. Investigation of the pupil diameter differences in anisometropic amblyopia. Turk J Ophthalmol. 2013;43:45-50.
13. Okutucu S, Civelekler M, Aparci M, Sabanoglu C, Dikmetas O, Aksoy H, Yetis Sayin B, Oto A. Computerized dynamic pupillometry indices mirrors the heart rate variability parameters. Eur Rev Med Pharmacol Sci. 2016;20:2099-2105.
14. Aydogmus Y, Uzun S, Gundogan FC, Ulas UH, Ebiloglu T, Goktas MT. Is overactive bladder a nervous or bladder disorder? Autonomic imaging in patients with overactive bladder via dynamic pupillometry. World J Urol. 2017;35:467-472.
15. Jackson KG, Malphrus EL, Blum E, Kalloo NB, Finkel JC. Pupillometric assessment of dysautonomia in pediatric bowel and bladder dysfunction: a pilot study J Pediatr Urol. 2019;15:226.e1-226.e5.
16. Headon MP, Powell TP. Cellular changes in the lateral geniculate nucleus of infant monkeys after suture of the eyelids. J Anat. 1973;116:135-145.
17. Yoon SW, Park WH, Baek SH, Kong SM. Thicknesses of macular retinal layer and peripapillary retinal nerve fiber layer in patients with hyperopic anisometropic amblyopia. Korean J Ophthalmol. 2005;19:62-67.
18. Soyugelen G, Onursever N, Bostancı Ceran B, Can İ. Evaluation of macular thickness and retinal nerve fiber layer by optical coherence tomography in cases with strabismic and anisometropic amblyopia. Turk J Ophthalmol. 2011;41:318-324.
19. Karaca EE, Çubuk MÖ, Akçam HT, Uzun F, Yüksel E. Choroidal thickness in Turkish children with anisometric amblyopia. Semin Ophthalmol. 2017;32:291-296.
20. Moschos MM, Margetis I, Tsapakis S, Panagakis G, Chatzistephanou IK, Iliakis E. Multifocal visual evoked potentials in amblyopia due to anisometropia. Clin Ophthalmol. 2010;4:849-853.
21. Arden GB, Wooding SL. Pattern ERG in amblyopia. Invest Ophthalmol Vis Sci. 1985;26:88-96.
22. Kase M, Nagata R, Yoshida A, Hanada I. Pupillary light reflex in amblyopia. Invest Ophthalmol Vis Sci. 1984;25:467-471.
23. Yetkin E, Tekin K, Kiziltoprak H, Sekeroglu MA, Cankurtaran V, Yasar HH. Evaluation of static and dynamic pupil characteristics in hyperopic anisometropic amblyopia. Eur J Ophthalmol. 2019;29:486-493.
24. Yuksel N, Yuksel E, Ozer MD. Evaluation of anterior segment parameters using the Pentacam in hyperopic anisometropic amblyopic and normal eyes. J AAPOS. 2014;18:248-250.
25. Cakmak HB, Cagil N, Simavli H, Duzen B, Simsek S. Refractive error may influence mesopic pupil size. Curr Eye Res. 2010;35:130-136.

DOI: 10.4274/tjo.galenos.2019.22687
Turk J Ophthalmol 2019;49:315-322

Original Article

Defining Cystoid Macular Degeneration in Diabetic Macular Edema: An OCT-Based Single-center Study

Gökçen Yalçın*, Şengül Özdek*, Fatma Nur Baran Aksakal**

*Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Gazi University Faculty of Medicine, Department of Public Health, Ankara, Turkey

Abstract

Objectives: To describe cystoid macular degeneration (CMD), which has no clear definition in diabetic macular edema (DME), and examine its features in optical coherence tomography (OCT) and fundus fluorescein angiography (FFA).

Materials and Methods: This study was conducted using OCT images of patients who were followed in Gazi University between November 2011 and March 2015. A total of 259 eyes (187 patients) found to have cystic changes on OCT were included. Macular ischemia, peripheral ischemia, and type of edema were identified on FFA. Vitreomacular interface abnormalities, foveal contour integrity, internal reflectivity of the cysts, and outer retinal layer defects were analyzed from OCT images. The horizontal and vertical diameters of the largest cyst within 1000 µm of the foveal center were measured for the definition of CMD. Cut-offs for these values were determined by receiver operating characteristic curve analysis. Cystoid macular edema (CME) and CMD groups were created and their characteristics were analyzed.

Results: The horizontal and vertical diameters of the largest cyst were moderately positively correlated with visual acuity (rs=0.349, r=0.419, respectively). Eyes with horizontal diameter of the largest cyst ≥450 µm were classified as CMD; in this group, sensitivity in the prediction of visual acuity ≤20/60 was 58%. Eyes with horizontal diameter of the largest cyst <450 µm were classified as CME; in this group, specificity in the prediction of visual acuity >20/60 was 73%. For the threshold of 300 µm determined for vertical diameter of the largest cyst, sensitivity was 62% and specificity was 69%. The CME and CMD groups were formed according to these cut-off values. Compared to the CME group, the CMD group had greater central subfield thickness and higher prevalence of outer retinal damage, severe disruption of foveal contour, macular ischemia, and diffuse/mixed type edema.

Conclusion: In eyes with DME, CMD can be defined as the largest cyst within 1000 µm of the foveal center having a horizontal diameter of ≥450 µm and vertical diameter ≥300 µm, especially if associated with macular ischemia, outer retinal damage, loss of foveal contour, and diffuse/mixed type edema.

Keywords: Diabetic macular edema, diabetic retinopathy, cystoid macular degeneration, chronic macular edema, optical coherence tomography

Introduction

Diabetic macular edema (DME) is the most common cause of visual deterioration in diabetic retinopathy (DR).[1] The 25-year cumulative prevalence of DME in Type 1 DM was stated as 29% in a report of the Wisconsin Epidemiologic Study of DR.[2] There are many definitions and classifications of types of DME, such as focal/diffuse edema, cystoid macular edema (CME), serous macular detachment, ischemic and tractional diabetic maculopathy. Although Otani et al.[3] defined CME as

Address for Correspondence: Gökçen Yalçın MD, Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone:+90 533 415 90 09 E-mail: gokcen_dnz@hotmail.com **ORCID-ID:** orcid.org/0000-0002-2429-2365
Received: 12.12.2018 **Accepted:** 17.06.2019

Cite this article as: Yalçın G, Özdek Ş, Baran Aksakal FN. Defining Cystoid Macular Degeneration in Diabetic Macular Edema: An OCT-Based Single-center Study. Turk J Ophthalmol. 2019;49:315-322

hyporeflective spaces separated by hyperreflective septa, there is no quantitative value for the cyst diameters when defining CME in the hitherto literature.

Another definition used between clinicians is cystoid macular degeneration (CMD). CMD was first defined in chronic retinal vein occlusion, in a histopathological experimental study.[4] CMD was seen to develop after CME with associated photoreceptor cell loss.[4] CMD was also defined in chronic central serous chorioretinopathy (CSCR) as cystoid spaces in optical coherence tomography (OCT) with no fluorescein leakage.[5] This term was always related with poorer visual acuity.[5,6] In age-related macular degeneration (AMD), CMD was also defined as the presence of degenerated pseudocyst or retinal degeneration that had intraretinal cystic spaces.[7] However, it is important to differentiate between CME and CMD in AMD because degenerative cysts are not an indicator of the activity of the lesion.

The aim of this study was to define and characterize CMD in DME, for which there is no clear definition. CMD is thought to be the result of chronic edema and may be associated with an unfavorable visual outcome. Determination of DME characteristics is necessary to predict visual prognosis and select appropriate treatment.

Materials and Methods

In this retrospective cross-sectional study, an evaluation was made of 398 OCT scans of the eyes of 223 patients who were followed up with the diagnosis of DME at Gazi University Department of Ophthalmology between November 2011 and March 2015. A total of 259 eyes of 187 patients (92 female/95 male) who met the inclusion criteria were included in the study. The study was approved by the Local Ethics Committee of Gazi University.

Eyes with clinically significant macular edema as defined by ETDRS, that had fundus fluorescein angiography (FFA) and high-quality spectral OCT were included in the study. If the patient had received any prior treatment, OCT images obtained at least 3 months after the last treatment (intravitreal injection and/or laser therapy) were included in the study. Eyes with visually significant cataract or any other pathology causing visual deterioration such as corneal opacity, significant vitreous hemorrhage, optic atrophy, amblyopia, macular edema due to other causes such as uveitis, retinal vein occlusion and concurrent macular degeneration, or macular hole were excluded from the study. Eyes which had undergone cataract surgery within the last 6 months were also excluded from the study to exclude Irvine-Gass syndrome.

The demographic features of the patients (age, gender, diabetes duration) and stage and duration of DR were recorded. Best corrected visual acuity (BCVA) measured with Snellen chart, fundus examination, OCT, and FFA images were evaluated. BCVA was converted to LogMAR for statistical analysis. All OCT scans and FFA investigations were performed with Heidelberg Spectralis OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany).

Macular ischemia and type of edema were noted from FFA images. Macular ischemia was defined as an enlarged foveal avascular zone (≥1000 μm) or capillary non-perfusion areas within one disc diameter distance of the foveal center.[8]

Edema was classified as focal, diffuse, or mixed type. Focal edema was defined as local leakage areas with well-defined borders, and the term diffuse edema was used when large, poorly defined leakage areas affected the fovea. If there were features of both types of leakage, the edema was defined as mixed type.[9,10]

Central subfield thickness (CSFT), defined as the average thickness in the central 1000 μm-diameter circle of the ETDRS grid in OCT, was used for quantitative analysis of DME.[11] In qualitative analysis of OCT scans, the presence of intraretinal cystic changes, serous foveal detachment (SFD), vitreomacular interface (VMI) abnormalities, outer retinal layer defects [inner segment/outer segment (IS/OS) band, external limiting membrane (ELM)], integrity of the foveal contour, and internal reflectivity of the cysts were evaluated. Cystic changes were defined as round or oval areas of low reflectivity separated by hyperreflective septa.[3] SFD was defined as shallow elevation of the posterior surface of the retina appearing as optically clear, dome-shaped areas between the neurosensorial retina and RPE on OCT scans.[12,13]

VMI abnormalities were evaluated in six groups, with modifications made to the classification of the International Vitreomacular Traction Study group.[14]

1. Total perifoveal detachment: Posterior vitreous surface is completely detached from the macular region but not from the optic disc as seen in OCT
2. Vitreomacular adhesion (VMA):
   a) Focal VMA (area of adhesion ≤1500 μm)
   b) Broad VMA (area of adhesion >1500 μm)
3. Epiretinal membrane
4. Vitreomacular traction (VMT):
   a) Focal VMT (area of traction ≤1500 μm)
   b) Broad VMT (area of traction >1500 μm)

Outer retinal layer defect was defined as a loss of continuity of either the ELM or IS/OS band in the central 0.1 mm of the fovea. Shadowing behind the cysts and hard exudates were separated carefully.[15]

Integrity of the foveal contour was evaluated in three groups: 1) normal foveal depression; 2) normal foveal depression was disturbed but had not disappeared completely (mild distortion), 3) the foveal depression was completely flat or elevated (severe distortion).

Internal reflectivity of the cysts was classified as hyporeflective if similar to the vitreous, isoreflective if similar to the retinal layers, or heterogeneous (as defined in an earlier study).[16]

The largest cystoid space was determined for each eye and the horizontal and vertical diameters of the largest cyst in the area within 1000 μm of the foveal center were noted. All measurements were performed by the same investigator (N.G.Y.) using a manual caliper (Figure 1). To ensure high scan quality, scans with quality score <20 were not included in the evaluation. In addition, 25-line raster scans were carefully

evaluated to make sure that there were no hyperreflective septa within our measurements of horizontal diameter of the largest cyst. Correlations between BCVA and the horizontal and vertical diameters of the largest cyst were analyzed using Pearson and Spearman correlation tests. The diameters were also analyzed for correlation with predetermined OCT and FFA findings.

The minimum BCVA to read newspaper print is known to be 20/60 (Snellen), and BCVA <20/60 is defined as severe visual loss.[17] The relationship between BCVA and the horizontal and vertical diameters of the largest cyst resulting in severe visual loss was evaluated with receiver operating characteristic (ROC) analyses.

Cut-off values to differentiate the CME and CMD groups were determined from this analysis. The CME and CMD groups were created and the defined OCT and FFA findings were analyzed in the groups to determine the features of CMD.

Statistical Analyses

Data obtained from the study were recorded using Excel for Windows (version 2010, Microsoft, Redmond, WA) and statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 15.0, SPSS, Chicago, IL). The statistical level of significance was set to $p<0.05$. The Kolmogorov-Smirnov test, histograms, and P-P plots were used for the continuous variables to test the conformity to normal distribution. For comparisons of two groups, the independent samples t-test or Mann-Whitney U test were used according to the normality result. One-way ANOVA and LSD test for post-hoc analyses were used for comparisons of three or more groups if the variables were normally distributed, and the Kruskal-Wallis test was used if the variables were not normally distributed. The Mann-Whitney U test with Bonferroni correction was used for post-hoc analysis if the result revealed a significant difference. In correlation analysis, Pearson or Spearman correlation test were used according to the normality result. Pearson chi-square or Yate's corrected chi-square tests were used for categorical variables. ROC curve analysis was used for the predictive value of the horizontal and vertical diameters of the largest cyst for severe visual loss.

Results

A total of 259 eyes of 187 patients (49.2% women and 50.8% men) met the inclusion criteria. DME was detected in 138 right eyes (53.3%) and 121 left eyes (46.7%). There were 72 patients (38.5%) with bilateral involvement and 115 patients (61.5%) with unilateral DME. Other demographic features of the cases are shown in Table 1. There was history of prior intravitreal injection and/or laser therapy in 198 eyes (76.5%). The mean BCVA of the patients was 0.5±0.02 (0-1.6) LogMAR.

The mean CSFT was 474±131 (254-1121) µm. Cystic changes were detected in most cases (251 eyes, 96.9%). Therefore, the final analysis of the study was made in these 251 eyes. The horizontal diameter of the largest cyst did not conform to normal distribution while the vertical diameter of the largest cyst showed normal distribution. The median of the horizontal diameter was 433 (126-2213) µm and the mean of the vertical diameter was 305±142 (77-1059) µm.

The correlation between the horizontal and vertical diameters of the largest cyst and BCVA showed weak to moderate positive correlation (horizontal: $r_s=0.349$; $p<0.001$, Figure 2a; vertical: $r=0.419$; $p<0.001$, Figure 2b). The correlation between the horizontal diameter of the largest cyst and CSFT showed moderate positive correlation ($r_s=0.487$; $p<0.001$, Figure 2c). The correlation between the vertical diameter of the largest cyst and CSFT showed a medium to strong positive correlation ($r_s=0.798$; $p<0.001$, Figure 2d). There was also a medium to strong positive correlation between the horizontal and vertical diameters ($r_s=0.678$; $p<0.001$, Figure 2e).

Data in OCT and FFA related to the horizontal and vertical diameter of the largest cyst are given in Table 2. There was a statistically significant difference in the median horizontal diameter of the largest cyst between edema types in FFA ($p=0.035$). When the binary comparisons of groups were examined, the median horizontal diameter of the largest cyst in the mixed edema group (471 µm) was significantly higher than that in the focal edema group 392 µm ($p=0.01$). Although the median horizontal diameter of the largest cyst in diffuse edema (441 µm) was higher than that in focal edema, the difference was not statistically significant ($p=0.04$, Bonferroni-corrected).

There was no statistically significant difference between the horizontal and vertical diameters of the largest cyst within the groups in terms of VMI anomalies, presence of SFD, or internal reflectivity of the cysts.

A cut-off value for the diameter of the largest cyst was needed to define CMD. To determine a cut-off value for the horizontal diameter of the largest cyst, a ROC curve was drawn, which has previously been reported to show that the horizontal diameter of the largest cyst can predict poor visual acuity.

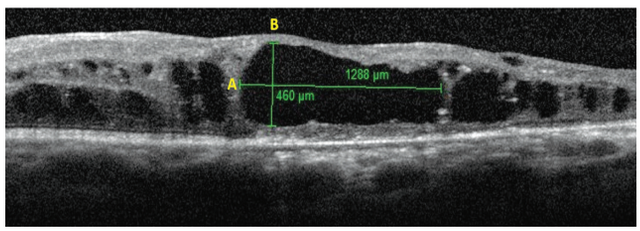


Figure 1. Example optical coherence tomography image showing measurements of the horizontal diameter A) and vertical diameter B) of the largest cyst

Table 1. The demographic features of the patients

	Mean ± SD	Number	%
Age (years)	60.3±0.62		
Gender (F/M)		92/95	49.2/50.8
Duration of DM (years)	15.4±7.23		
Type of DM (Type 1/Type 2) Type of DR (Non-PDR/PDR)		11/94* 194/65	10.5/89.5 74.9/25.1

SD: Standard deviation, F: Female, M: Male, DM: Diabetes mellitus, DR: Diabetic retinopathy, PDR: Proliferative diabetic retinopathy
*This information was not included in all patient records

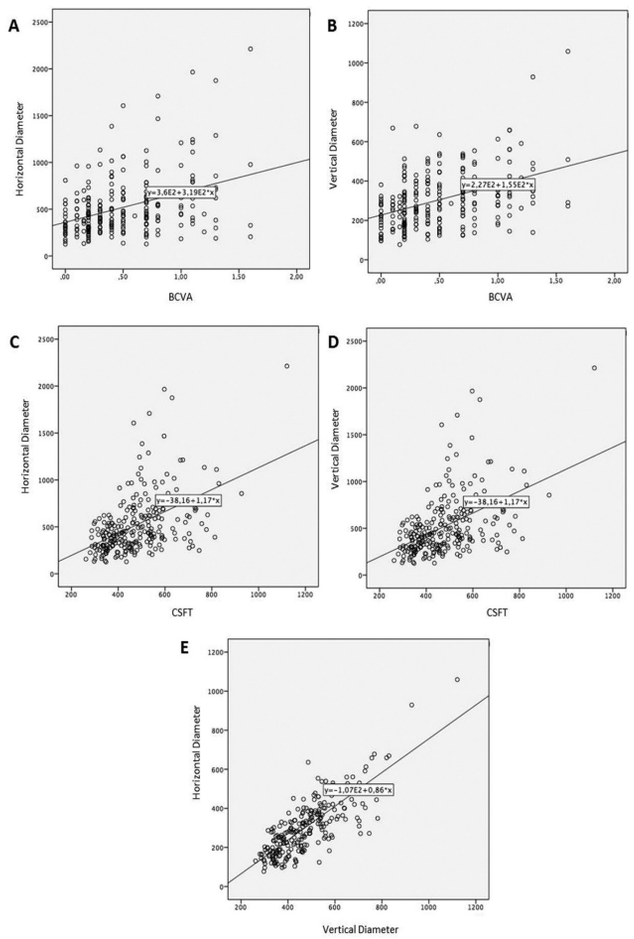


Figure 2. Correlation graphs for horizontal and vertical diameters of the largest cyst and best corrected visual acuity (BCVA) and central subfield thickness (CSFT): A) horizontal diameter and BCVA; B) vertical diameter and BCVA; C) horizontal diameter and CSFT; D) vertical diameter and CSFT; E) horizontal diameter and vertical diameter

Assuming that other predictors were constant, the horizontal diameter of the largest cyst at 450 µm predicts visual acuity loss with 58% sensitivity and 73% specificity. The predictive ROC model showed moderate significance (AUC=0.665; 95% CI=0.597-0.733; p<0.001, Figure 3a).

The same analyses were applied using the vertical diameter of the largest cyst to determine another cut-off value to define CMD. A ROC curve was drawn, which has been reported to show that the vertical diameter of the largest cyst can predict poor visual acuity. Assuming that other predictors were constant, the vertical diameter of the largest cyst at 300 µm predicted visual acuity loss with 62% sensitivity and 69% specificity with moderately significant predictive power (AUC=0.692; 95% CI=0.626-0.757; p<0.001, Figure 3b).

Using these cut off-values, eyes with a horizontal diameter of the largest cyst ≥450 µm were classified as CMD (CMD-H group) and those with <450 µm were classified as CME (CME-H group), while eyes with vertical diameter of the largest cyst ≥300 µm and <300 µm were classified as CMD (CMD-V group) and CME (CME-V group), respectively.

OCT and FFA parameters related to these CME and CMD groups are shown in Table 3. In comparing these two groups, there were no statistically significant differences in terms of VMI anomalies, presence of SFD, or internal reflectivity of the cysts.

Discussion

The definition of CMD was previously made for CSCR and AMD, but there has been no reported definition in DME. It is important to define CMD and identify the related features to have more information about the prognosis of edema and the benefit of treatment. It has been associated with poor visual acuity in CSCR, and is said to affect the need for treatment in AMD.[5,6,7]

Cyst formation begins with intercellular fluid accumulation. Coalescence of the extracellular fluid occurs due to the disruption

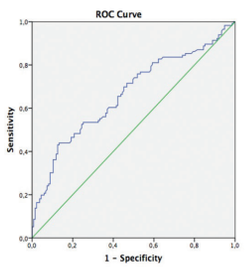
Table 2. Optical coherence tomography and fundus fluorescein angiography parameters associated with the horizontal and vertical diameters of the largest cyst

		Horizontal diameter Median (Min-max)	P value	Vertical diameter (Mean ± SD)	P value
Outer retina	Disrupted	536 (189-2213)	0.0001*	367±161	0.0001**
	Intact	412 (126-1606)		277±123	
Macular ischemia	Present	448 (184-2213)	0.019*	331±151	0.01**
	Absent	407 (126-1606)		284±131	
Foveal contour	Normal	300 (155-1709)	0.0001***	206±95	0.0001†
	Mild distortion	353 (126-790)		216±69	
	Severe distortion	534 (128-2213)		362±144	
Type of edema	Focal	392 (126-1606)	0.035***	259±118	0.001†
	Diffuse	441 (162-1875)		327±144	
	Mixed	471 (133-2213)		334±152	

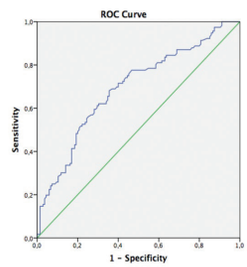
* Mann-Whitney U test, **Independent samples T-test, *** Kruskal-Wallis test, †One-Way ANOVA

of Müller cells, whose pump-like function keeps the macula dry.[18] In the chronic stage, fluid accumulates intracellularly. The subsequent death of Müller cells and neuroglia results in the formation of large cystoid cavities.[19] Otani et al.[3] reported the acute and chronic morphologies of DME in an OCT-based study and stated that the disappearance of septa resulted in confluent large cysts which might fill all layers of the retina. Consistent with this pathogenesis, Yamomoto et al.[20] found that eyes with CME had lower visual acuities than other types in OCT. In light of these data, it can be considered that in the chronic phase of cyst formation, the horizontal diameter of the cyst enlarges, damaging the adjacent retina. This data formed the basis of this study to define CMD. Also, Das et al.[18] showed that eyes which had cystic changes with septa had higher visual acuity values than eyes which had nonseptated cystic spaces.

The baseline characteristics of our study, such as mean age and male predominance, were similar to the TURK-DEM study, which reflected the overall DME patients in Turkey.[21] The results of that study showed a moderate degree of correlation between the horizontal diameter of the largest cyst and visual acuity (LogMAR). This was encouragement for further analysis. Similarly, a moderate degree of correlation was determined between the vertical diameter of the largest cyst and visual acuity (LogMAR) (correlation coefficients; r_s=0.35, r=0.42, relatively). The high correlation of the two diameters of the cyst can be interpreted as enlargement of the cyst in these two planes. In a previous study, height of the foveal cystoid space and inferior subfield retinal thickness were found to be correlated.[22] Retinal thickening in the inferior quadrant in particular was interpreted as a result of the disrupted retinal integrity with long-term cystic changes and the accumulation of fluid in the inferior zone due to gravity.[23] Consistent with these findings and relationships, we believe that cystoid degeneration occurs due to increased cystic changes in both the horizontal and vertical planes in prolonged edema.



Horizontal diameter	Sensitivity	1-Spescifity	Spescifity
350	,767	,570	,430
400	,698	,467	,533
450	,578	,370	,730
500	,534	,281	,719
550	,474	,207	,793



Vertical diameter	Sensitivity	1-Spescifity	Spescifity
200	,845	,644	,356
250	,776	,474	,562
300	,621	,311	,689
350	,457	,193	,807
400	,302	,141	,859

Figure 3. Receiver operating characteristic (ROC) curves and sensitivity/specificity values for the prediction of severe vision loss by A) horizontal diameter of the largest cyst (area under the curve=0.665; p<0.001) and B) vertical diameter of the largest cyst (area under the curve=0.692; p<0.001)

As expected, there was medium to high correlation between the vertical diameter of the largest cyst and CSFT (correlation coefficient r_s=0.798). Also, a moderate correlation between the horizontal diameter of the largest cyst and CSFT was observed (correlation coefficient r_s= 0.487). Large cysts tend to form in the foveal region, which has no inner retinal layers.[24,25] At the center of the fovea, where there are no inner layers, the retina is more vulnerable to the development of large cysts and increases in mechanical stresses when the axial expansion of cysts is not sufficient to compensate for the increased volume.[26] In light of this pathogenesis and the findings of the current study, we hypothesize that cyst enlargement continues in the horizontal plane after the vertical expansion exceeds the capacity of the retina. This process occurs with the degeneration of the retina.

In some previously published studies, it has been suggested that cysts have a damaging effect on bipolar and ganglion cells.[17,27,28] A relatively new definition, disorganization of retinal inner layers (DRIL), refers to the disruption of the bipolar, horizontal, and amacrine cell synaptic field. Consequently, transmission between photoreceptors and ganglion cell complex is impaired.[29] DRIL was found to be responsive to anti-vascular endothelial growth factor therapy.[30,31] Yohannan et al.[32] reported

Table 3. Optical coherence tomography and fundus fluorescein angiography parameters in cystoid macular edema (CME) and cystoid macular degeneration (CMD) groups based on horizontal (-H) and vertical (-V) diameters of the largest cyst

		CME-H	CMD-H	P value	CME-V	CMD-V	P value
CSFT (µm) Mean ± SD		441±112	571±132	0.0001*	400±82	568±120	0.0001*
Outer retinal layer defect (n,%)		31, 23.1%	46, 39.3%	0.006†	28, 20.6%	49, 42.6%	0.0001†
Foveal contour (n,%)	Normal	17, 12.7%	6, 5.1%	0.0001†	19, 14%	4, 3.5%	0.0001†
	Mild distortion	56, 41.8%	18, 15.4%		63, 46.3%	11, 9.5%	
	Severe distortion	61, 45.5%	93, 79.5%		54, 39.7%	100, 87%	
Macular ischemia (n,%)		56, 41.8%	54, 46.2%	0.487†	50, 36.8%	60, 52.2%	0.014†
Type of edema (n,%)	Focal	54, 40.2%	38, 32.5%	0.298†	65, 47.8%	27, 23.5%	0.0001†
	Diffuse	40, 29.9%	34, 29%		32, 23.5%	42, 36.5%	
	Mixed	40, 29.9%	45, 38.5%		39, 28.7%	46, 40%	

*Independent samples T-test, †Pearson chi-square test CFST: Central subfield thickness, SD: Standard deviation

that the presence of a cyst is associated with decreased retinal sensitivity independent of increased retinal thickness and IS/OS junction disruption.

The presence of macular cystoid spaces has been found to be predictive of reduction in BCVA, and larger cystoid spaces were found to be more disruptive than small ones in a previous study by Sophie et al.[33] In another study, Koleva-Georgieva and Sivkova[34] showed a negative correlation between BCVA and cystoid DME groups (patients were grouped according to the horizontal diameter of cystoid spaces: <300 µm as mild, 300-600 µm as intermediate, and >600 µm as severe cystoid DME). In the hitherto literature there is no reported definition of CME according to cyst size with a specific cut-off value using OCT. In the current study, it was also aimed to find a cut-off value to distinguish CMD from CME. With this finding, the starting point of the degenerative effect of a cyst can be determined. In the current study, the horizontal and vertical diameters of the largest cyst were higher in cases with outer retinal damage, macular ischemia, and diffuse or mixed edema. These conditions are known to be associated with poor visual prognosis.[35,36,37,38,39,40,41,42,43,44,45,46]

In this study, CME and CMD groups were formed according to the horizontal and vertical diameters of the largest cyst. Horizontal cyst diameter ≥450 µm was defined as CMD. In this group, sensitivity was 58% for the prediction of visual acuity <20/60. In other words, eyes with horizontal cyst diameter ≥450 µm had a 58% probability of visual acuity <20/60. Horizontal cyst diameter <450 µm was defined as CME and had 73% specificity for the prediction of visual acuity ≥20/60. Therefore, eyes with horizontal cyst diameter <450 µm had 73% probability of visual acuity ≥20/60. Vertical cyst diameter ≥300 µm was defined as CMD. In eyes with vertical cyst diameter ≥300 µm, the probability of visual acuity <20/60 (sensitivity) was 62%. Vertical cyst diameter <300 µm was defined as CME, and the probability of visual acuity ≥20/60 (specificity) was 69% in this group.

A higher rate of outer retinal damage was observed in the CMD groups than in the CME groups. Likewise, macular ischemia was detected at a higher rate in the CMD groups than in the CME groups. Degeneration and macular ischemia seem to be related processes. In a previously published study, vascular hyperpermeability and ischemia were shown to cause necrosis and apoptosis in the neuroglia cells and this process resulted in large cystoid cavities. A vicious circle ensues with the enlargement of the cystoid spaces causing enlargement of the foveal avascular zone and increased foveal ischemia.[47] In addition, the occurrence of cystoid spaces in the capillary nonperfusion areas and lack of reperfusion of these areas after the resolution of the chronic cystoid edema was shown in a previous OCT angiography study.[48] The findings of the current study, which showed that more degeneration findings are present in ischemic cases, supported these data.

In the current study, the integrity of the foveal contour was also studied with an expectation that the presence of normal foveal contour or mild distortion were more likely to be associated with CME groups and severe distortion with the CMD groups. Indeed, our results showed that severe distortion of the foveal contour was more prevalent in CMD groups. Although Jun et al.[49] evaluated foveal contour integrity in various ocular diseases, the current study is the first to use this parameter for grouping and analysis in DME to define CMD.

In a previous study, Liang et al.[16] showed that accumulations in a cyst isoreflective to the plexiform layer were associated with fibrin and inflammatory debris. The heterogeneous reflectivity group of our study refers to this finding. Higher reflectivity of cystoid spaces was observed by Barthelmes et al.[50] in exudative diseases such as DME compared to the normal vitreous and cystic spaces in degenerative diseases.

Although there was no supporting finding in our study, we hypothesize that the internal reflectivity of the cysts was related with chronicity and degeneration. Initially, the cyst is usually isoreflective. Then, cyst reflectivity becomes heterogeneous on OCT due to the debris accumulation as a result of degeneration. The degenerated cyst becomes hyporeflective in the chronic stage. In an earlier study supporting our hypothesis, the optical intensity of the cystoid space was thought to be a finding indicating chronicity.[51] Contradictory to our hypothesis, the mean density of cystoid spaces was found to be negatively correlated with retinal sensitivity.[52] Further studies are needed to clarify the relationship between the reflectivity of cystoid spaces and the degeneration process.

To the best of our knowledge, this is the first study to determine characteristics of CMD in DME. With these findings, degenerative cases can be diagnosed early in the management of DME. There were some limitations of this study. One is the retrospective design, and another is that there was no follow-up or evaluation of the treatment which was administered. The interpretation of some data such as foveal contour may contain bias. This subjective evaluation can be considered one of the limitations of the study. Future prospective studies investigating treatment response in eyes with CMD with follow-up information would be helpful to predict eyes with poor visual prognosis (such as those with CMD) and eyes with CME, which probably have better prognosis.

Conclusion

In conclusion, cystoid degeneration in DME can be defined as the largest cyst in the central fovea having a horizontal diameter >450 µm and vertical diameter >300 µm, especially with concomitant macular ischemia, outer retinal damage, loss of foveal contour, and diffuse/mixed edema subtype. This definition can provide a new perspective to professionals in patient assessment and may help estimate the benefit of treatment.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Gazi University with the ethics committee decision numbered 37 and dated 26 January 2015

Informed Consent: Written informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Şengül Özdek, Design: Şengül Özdek, Fatma Nur Baran Aksakal, Data Collection or Processing: Nuriye Gökçen Yalçın, Analysis or Interpretation: Nuriye Gökçen Yalçın, Şengül Özdek, Fatma Nur Baran Aksakal, Literature Search: Nuriye Gökçen Yalçın, Writing: Nuriye Gökçen Yalçın, Şengül Özdek

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. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol. 2009;54:1-32.
2. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology. 1984;91:1464-1474.
3. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol. 1999;127:688-693.
4. Wallow IH, Danis RP, Bindley C, Neider M. Cystoid macular degeneration in experimental branch retinal vein occlusion. Ophthalmology 1988;95:1371-1379.
5. Iida T, Yannuzzi LA, Spaide RF, Borodoker N, Carvalho CA, Negrao S. Cystoid macular degeneration in chronic central serous chorioretinopathy. Retina. 2003;23:1-7.
6. Piccolino FC, De La Longrais RR, Manea M, Cicinelli S. Posterior cystoid retinal degeneration in central serous chorioretinopathy. Retina. 2008;28: 1008-1012.
7. Querques G, Coscas F, Forte R, Massamba N, Sterkers M, Souied EH. Cystoid macular degeneration in exudative age-related macular degeneration. Am J Ophthalmol. 2011;152:100-107.
8. Chung EJ, Roh MI, Kwon OW, Koh HJ. Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema. Retina 2008;28:957-963.
9. Kang SW, Park CY, Ham DI. The Correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. Am J Ophthalmol. 2004;137:313-322.
10. Smith R, Lee C. Quantification of diabetic macular edema. Arch Ophthalmol. 1987;105:218-222.
11. Huang J, Liu X, Wu Z, Xiao H, Dustin L, Sadda S. Macular thickness measurements in normal eyes with time-domain and Fourier-domain optical coherence tomography. Retina. 2009;29:980-987.
12. Ozdemir H, Karacorlu M, Karacorlu S. Serous macular detachment in diabetic cystoid macular oedema. Acta Ophthalmol Scand. 2005;83:63-66.
13. Gaucher D, Sebah C, Erginay A, Haouchine B, Tadayoni R, Gaudric A, Massin P. Optical coherence tomography features during the evolution of serous retinal detachment in patients with diabetic macular edema. Am J Ophthalmol. 2008;145:289-296.
14. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, Sadda SR, Sebag J, Spaide RF, Stalmans P. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120:2611-2619.
15. Maheshwary AS, Oster SF, Yuson RM, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. Am J Ophthalmol. 2010;150:63-67.
16. Liang MC, Vora RA, Duker JS, Reichel E. Solid-appearing retinal cysts in diabetic macular edema: a novel optical coherence tomography finding. Retin Cases Brief Rep. 2013;7:255-258.
17. Colenbrander A. Visual standards: Aspects and ranges of vision loss with emphasis on population surveys. Report for the International Council of Ophthalmology, 29th International Congress of Ophthalmology, Sydney, Australia; 2002
18. Das R, Spence G, Hogg RE, Stevenson M, Chakravarthy U. Disorganization of Inner Retina and Outer Retinal Morphology in Diabetic Macular Edema. JAMA Ophthalmol. 2018;136:202-208.
19. Yanoff M, Fine BS, Brucker AJ, Eagle RC Jr. Pathology of human cystoid macular edema. Surv Ophthalmol. 1984;28: 505-511.
20. Yamamoto S, Yamamoto T, Hayashi M, Takeuchi S. Morphological and functional analyses of diabetic macular edema by optical coherence tomography and multifocal electroretinograms. Graefes Arch Clin Exp Ophthalmol. 2001;239:96-101.
21. Eldem B, Ozdek S, Saatci AO, Ozmert E, Ulay E, Nomak G. Clinical characteristics of patients with newly diagnosed diabetic macular edema in Turkey: A real-life registry study-TURK-DEM. J Ophthalmol. 2017;2017:3596817.
22. Murakami T, Ueda-Arakawa N, Nishijima K, Uji A, Horii T, Ogino K, Yoshimura N. Integrative understanding of macular morphologic patterns in diabetic retinopathy based on self-organizing map. Invest Ophthalmol Vis Sci. 2014;55:1994-2003.
23. Mori Y, Murakami T, Suzuma K, Ishihara K, Yoshitake S, Fujimoto M, Dodo Y, Yoshitake T, Miwa Y, Tsujikawa A. Relation between macular morphology and treatment frequency during twelve months with ranibizumab for diabetic macular edema. PLoS One. 2017;12:e0175809.
24. Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A, Massin P. Characterization of macular edema from various etiologies by optical coherence tomography. Am J Ophthalmol. 2005;140:200-206.
25. Bolz M, Ritter M, Schneider M, Simader C, Scholda C, Schmidt-Erfurth U. A systematic correlation of angiography and high-resolution optical coherence tomography in diabetic macular edema. Ophthalmology. 2009;16:66-72.
26. Shereef H, Comyn O, Sivaprasad S, Hykin P, Cheung G, Narendran N, Yang YC. Differences in the topographic profiles of retinal thickening in eyes with and without serous macular detachment associated with diabetic macular oedema. Br J Ophthalmol. 2014;98:182-187.
27. Tso M. Pathology of cystoid macular edema. Ophthalmology. 1982;89:902-915.
28. Murakami T, Nishijima K, Sakamoto A, Ota M, Horii T, Yoshimura N. Association of pathomorphology, photoreceptor status, and retinal thickness with visual acuity in diabetic retinopathy. Am J Ophthalmol. 2011;151:310-317.
29. Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, Aiello LP. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132:1309-1316.
30. Fickweiler W, Schauwvlieghe AME, Schlingemann RO, Maria Hooymans JM, Los LI, Verbraak FD; BRDME Research Group. Predictive value of optical coherence tomographic features in the bevacizumab and ranibizumab in patients with diabetic macular edema (BRDME) Study. Retina. 2018;38:812-819.
31. Santos AR, Costa MÂ, Schwartz C, Alves D, Figueira J, Silva R, Cunha-Vaz JG.
32. Optical coherence tomography baseline predictors for initial best-corrected visual acuity response to intravitreal anti-vascular endothelial growth factor treatment in eyes with diabetic macular edema: The CHARTRES Study. Retina. 2018;38:1110-1119.
33. Yohannan J, Bittencourt M, Sepah YJ, Hatef E, Sophie R, Moradi A, Liu H, Ibrahim M, Do DV, Coulantuoni E, Nguyen QD. Association of retinal sensitivity to integrity of photoreceptor inner/outer segment junction in patients with diabetic macular edema. Ophthalmology. 2013;120:1254-1261.
34. Sophie R, Lu N, Campochiaro PA. Predictors of Functional and Anatomic Outcomes in Patients with Diabetic Macular Edema Treated with Ranibizumab. Ophthalmology. 2015;122:1395-1401.
35. Koleva-Georgieva D, Sivkova N. Assessment of serous macular detachment in eyes with diabetic macular edema by use of spectral-domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2009;247:1461-1469.

36. Maheshwary AS, Oster SF, Yuson RM, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. Am J Ophthalmol. 2010;150:63-67.
37. Shin HJ, Lee SH, Chung H, Kim HC. Association between photoreceptor integrity and visual outcome in diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2012;250:61-70.
38. 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.
39. Chhablani J, Kim J, Cheng L, Kozak I, Freeman W. External limiting membrane as a predictor of visual improvement in diabetic macular edema after pars plana vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2012;250:1415-1420.
40. Otani T, Yamaguchi Y, Kishi S. Correlation between visual acuity and foveal microstructural changes in diabetic macular edema. Retina. 2010;30:774-780.
41. Forooghian F, Stetson PF, Meyer SA, Chew EY, Wong WT, Cukras C, Meyerle CB, Ferris FL 3rd. Relationship between photoreceptor outer segment length and visual acuity in diabetic macular edema. Retina. 2010;30:63-70.
42. Eliwa TF, Hussein MA, Zaki MA, Raslan OA. Outer retinal layer thickness as good visual predictor in patients with diabetic macular edema. Retina. 2018;38:805-811.
43. Chung EJ, Roh MI, Kwon OW, Koh HJ. Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema. Retina. 2008;28:957-963.
44. Sim DA, Keane PA, Zarranz-Ventura J, Fung S, Powner MB, Platteau E, Bunce CV, Fruttiger M, Patel PJ, Tufail A, Egan CA. The effects of macular ischemia on visual acuity in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2013;54:2353-2360.
45. Ticho U, Patz A. The role of capillary perfusion in the management of diabetic macular edema. Am J Ophthalmol. 1973;76: 880-886.
46. Jonas JB, Martus P, Degenring RF, Kreissig I, Akkoyun I. Predictive factors for visual acuity after intravitreal triamcinolone treatment for diabetic macular edema. Arch Ophthalmol. 2005;123:1338-1343.
47. Gandorfer A. Diffuse diabetic macular edema: pathology and implications for surgery. Dev Ophthalmol. 2007;39:88-95
48. Murakami T, Nishijima K, Sakamoto A, Ota M, Horii T, Yoshimura N. Foveal cystoid spaces are associated with enlarged foveal avascular zone and microaneurysms in diabetic macular edema. Ophthalmology. 2011;118:359-367.
49. Mané V, Dupas B, Gaudric A, Bonnin S, Pedinielli A, Bousquet E, Erginay A, Tadayoni R, Couturier A. Correlation between cystoid spaces in chronic diabetic macular edema and capillary nonperfusion detected by optical coherence tomography angiography. Retina. 2016;36(Suppl 1):102-110.
50. Jun JJ, Duker JS, Baumal CR, McCabe F, Reichel E, Rogers AH, Seddon JM, Tolentino FI. Cystoid macular edema without macular thickening: a retrospective optical coherence tomographic study. Retina. 2010;30:917-923.
51. Barthelmes D, Sutter FK, Gillies MC. Differential optical densities of intraretinal spaces. Invest Ophthalmol Vis Sci. 2008;49:3529-3534.
52. Wolter JR. The histopathology of cystoid macular edema. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1981;216:85-101.
53. Velaga SB, Nittala MG, Parinitha B, Sadda SR, Chhablani JK. Correlation between retinal sensitivity and cystoid space characteristics in diabetic macular edema. Indian J Ophthalmol. 2016;64:452-458.

DOI: 10.4274/tjo.galenos.2019.95226
Turk J Ophthalmol 2019;49:323-327

Original Article

Effectiveness of Intravitreal Dexamethasone Implant Treatment for Diabetic Macular Edema in Vitrectomized Eyes

Hüseyin Baran Özdemir, Murat Hasanreisoğlu, Murat Yüksel, Mestan Ertop, Gökhan Gürelik, Şengül Özdek

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

Abstract

Objectives: To report the effectiveness and long-term outcomes of intravitreal dexamethasone implantation for diabetic macular edema (DME) in vitrectomized eyes

Materials and Methods: Medical records of patients were retrospectively reviewed. Time of pars plana vitrectomy (PPV), PPV indications, interval between DEX injection and PPV, other intravitreal treatment prior to DEX application, best corrected visual acuity (BCVA), intraocular pressure (IOP), and central retinal thickness (CRT) measured by optical coherence tomography were recorded.

Results: Seventeen eyes of 17 patients were included in the study. The mean follow-up after DEX injection was 21±2.4 months (12-43 months). The female/male ratio was 11/6. Mean age was 60.7 years (46-70 years). Sixteen eyes (94.1%) were pseudophakic at the time of DEX treatment. The most common indication for PPV was tractional retinal detachment (8 eyes, 47.1%). Ten eyes (58.8%) received a single injection and a total of 30 DEX implantations were performed. Mean BCVA was 0.77 logarithm of the minimum angle of resolution (logMAR) units before the first injection and improved to 0.64, 0.68 and 0.66 logMAR after 1, 3 and 6 months, respectively ($p<0.01$). CRT decreased significantly from 452 µm at baseline to 310, 368±34 and 375 µm after 1, 3 and 6 months, respectively ($p<0.04$). Mean IOP was 16±1.2 mmHg at baseline and 18.2, 18.8 and 18.5 mmHg after 1, 3, and 6 months ($p>0.05$). Two eyes (%8) received topical anti-glaucoma medication (IOP≥25 mmHg). Similar results were observed in eyes receiving repeated DEX injections.

Conclusion: Intravitreal DEX injection treatment seems to be effective for improving BCVA and decreasing CRT in vitrectomized eyes with DME. This effect seemed to last for 6 months in most eyes, but maximized at 3 months. Patients with repeated injections often require injection before 6 months.

Keywords: Diabetic macular edema, DMÖ, dexamethasone implant, pars plana vitrectomy

Introduction

Diabetic retinopathy is among the leading causes of blindness in developed societies.[1] Patients with diabetic retinopathy often suffer from vision loss due to diabetic macular edema (DME).[2] Although multiple factors play a role in the pathogenesis of DME, one of the main mechanisms involves the inflammatory pathway, which comprises many mediators such as vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and interleukin-1 beta.[3,4] For this reason, intravitreal corticosteroids are often employed in the treatment of DME.[5,6,7,8] Intravitreal dexamethasone and triamcinolone acetate are the corticosteroids most commonly used to treat DME.[9,10]

Address for Correspondence: Hüseyin Baran Özdemir MD, Gazi University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone:+90 505 871 92 39 E-mail: baranozdemir@gmail.com **ORCID-ID:** orcid.org/0000-0002-5585-253X
Received: 09.03.2019 **Accepted:** 25.06.2019

Cite this article as: Özdemir HB, Hasanreisoğlu M, Yüksel M, Ertop M, Gürelik G, Özdek Ş. Effectiveness of Intravitreal Dexamethasone Implant Treatment for Diabetic Macular Edema in Vitrectomized Eyes. Turk J Ophthalmol. 2019;49:323-327

Despite therapeutic advances, diabetic patients may still require pars plana vitrectomy (PPV). The most common indications for PPV are vitreous hemorrhage due to proliferative diabetic retinopathy, tractional retinal detachment, and refractory DME.[11] Intravitreal anti-VEGF and corticosteroid injections are often needed after PPV as well. Some reports have indicated that intravitreal drugs administered to vitrectomized patients have reduced half-life and efficacy.[12]

Slow-release intravitreal implants were introduced to the market with the aim of providing long-lasting intraocular drug activity.[13,14] An intravitreal dexamethasone implant (DEX; Ozurdex, Allergan, Irvine, CA, USA) was developed for injection into the vitreous cavity and is indicated for DME.[15] DEX, a biodegradable polymer composed of a combination of 0.7 mg dexamethasone and poly(lactic acid-co-glycolic acid), slowly degrades in the vitreous cavity to release DEX over a period of 6 months.[16] This sustained-release feature of DEX is proposed to reduce the number of injections needed in vitrectomized eyes compared to other intravitreal treatments.

The aim of this study was to report the effectiveness and long-term outcomes of DEX used for the treatment of DME in vitrectomized eyes.

Materials and Methods

This retrospective study included patients over 18 years of age who had previously undergone PPV surgery in the Ophthalmology Department of Gazi University and who were subsequently given DEX injections due to DME between July 2015 and December 2017. The study was approved by a local ethics committee (Numune Training and Research Hospital Ethics Committee, decision E-19-2466) and conducted in adherence with the principles of the Declaration of Helsinki. Patients with less than 1 year of follow-up after DEX injection were not included in the study.

The patients were evaluated in terms of age; sex; affected eye; date and reason for PPV surgery; number of DEX injections; time interval between injections, if applicable; complications; total follow-up time; and best corrected visual acuity (BCVA), intraocular pressure (IOP), anterior segment examination findings (especially lens status), fundus examination findings, and central foveal thickness (CFT) obtained by optical coherence tomography (OCT) before and at 1, 3, and 6 months after injection. BCVA values were obtained with Snellen chart and converted from decimal to logarithm of the minimum angle of resolution (logMAR) before statistical analysis. CFT measurements in OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) were made using the values acquired automatically by the device.

Statistical Analyses

SPSS software (version 22.0, SPSS, Inc. Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to determine whether the data showed normal distribution. A Wilcoxon signed-rank test was used to evaluate changes in BCVA, IOP, and CFT values between pre- and post-treatment time points. Changes with p values <0.05 were considered significant.

Results

Seventeen eyes of 17 patients (11 women, 6 men) were included in the study. The demographic characteristics of

Table 1. Demographic and clinical characteristics of the patients included in the study

Number of patients	**17**
Number of eyes	17
Age (years),	60.7±7.2 (46–70)
Sex (female:male)	11:6
Follow-up time (months)	21±10.1 (12–43)
PPV indication (n=17) • Tractional retinal detachment associated with proliferative diabetic retinopathy? • Epiretinal membrane • Vitreous hemorrhage associated with proliferative diabetic retinopathy	 8 eyes (47.1%) 7 eyes (41.2%) 2 eyes (11.8%)
Median time between PPV and DEX (months)	14±23.1 (3–81)
Eyes treated with anti-VEGF before DEX	13 (76.5%)
Mean time between last anti-VEGF and DEX administration (months)	5.2±4.6 (3–16)
Lens status before DEX (n=17) • Phakic • Pseudophakic	 1 (5.9%) 16 (94.1%)
Number of injections (n=30) • 1 • 2 • 3 • 5	 10 (58.9%) 3 (17.6%) 3 (17.6%) 1 (5.9%)

PPV: Pars plana vitrectomy, DEX: Intravitreal dexamethasone implant, VEGF: Vascular endothelial growth factor

the patients are shown in Table 1. Sixteen eyes (94.1%) were pseudophakic. Thirteen eyes (76.5%) had been treated with anti-VEGF before treatment with DEX. In all patients, the time between the last intravitreal anti-VEGF administration and DEX was at least 3 months, with a mean of 5.2±4.6 months (3-16 months). Ten eyes (58.8%) received a single DEX injection and 7 eyes (41.2%) received multiple injections. A total of 30 DEX injections were administered.

Mean BCVA was 0.77±0.35 logMAR before the first DEX injection and increased significantly to 0.64±0.33 (p=0.007), 0.68±0.08 (p=0.009), and 0.66±0.36 (p=0.016) at 1, 3, and 6 months after DEX injection, respectively. When patients who were treated with a single dose of DEX and those who required repeat DEX injection within 6 months or after more than 6 months were examined separately, it was observed that the change in final BCVA compared to initial BCVA was similar in all three subgroups (p=0.719). BCVA increased more than 2 rows in 7 eyes (41.1%).

Mean CRT was 452±97 µm before DEX injection and decreased significantly to 310±103 µm (p=0.001), 368±140 µm (p=0.004), and 375±125 µm (p=0.041) at 1, 3, and 6 months after treatment, respectively. Change in CRT between initial and final values was also statistically similar in subgroup analysis of patients treated with a single dose of DEX and those who required repeat DEX injection within 6 months or after more than 6 months (p=0.180). The reduction in CRT was maintained for 6 months in patients who required a single dose of DEX.

Mean IOP increased with the first DEX injection from an initial value of 16±3.6 mmHg to 18.2±3.88 (p=0.027), 18.8±1.8 (p=0.221), and 18.5±1.2 mmHg (p=0.285) at 1, 3, and 6 months after DEX treatment, respectively. Two eyes required topical antiglaucoma therapy (IOP>25 mmHg).

The only patient who was phakic at the beginning of follow-up developed nuclear cataract and underwent cataract surgery 10 months after a single DEX injection. No additional complications were observed. The median time between first and second DEX injections was 5 months (4-27 months). Of the 7 eyes that received another injection, 5 (71.4%) required the second dose of DEX within 6 months.

Discussion

There is still debate regarding the agents to be used for the treatment of DME in diabetic eyes that have undergone PPV surgery. In the present study, a single DEX injection to vitrectomized eyes reduced CRT and improved vision compared to pre-treatment values for 6 months in more than half of the patients (10/17 eyes, 58.8%). Thirty percent of the eyes required a repeat injection before 6 months, and the treatment response in the eyes that received a second DEX injection (7/17 eyes, 41.2%) was similar to the results of the first DEX injection. These findings are consistent with previously published results.

The CHAMPLAIN trial by Boyer et al.[17] was the first study to examine the outcomes of DEX injection in vitrectomized eyes. The results of this prospective study including 55 PPV patients followed for 26 weeks indicated that DEX injection was effective for the treatment of DME and had an acceptable safety profile. It was reported that DEX took effect within 1 week and reached maximum effect at 8 weeks. Shah et al.[18] demonstrated that the activity of DEX in vitrectomized eyes increases over the first month and lasts for at least 3 months. We also observed maximum effect in the first month in the present study, but DEX activity lasted longer than 3 months in the majority of our patients and a single injection was sufficient for 58.8% of them.

The half-life of intravitreal drugs is associated with the presence of the vitreous. Most studies investigating the pharmacokinetics of intravitreal drugs in vitrectomized eyes were based on the results of animal experiments.[12] Studies conducted in the eyes of macaque monkeys showed that anti-VEGF had a shorter half-life in vitrectomized eyes.[19,20] In studies of rabbit eyes, it was reported that the pharmacokinetics of ranibizumab and bevacizumab do not differ between vitrectomized and nonvitrectomized eyes.[21,22] Chin et al.[23] reported that triamcinolone acetate clearance was accelerated in vitrectomized eyes. Similarly, the half-life of triamcinolone acetate has been shown to be shorter in vitrectomized eyes that undergo sub-Tenon's injection.[24] In a DEX study by Chang-Lin et al.[16] comparing vitrectomized and nonvitrectomized rabbit eyes, the pharmacokinetic profile of DEX was similar in both groups.

Although animal studies give some insight into drug pharmacokinetics, they cannot provide exact information due to differences in vitreous volume compared to the human eye, and because animal studies generally involve lensectomy as well as vitrectomy and there is no pseudophakia model.[25] Yanyalı et al.[26] observed no significant clinical effect in vitrectomized eyes treated with bevacizumab due to DME. Studies on ranibizumab have shown that vitrectomized eyes require more injections compared to normal eyes for the treatment of DME, but there was no significant difference in terms of efficacy.[27,28] The Diabetic Retinopathy Clinical Research Network (DRCR.net) group reported that favorable outcomes were obtained with ranibizumab in the vitrectomized eyes of patients who were followed for a mean of 3 years.[29] In that study, it was reported that there was no significant difference between the two groups in terms of number of injections, but the clinical effect emerged more slowly and more injections were needed in the first year of treatment in vitrectomized eyes. The sustained-release DEX was reported to have similar pharmacokinetics in vitrectomized and nonvitrectomized rabbit eyes. As with anti-VEGF studies, most of the results from human eyes have been obtained from retrospective data.

Comparisons of the effectiveness of DEX in the treatment of DME in vitrectomized versus nonvitrectomized eyes in the literature have also been based on retrospective data. In their retrospective review of vitrectomized and nonvitrectomized groups including 24 eyes each, Medeiros et al.[30] demonstrated that DEX had similar effectiveness in both groups in terms of visual improvement and decrease in CRT. Çevik et al.[31] also reported that DEX was similarly effective in the treatment of

DME in eyes with and without vitrectomy. Bastakis et al.[32] reported that previous vitrectomy did not adversely affect the effectiveness of DEX in patients with refractory DME, and that the maximum effect was observed within the first 3 months in both vitrectomized and nonvitrectomized eyes.

Study Limitations

The limitations of our study include its retrospective nature, the lack of a control group, and the small number of patients. Prospective, randomized studies should be expected to provide more accurate results when comparing the efficacy of DEX between eyes with and without previous vitrectomy. However, the results of comparative retrospective studies in the literature show that DEX can be used safely in patients with DME who have undergone vitrectomy. Strengths of our study are the long-term follow-up, the good collection of retrospective data, and the inclusion of real-life patient data.

Conclusion

In conclusion, DEX is a safe and effective treatment for DME patients with history of PPV. DEX provides long-term vision increase and CRT decrease with a single injection in the majority of patients and shows a safe IOP profile, which suggests that it should be considered as first-line treatment in vitrectomized patients. It should be kept in mind that the effect may be shorter and that frequent injections may be necessary in patients with refractory DME.

Ethics

Ethics Committee Approval: Ankara Numune Training and Research Hospital Clinical Research Ethics Committee / E-19-2466

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Hasanreisoğlu, Şengül Özdek, Gökhan Gürelik, Concept: Hüseyin Baran Özdemir, Murat Hasanreisoğlu, Design: Hüseyin Baran Özdemir, Murat Hasanreisoğlu, Data Collection or Processing: Hüseyin Baran Özdemir, Murat Yüksel, Mestan Ertop, Murat Hasanreisoğlu, Analysis or Interpretation: Hüseyin Baran Özdemir, Murat Hasanreisoğlu, Literature Search: Hüseyin Baran Özdemir, Writing: Hüseyin Baran Özdemir, Murat Hasanreisoğlu

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. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376:124-136.
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015;2:17.
3. Das A, McGuire PG, Rangasamy S. Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets. Ophthalmology. 2015;122:1375-1394.
4. Rangasamy S, McGuire PG, Das A. Diabetic retinopathy and inflammation: novel therapeutic targets. Middle East Afr J Ophthalmol. 2012;19:52-59.
5. Diabetic Retinopathy Clinical Research N, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372:1193-1203.
6. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW; Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016;123:1351-1359.
7. Nurözler Tabakcı B, Ünlü N. Corticosteroid Treatment in Diabetic Macular Edema. Turk J Ophthalmol. 2017;47:156-160.
8. Akıncıoğlu D, Küçükevcilioğlu M, Durukan AH, Aykaş S, Ayyıldız Ö, Erdurman FC. Outcomes of Intravitreal Dexamethasone Implant in the Treatment of Recalcitrant Diabetic Macular Edema. Turk J Ophthalmol. 2017;47:274-278.
9. Yang Y, Bailey C, Loewenstein A, Massin P. Intravitreal Corticosteroids in Diabetic Macular Edema: Pharmacokinetic Considerations. Retina. 2015;35:2440-2449.
10. Lattanzio R, Cicinelli MV, Bandello F. Intravitreal Steroids in Diabetic Macular Edema. Dev Ophthalmol. 2017;60:78-90.
11. Gupta V, Arevalo JF. Surgical management of diabetic retinopathy. Middle East Afr J Ophthalmol. 2013;20:283-292.
12. Edington M, Connolly J, Chong NV. Pharmacokinetics of intravitreal anti-VEGF drugs in vitrectomized versus non-vitrectomized eyes. Expert Opin Drug Metab Toxicol. 2017;13:1217-1224.
13. Zucchiatti I, Lattanzio R, Querques G, Querques L, Del Turco C, Cascavilla ML, Bandello F. Intravitreal dexamethasone implant in patients with persistent diabetic macular edema. Ophthalmologica. 2012;228:117-122.
14. Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, Tolentino M, Gupta A, Duarte L, Madreperla S, Gonder J, Kapik B, Billman K, Kane FE; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011;118:626-635.
15. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121:1904-1914.
16. Chang-Lin JE, Attar M, Acheampong AA, Robinson MR, Whitcup SM, Kuppermann BD, Welty D. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci. 2011;52:80-86.
17. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, Liu CC, Lou J, Whitcup SM; Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina. 2011;31:915-923.
18. Shah AR, Xi M, Abbey AM, Yonekawa Y, Faia LJ, Hassan TS, Ruby AJ, Wolfe JD. Short-term Efficacy of Intravitreal Dexamethasone Implant in Vitrectomized Eyes with Recalcitrant Diabetic Macular Edema and Prior Anti-VEGF Therapy. J Ophthalmic Vis Res. 2016;11:183-187.
19. Niwa Y, Kakinoki M, Sawada T, Wang X, Ohji M. Ranibizumab and Aflibercept: Intraocular Pharmacokinetics and Their Effects on Aqueous VEGF Level in Vitrectomized and Nonvitrectomized Macaque Eyes. Invest Ophthalmol Vis Sci. 2015;56:6501-6505.
20. Kakinoki M, Sawada O, Sawada T, Saishin Y, Kawamura H, Ohji M. Effect of vitrectomy on aqueous VEGF concentration and pharmacokinetics of bevacizumab in macaque monkeys. Invest Ophthalmol Vis Sci. 2012;53:5877-5880.

21. Ahn J, Kim H, Woo SJ, Park JH, Park S, Hwang DJ, Park KH. Pharmacokinetics of intravitreally injected bevacizumab in vitrectomized eyes. J Ocul Pharmacol Ther. 2013;29:612-618.
22. Ahn SJ, Ahn J, Park S, Kim H, Hwang DJ, Park JH, Park JY, Chung JY, Park KH, Woo SJ. Intraocular pharmacokinetics of ranibizumab in vitrectomized versus nonvitrectomized eyes. Invest Ophthalmol Vis Sci. 2014;55:567-573.
23. Chin HS, Park TS, Moon YS, Oh JH. Difference in clearance of intravitreal triamcinolone acetonide between vitrectomized and nonvitrectomized eyes. Retina. 2005;25:556-560.
24. Park HJ, Lee JE, Kim SI, Pak KY, Oum BS, Lee JS, Jung JH, Lee JE. Intravitreal pharmacokinetics after posterior subtenon triamcinolone acetonide injection in vitrectomized rabbit eyes. Retina. 2014;34:801-806.
25. Kerimoğlu H. Intravitreal Anti-VEGF Drug Injections in Vitrectomized Eyes. Ret-Vit. 2018;27:307-313.
26. Yanyali A, Aytug B, Horozoglu F, Nohutcu AF. Bevacizumab (Avastin) for diabetic macular edema in previously vitrectomized eyes. Am J Ophthalmol. 2007;144:124-126.
27. Koyanagi Y, Yoshida S, Kobayashi Y, Kubo Y, Yamaguchi M, Nakama T, Nakao S, Ikeda Y, Ohshima Y, Ishibashi T, Sonoda KH. Comparison of the Effectiveness of Intravitreal Ranibizumab for Diabetic Macular Edema in Vitrectomized and Nonvitrectomized Eyes. Ophthalmologica. 2016;236:67-73.
28. Chen YY, Chen PY, Chen FT, Chen YJ, Wang JK. Comparison of efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema. Int Ophthalmol. 2018;38:293-299.
29. Bressler SB, Melia M, Glassman AR, Almukhtar T, Jampol LM, Shami M, Berger BB, Bressler NM; Diabetic Retinopathy Clinical Research Network. Ranibizumab Plus Prompt or Deferred Laser for Diabetic Macular Edema in Eyes with Vitrectomy before Anti-Vascular Endothelial Growth Factor Therapy. Retina. 2015;35:2516-2528.
30. Medeiros MD, Alkabes M, Navarro R, Garcia-Arumi J, Mateo C, Corcostegui B. Dexamethasone intravitreal implant in vitrectomized versus nonvitrectomized eyes for treatment of patients with persistent diabetic macular edema. J Ocul Pharmacol Ther. 2014;30:709-716.
31. Çevik SG, Yılmaz S, Çevik MT, Akalp FD, Avcı R. Comparison of the Effect of Intravitreal Dexamethasone Implant in Vitrectomized and Nonvitrectomized Eyes for the Treatment of Diabetic Macular Edema. J Ophthalmol. 2018;2018:1757494.
32. Bastakis GG, Dimopoulos D, Stavrakakis A, Pappas G. Long-term efficacy and duration of action of dexamethasone implant, in vitrectomised and non-vitrectomised eyes with persistent diabetic macular oedema. Eye (Lond). 2019;33:411-418.

DOI: 10.4274/tjo.galenos.2019.89804
Turk J Ophthalmol 2019;49:328-333

Original Article

Outcomes of Vitrectomy Under Air for Idiopathic Macular Hole

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

İstanbul Retina Institute, Ophthalmology Clinic, İstanbul, Turkey

Abstract

Objectives: To evaluate the outcomes of 23-gauge pars plana vitrectomy (PPV) under air compared with standard PPV for idiopathic macular hole (MH).

Materials and Methods: In this prospective, comparative, interventional case series, 42 eyes of 42 patients with idiopathic MH were enrolled. Twenty-one eyes had vitrectomy with an air-infused technique and 21 eyes underwent vitrectomy with a traditional balanced salt solution-infused technique as a control group. Effective vitrectomy time, total surgery time, microperimetry (MP1), and anatomical and functional results were evaluated.

Results: The mean effective vitrectomy time was significantly lower in the air group than in the control group (7.5±0.3 min and 13.3±0.5 min, respectively, P<0.001). The mean total surgery time was significantly lower in the air group than the control group (21.8±2.0 min and 25.9±1.1 min, respectively, P<0.001). There were no statistically significant changes between preoperative and 3-month postoperative retinal sensitivity values evaluated by MP1 in either group. Anatomical success at 3 months was 100% in both groups. Intraoperative complications noted during the air-infused vitrectomy were retinal touch (10%) and sudden hypotony (10%); in the two pseudophakic eyes, migration of air into the anterior chamber occurred in one (50%) and fogging of the intraocular lens in one eye (50%).

Conclusion: Vitrectomy under air infusion for idiopathic MH showed some advantages over a traditional vitrectomy technique in terms of vitreous visualization, effective vitrectomy time, and total surgery duration, without significantly increasing intraoperative and postoperative complication rates. Postoperative microperimetry results indicated no specific damage to the retina or optic nerve related to the continuous air infusion.

Keywords: Idiopathic macular hole, pars plana vitrectomy, vitrectomy under air

Introduction

A full-thickness macular hole (MH) is defined as an anatomical defect in the fovea with interruption of all neural retinal layers from the internal limiting membrane (ILM) to the retinal pigment epithelium.[1] An annual incidence of 7.4 per 100 000 inhabitants has been reported recently.[2] The Gass classification of MH is based on careful clinical examination and divides MHs into four stages.[3] Although this system is still quoted widely and adaptations of it are in clinical use, optical coherence tomography (OCT)-based anatomical data have added much to our understanding of the pathogenesis and progression of MH.[1,4]

Recently, MH surgery has greatly benefited from the advent of small-gauge transconjunctival sutureless vitrectomy.[5] This is hypothesized to aid in MH closure by relieving the anteroposterior traction at the macula and creating a space for an endotamponading agent. ILM peeling and gas tamponade

Address for Correspondence: Murat Karaçorlu MD, İstanbul Retina Institute, Ophthalmology Clinic, İstanbul, Turkey
Phone:+90 212 231 31 21 E-mail: mkaracorlu@gmail.com **ORCID-ID:** orcid.org/0000-0001-5561-3339
Received: 30.01.2019 **Accepted:** 07.05.2019

Cite this article as: Karaçorlu M, Hocaoğlu M, Sayman Muslubaş I, Ersöz MG, Arf S.
Outcomes of Vitrectomy Under Air for Idiopathic Macular Hole. Turk J Ophthalmol. 2019;49:328-333

are believed to facilitate MH closure by removing tangential tractions.[6] There is evidence that ILM peeling aids primary and final MH closure.[7,8] The closure rate has been reported to be similar (>86%) with sulfur hexafluoride and perfluoropropane (C3F8) tamponade, irrespective of hole size, stage, or duration.[6] The duration of tamponade required for hole closure has been a matter of debate. There are arguments in favor of extensive vitreous removal, although there is no way of proving that extensive vitrectomy is better than partial vitrectomy. Extensive vitrectomy means separation of the posterior hyaloid membrane up to the equator, followed by shaving of the vitreous base. The removal of as much vitreous as possible allows injection of more gas mixture into the eye and subsequently prolongs the effect of the gas tamponade.[9]

Despite new technological advancements in vitreoretinal surgery, access to the vitreous base, especially in phakic eyes, is technically challenging. Continuous infusion of balanced salt solution (BSS) is used to replace the vitreous, but air has physical properties with advantages over BSS in certain conditions. We have proposed air-infused vitrectomy with 23-gauge instrumentation for better visualization and more efficient clearing of the vitreous cavity (Frankfurt Retina Meeting; April 19-20; 2008).

The use of vitreous cutters and other instruments at the interface between perfluorocarbon liquid,[10,11,12,13] silicone oil,[14,15,16,17] or air,[17,18,19,20,21] and residual vitreous, epiretinal membrane, and retina has been described as interface vitrectomy.[22] These tamponading substances stabilize the vitreoretinal tissue because of their elevated surface tension and provide a more stable surgical field during removal of the vitreous. Vitrectomy performed under air possesses the advantage of better visualization of the peripheral vitreous and vitreous base.

Air-perfused vitrectomy has been shown to provide some benefits in cases of rhegmatogenous retinal detachment (RRD) and macular diseases.[19,20,21] The aim of this research was to gain insight into the efficacy of air-perfused core and peripheral vitrectomy for full-thickness MH.

Materials and Methods

A prospective, comparative study was designed. The study protocol was approved by the Ethics Committee of Şişli Memorial Hospital, İstanbul (protocol number: 0067). The study was in accordance with the principles of the Declaration of Helsinki. We enrolled 42 patients (42 eyes) with a clinical diagnosis of stage 4 idiopathic MH with complete posterior vitreous detachment who underwent small-gauge vitreoretinal surgery. The study group consisted of 21 patients who underwent vitrectomy under air infusion, and the control group of 21 patients who underwent standard vitrectomy under fluid infusion. The patients were selected randomly. Written informed consent was obtained from all participants.

All subjects underwent a comprehensive ophthalmologic evaluation, including best corrected visual acuity (BCVA), intraocular pressure, anterior segment and fundus examination, spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and microperimetry (MP1) (MP-1 Microperimeter, Nidek Technologies, Padua, Italy).

The following parameters were recorded and analyzed: demographic characteristics, preoperative and postoperative lens status, effective vitrectomy time, total surgery time, and preoperative and three-month postoperative BCVA and MP1 sensitivity.

MP1 used a red cross as the fixation target and a standardized grid of 76 Goldmann III stimuli covering the central 20°, white background illumination of 1.27 cd/m^2, and a projection time of 200 ms, which has been described previously.[23] A 4-2 staircase strategy was carried out and the contralateral eye was occluded during the test. All subjects underwent MP1 with dilated pupils. Differential light threshold values were compared by calculating selected points, which were averaged automatically by the MP1 software program for mean sensitivity in a polygon. MP1 (central 20°) was performed before the surgical procedure and three months postoperatively in both groups. We evaluated the difference between preoperative and postoperative MP1 results as an indirect measurement of probable adverse effect of air infusion to determine possible complications of the procedure.

All pars plana vitrectomy (PPV) procedures were performed under general anesthesia by the same surgeon (M.K.). The surgical procedures used a 3-port, transconjunctival sutureless 23-gauge vitrectomy system. In the air group, air infusion was started at the beginning of the procedure. The air pressure setting was 40 mmHg and vitrectomy was performed with a cutting rate of 2500 per min, and up to 300 mmHg of linear aspiration using the Associate 2500 vitrectomy system (DORC, Zuidland, Netherlands). The air highlighted a ring of vitreous corresponding with the vitreous base because of the air bubble pushing the vitreous residue towards the retina. The residual vitreous was removed by placing the cutter into the vitreous and shaving it until the interface profile was changed with the disappearance of the ring of vitreous as previously described.[21] Vacuum was not applied to the vitreous cutter within the air to avoid plugging with an air lock.[22] Scleral depression during peripheral vitrectomy was not required in the air group. At the end of the air-infused vitrectomy, an air-BSS interchange was used to remove air from the vitreous cavity. Triamcinolone acetonide-assisted peeling of the ILM was then performed circumferentially around the MH with end-gripping intraocular forceps. In case of fogging due to condensation of the lens, the posterior surface of the lens was coated with viscoelastic material.

In the standard vitrectomy group, the vitreous was removed with a cutting rate of 2500/min and up to 300 mmHg of linear aspiration up to the far periphery under fluid infusion, with dynamic scleral depression in all cases. Triamcinolone acetonide-assisted ILM peeling was performed subsequently in the same manner. Finally, surgery was completed by air-gas exchange with 12-13% C3F8 gas in both groups. None of the patients underwent vitrectomy in combination with cataract removal.

The effective vitrectomy time (from initiation of vitrectomy to the end of vitreous removal) did not include the time spent on staining and peeling the ILM.

During the postoperative period, patients were advised to maintain face-down positioning for 5-7 days. All patients were routinely examined on day one after the surgery, and at one week, one month, and three months. VA was measured with the ETDRS charts. Anatomical success was defined as apposition of the MH edges as well as the absence of any fluid cuff around the hole, as determined by clinical examination and OCT.

Statistical Analysis

Quantitative data were expressed as means and standard deviations. The two groups were compared by using an independent-samples t-test and Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Wilcoxon signed rank test was used to compare the preoperative and postoperative MP1 sensitivity and VA. $p<0.05$ was considered statistically significant. Statistical analyses used SPSS version 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Both groups had similar distributions of age, sex, lens status, BCVA, and retinal sensitivity. Preoperative characteristics are summarized in Table 1. The control group differed from the air group in its longer mean effective vitrectomy time and mean total surgery time (Table 2). Intraoperative complications noted during the air-infused vitrectomy were retinal touch (n=2), sudden hypotony (n=2), migration of air into the anterior chamber in a pseudophakic eye with posterior capsule defect (n=1), and fogging of the intraocular lens (n=1). Lenticular touch or lenticular opacification secondary to air infusion were not seen. In the standard vitrectomy group, no specific intraoperative complications were noted. Both groups were similar in postoperative BCVA and retinal sensitivity (Table 3). The single-procedure MH closure rate was 100% in both groups. Visually significant cataract did not develop during the three-month follow-up period.

Discussion

We found that air-infused vitrectomy significantly reduces effective vitrectomy time and total duration of surgery. Despite some difficulties and intraoperative complications during the learning curve of this technique, it seems equally safe and

Table 1. Preoperative characteristics

Characteristics	Overall (n=42)	Vitrectomy under air group (n=21)	Standard vitrectomy group (n=21)	p
Mean (±SD) age (years)	59.6±6.1	60.7±7.0	58.6±5.0	0.27*
Sex: female/male, %	71/29	71/29	71/29	>0.99†
Lens status				
Phakic, n (%)	37(88)	19(90)	18(86)	>0.99‡
Pseudophakic, n (%)	5(12)	2(10)	3(14)	>0.99‡
Mean (±SD) preoperative VA (LogMAR)	0.6±0.21	0.61±0.20	0.59±0.22	0.72*
Mean preoperative Snellen VA equivalent	20/80	20/80	20/80	0.72*
Range	20/40-20/200	20/40–20/200	20/40–20/200	
Mean (±SD) preoperative MP1 sensitivity (dB)	13.8±1.5	13.4±1.2	14.1±1.8	0.16*
Range	10.2-16.8	10.2-15.1	10.6-16.8	

SD: Standard deviation, VA: Visual acuity, LogMAR: Logarithm of the minimum angle of resolution, dB: Decibel, MP1: Microperimetry
†Chi-square test, *independent-samples test, ‡Fisher's exact test

Table 2. Intraoperative and postoperative outcomes

Characteristics	Overall (n=42)	Vitrectomy under air group (n=21)	Standard vitrectomy group (n=21)	p
Mean (±SD) effective vitrectomy time (min)	10.4±3.1	7.5±0.3	13.3±0.5	<0.001*
Range	7-16	7-10	12-16	
Mean (±SD) total surgery time (min)	23.8±3.0	21.8±2.0	25.9±1.1	<0.001*
Range	19-30	19-26	21-30	
Mean (±SD) postoperative VA (LogMAR)	0.32±0.14	0.34±0.15	0.30±0.13	0.45†
Mean (±SD) postoperative Snellen VA equivalent	20/42	20/44	20/40	0.45†
Range	20/25-20/100	20/25-20/100	20/25-20/100	
Mean (±SD) postoperative MP1 sensitivity (dB)	14.35±1.6	14.2±1.6	14.5±1.6	0.54†
Range	10.2-17.3	10.5-16.8	10.2-17.3	

SD: Standard deviation, n: Number, min: Minute, VA: Visual acuity, LogMAR: Logarithm of the minimum angle of resolution, MP1: Microperimetry
*Mann-Whitney U test, †independent t-test

Table 3. Comparisons of mean preoperative and postoperative retinal sensitivity and best corrected visual acuity						
	Mean (±SD) MP1 sensitivity (dB)			Mean (±SD) VA (logMAR)		
Vitrectomy technique	Preoperative	3 months postoperative	p	Preoperative	3 months postoperative	p
Vitrectomy under air (n=21)	13.4±1.2	14.2±1.6	0.29*	0.61±0.20	0.34±0.15	<0.001*
Standard vitrectomy (n=21)	14.1±1.8	14.5±1.6	0.53*	0.59±0.22	0.30±0.13	<0.001*
dB: Decibel, SD: Standard deviation, n: number, LogMAR: Logarithm of the minimum angle of resolution, MP1: Microperimetry, VA: Visual acuity *Wilcoxon signed-rank test						

comparable with standard vitrectomy technique in terms of anatomical and functional success. Although there was no significant improvement in postoperative retinal sensitivity evaluated by MP1, we concluded that continuous air infusion was not associated with significant direct or indirect damage to retinal nerve fibers.

In the standard PPV technique, vitreous gel is removed and the intraocular contents are replaced with commercially available BSS. Performing vitreoretinal surgical manipulations at the interface between perfluorocarbon liquid,[10,11,12,13] silicone oil,[14,15,16,17] or air,[17,18,19,20,21,22] and residual vitreous, epiretinal membrane, and retina has been described as interface vitrectomy.[22] In 2005, Quiroz-Mercado et al.[11] described a technique for vitrectomy using perfluorocarbon liquids as irrigation fluids for tractional and RRD. They concluded that in selected cases the use of perfluorocarbon liquids offers several advantages over BSS, because of their properties (gravitational forces, miscibility with body fluids, and ability to transport oxygen). The main inconvenience of perfluorocarbon-infused vitrectomy is considerably higher surgical cost.[11]

Recently, Voleti et al.[18] proposed premature fluid-air exchange so that the vitrectomy can be done under air rather than BSS. Advantages of air instead of BSS in continuous infusion during vitrectomy derive from the specific physical-mechanical properties of air. The difference in refractive index allows for a wider view of the retina under air. Moreover, the air-vitreous interface is more pronounced than the BSS-vitreous interface. Additionally, the surface tension of the air results in downward pressure over the retina and helps to further establish the interface between air and vitreous, allowing for more definitive identification of residual vitreous. This dynamic stabilizes the retina under air and, in combination with small-gauge vitreous cutters with their ports close to the tip, affords safe and precise vitrectomy. All these aspects allow easier identification of residual vitreous that should be completely removed in certain diseases (for example, RRD, proliferative diabetic retinopathy, and MH) to improve the chances of surgical success.

A widened field of view and improved visualization of both the peripheral retina and the vitreous base interface were observed in all cases during air-infused vitrectomy, allowing effective identification and removal of residual vitreous. During air-infused vitrectomy, air pushes the vitreous to the retinal surface to help prevent dispersal of the vitreous fluid. In classic BSS-infused vitrectomy, vitreous mixes with irrigating solution, and during active vitrectomy the irrigating solution is mostly aspirated. However, in the air-infused system, the vitrectomy probe stays always in the vitreous and only vitreous is aspirated. This provides more efficacious vitrectomy and lessens the effective vitrectomy time and total surgery time, as observed in our study.

Shortly after the introduction of modern PPV, air injection and fluid-air exchange gained wide acceptance at every step of vitreoretinal surgery.[24] Fluid-air exchange during MH surgery is an essential step, required for successful closure of the hole. Visual field defects after MH surgery were reported,[25] and vitrectomy with humidified air for fluid-air exchange was subsequently proposed to prevent these defects.[26] Later, Gass et al.[27] noted that peripheral visual field defects after MH surgery is a complication with decreasing incidence. They proposed that a rather low pressure setting during fluid-air exchange, as well as special aspects of the surgical technique, might be responsible for the low incidence of peripheral visual field defects. A central 20° MP1 test performed 3 months postoperatively did not indicate diffuse loss of retinal sensitivity or significant visual field defects in the air-infused vitrectomy group.

It has been reported that vitrectomy under air may play a role in reducing the rate of iatrogenic retinal break formation compared with the standard vitrectomy technique. Sigler et al.[17] performed peripheral interface vitrectomy under air in 86 consecutive cases of RRD, none of which developed iatrogenic retinal breaks or new retinal breaks in the postoperative period. Reibaldi et al.[19] evaluated the incidence of iatrogenic retinal breaks in small-gauge vitrectomy under air compared with standard vitrectomy for idiopathic MH or idiopathic epiretinal membranes. The incidence rates of intraoperative and postoperative retinal breaks were significantly lower in the air group (2%) than the standard group (7%). Erdogan et al.[20] compared the efficacy and safety of peripheral vitrectomy under air infusion and fluid infusion in cases with RRD. They detected an iatrogenic retinal break rate of 2.5% in the air-infusion group, which was lower though not statistically significantly so, than the 10% in the standard vitrectomy group. In our study, with a smaller sample size, iatrogenic retinal break formation was not observed in either group.

Although the air allows a wider field of view, it can fog the posterior surface of the intraocular lens, leading to compromised

posterior segment visualization. Coating the posterior lens surface with viscoelastic material will help prevent this complication. In case of intraoperative hypotony during air-infused vitrectomy, the aspiration rate should be reduced or stopped until the intraocular pressure value returns to normal.

Study Limitations

The study was limited by the small sample size and limited follow-up.

Conclusion

Our study showed that 23-gauge vitrectomy under air significantly reduced the effective vitrectomy time and total surgical duration compared with standard 23-gauge vitrectomy. Several intraoperative complications including retinal touch, hypotony, fogging of the intraocular lens, and air in the anterior chamber were observed in the air group. Vitrectomy under air infusion seems to be associated with several problems that may be less common in standard PPV, but a definitive conclusion is not possible given the small number of participants. The final anatomical and functional outcomes were similar for both surgical techniques. Postoperative MP1 results were not associated with loss of retinal sensitivity or significant visual field defects in the air-infused vitrectomy group, suggesting that there is no specific direct or indirect damage to the retina or optic nerve related to the continuous air infusion. Further prospective controlled studies are necessary to confirm the efficacy and safety of this surgical technique.

Ethics

Ethics Committee Approval: The study were approved by the İstanbul Şişli Memorial Hospital of Ethics Committee (protocol number: 0067).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Karaçorlu, Concept: Murat Karaçorlu, Serra Arf, Design: Murat Karaçorlu, Serra Arf, Data Collection or Processing: Mümin Hocaoğlu, Işıl Sayman Muslubaş, M. Giray Ersöz, Analysis or Interpretation: Mümin Hocaoğlu, Murat Karaçorlu, Serra Arf, Literature Search: Mümin Hocaoğlu, Işıl Sayman Muslubaş, M. Giray Ersöz, Writing: Murat Karaçorlu, Mümin Hocaoğlu.

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. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, Sadda SR, Sebag J, Spaide RF, Stalmans P. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120:2611-2619.
2. Forsaa VA, Lindtjørn B, Kvaløy JT, Frøystein T, Krohn J. Epidemiology and morphology of full-thickness macular holes. Acta Ophthalmol. 2018;96:397-404.
3. Gass JD. Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol. 1995;119:752-759.
4. Neffendorf JE, Simpson ARH, Steel DHW, Desai R, McHugh DA, Pringle E, Jackson TL. Intravitreal gas for symptomatic vitreomacular adhesion: a synthesis of the literature. Acta Ophthalmol. 2018;96:685-691.
5. Rizzo S, Belting C, Cresti F, Genovesi-Ebert F. Sutureless 25- gauge vitrectomy for idiopathic macular hole repair. Graefes Arch Clin Exp Ophthalmol. 2007;245:1437-1440.
6. Modi A, Giridhar A, Gopalakrishnan M. Sulfurhexafluorıde (SF6) versus perfluoropropane (C3F8) gas as tamponade ın macular hole surgery. Retina. 2017;37:283-290.
7. Spiteri Cornish K, Lois N, Scott NW, Burr J, Cook J, Boachie C, Tadayoni R, la Cour M, Christensen U, Kwok AK. Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. Ophthalmology. 2014;121:649-655.
8. Yamashita T, Sakamoto T, Terasaki H, Iwasaki M, Ogushi Y, Okamoto F, Takeuchi M, Yasukawa T, Takamura Y, Ogata N, Nakamura Y; writing committee of Japan-Clinical Retina Research Team (J-CREST). Best surgical technique and outcomes for large macular holes: retrospective multicentre study in Japan. Acta Ophthalmol. 2018;96:9024-910.
9. Gaudric A, Tadayoni R. Macular Hole. Retina. In: Wilkinson CP, Wiedemann PW, (eds). (5th ed) Elsevier Health Sciences; 2013:1962-1978.
10. Chang S, Lincoff H, Zimmerman NJ, Fuchs W. Giant retinal tears. Surgical techniques and results using perfluorocarbon liquid. Arch Ophthalmol. 1989;107:761-766.
11. Quiroz-Mercado H, Guerrero-Naranjo J, Agurto-Rivera R, Leizaola-Fernández C, Suárez-Tatá L, Murillo-López S, Reategui-Escalante G, García-Aguirre G, Fromow-Guerra J. Perfluorocarbon-perfused vitrectomy: a new method for vitrectomy--a safety and feasibility study. Graefes Arch Clin Exp Ophthalmol. 2005;243:551-562.
12. Quiroz-Mercado H, Garcia-Aguirre G, Ustáriz-González O, Martín-Avià J, Martinez-Jardon S. Perfluorocarbon-perfused vitrectomy using a transconjunctival 25-gauge system. Retina. 2007;27:926-931.
13. Velez-Montoya R, Guerrero-Naranjo JL, Garcia-Aguirre G, Morales-Cantón V, Fromow-Guerra J, Quiroz-Mercado H. Perfluorocarbon-perfused 23 gauge three-dimensional vitrectomy for complicated diabetic tractional retinal detachment. Clin Ophthalmol. 2011;5:1709-1715.
14. Yang CM, Hsieh YT, Yang CH, Liu KR. Irrigation-free vitreoretinal surgery for recurrent retinal detachment in silicone oil-filled eyes. Eye (Lond). 2006;20:1379-1382.
15. Charles S, Randolph JC, Sigler EJ. Pars plana vitrectomy reoperation without removing silicone oil. Retina. 2012;32:1664-1665.
16. Sigler EJ, Randolph JC, Calzada JI. Traction retinal detachment under silicone oil treated with two-port, 25-gauge pars plana vitrectomy and scissor segmentation in a child with familial exudative vitreoretinopathy. Retin Cases Brief Rep. 2013;7:183-187.
17. Sigler EJ, Charles S, Calzada JI. Interface vitrectomy. Retina. 2014;34:616-617.
18. Voleti VB, Gee CJ, Devin F, Hubschman JP. Vitrectomy under air. Retina. 2012;32:1981-1982.
19. Reibaldi M, Rizzo S, Avitabile T, Longo A, Toro MD, Viti F, Saitta A, Giovannini A, Mariotti C. Iatrogenic retinal breaks in 25-gauge vitrectomy under air compared with the standard 25-gauge system for macular diseases. Retina. 2014;34:1617-1622.
20. Erdogan G, Unlu C, Karasu B, Kardes E, Ergin A. Comparing peripheral vitrectomy under air and fluid infusion for primary rhegmatogenous retinal detachment. Retina. 2016;36:1281-1284.
21. Altan T, Ozbilen KT, Cetin T, Kapran Z. Results of peripheral vitrectomy under air in rhegmatogenous retinal detachment. Ophthalmic Surg Lasers Imaging Retina. 2017;48:51-54.

22. Subhendu Kumar Boral, Suber S Huang. Interface vitrectomy. In: Retina & Vitreous Surgery: A Practical Guide to Theory, Practice and Management. New Delhi: Jaypee Brothers Medical Publishers; 2016;180-183.
23. Ozdemir H, Karacorlu SA, Sentürk F, Karacorlu M, Uysal O. Assessment of macular function by microperimetry in unilateral resolved central serous chorioretinopathy. Eye (Lond). 2008;22:204-208.
24. Escoffery RF, Olk RJ, Grand MG, Boniuk I. Vitrectomy without scleral buckling for primary rhegmatogenous retinal detachment. Am J Ophthalmol. 1985;99:275-281.
25. Hutton WL, Fuller DG, Snyder WB, Fellman RL, Swanson WH. Visual field defects after macular hole surgery. A new finding. Ophthalmology. 1996;103:2152-2158.
26. Ohji M, Nao-I N, Saito Y, Hayashi A, Tano Y. Prevention of visual field defect after macular hole surgery by passing air used for fluid-air exchange through water. Am J Ophthalmol. 1999;127:62-66.
27. Gass CA, Haritoglou C, Messmer EM, Schaumberger M, Kampik A. Peripheral visual field defects after macular hole surgery: a complication with decreasing incidence. Br J Ophthalmol. 2001;85:549-551.

DOI: 10.4274/tjo.galenos.2019.24294
Turk J Ophthalmol 2019;49:334-341

Original Article

Comparative Biochemical Outcomes, Effectiveness and Tolerance of Densiron 68 and Oxane HD for the Management of Complicated Retinal Detachment

Chafik Keilani*, Edouard Augstburger**, Mathieu Robin**, Amélie Beaugrand***, Raphaëlle Ores****, José-Alain Sahel****, Sarah Ayello-Scheer****

*Quinze-Vingts National Hospital, Department of Ophthalmology IV / Sorbonne University, Faculty of Medicine Pierre-et-Marie-Curie/Assistance Publique-Hopitaux de Paris, Paris, France
**Quinze-Vingts National Hospital, Department of Ophthalmology III, Paris, France
***Quinze-Vingts National Hospital, Department of Biomedical Informatics, Paris, France
****Quinze-Vingts National Hospital, Department of Ophthalmology, Paris, France

Abstract

Objectives: To compare biochemical outcomes, effectiveness, and tolerance of two high-density silicone oils (HDSOs), silicone oil-RMN3 (Oxane® HD) and silicone oil-Densiron-68 (Densiron® 68), for the management of complicated retinal detachment (RD) associated with inferior proliferative vitreoretinopathy (PVR).

Materials and Methods: This was a retrospective, single-centre, comparative case series of 23 patients treated between September 2014 and June 2016. The main inclusion criteria were RD with inferior PVR receiving Oxane® HD or Densiron® 68 following pars plana vitrectomy. The main outcome measures were anatomical success, rate of RD recurrence, and best-corrected visual acuity (BCVA) at 6 months. Secondary outcomes were short-term complications.

Results: Twenty-three eyes were included: 16 eyes with Densiron® 68 tamponade and 7 eyes with Oxane® HD tamponade. Anatomical success under HDSO was significantly higher in the Densiron® 68 group (100%) than in the Oxane® HD group (42.8%) (p=0.0455). Recurrent RD was observed in 42.8% of eyes under Oxane® HD, but in none of the patients under Densiron® 68 (p=0.001). Six months after surgery, mean BVCA values (+/- standard deviation) with Densiron® 68 and Oxane® HD were 0.83±0.62 logMAR and 1.81±0.65 logMAR, respectively. BVCA was significantly better in the Densiron® 68 group (p=0.006). No significant differences were observed with regard to intraocular pressure, emulsification, or intraocular inflammation.

Conclusion: Densiron® 68 appears to be more effective than Oxane® HD for the management of RD associated with PVR. A randomized, controlled, interventional study is needed to demonstrate this difference.

Keywords: High-density silicone oils, Densiron® 68, Oxane® HD, complicated inferior retinal detachment, proliferative vitreoretinopathy

Introduction

Silicone oil has been demonstrated to be an effective long-term internal tamponade agent for the treatment of superior breaks and retinal detachment (RD) complicated by proliferative vitreoretinopathy (PVR) and is currently widely used.[1,2,3,4] Although lighter-than-water silicone oils can provide an effective tamponade effect for the superior retina, they provide little

Address for Correspondence: Chafik Keilani MD, Quinze-Vingts National Hospital, Department of Ophthalmology IV / Sorbonne University, Faculty of Medicine Pierre-et-Marie-Curie/Assistance Publique-Hopitaux de Paris, Paris, France Phone: 0033649099674 E-mail: chafik.keilani@aphp.fr
ORCID-ID: orcid.org/0000-0002-7639-8030 **Received:** 09.01.2019 **Accepted:** 16.05.2019

Cite this article as: Keilani C, Augstburger E, Robin M, Beaugrand A, Ores R, Sahel JA, Ayello-Scheer S. Comparative Biochemical Outcomes, Effectiveness and Tolerance of Densiron 68 and Oxane HD for the Management of Complicated Retinal Detachment. Turk J Ophthalmol. 2019;49:334-341

support for the inferior retina. This can result in the accumulation of fluid in the inferior quadrants of the retina during silicone oil tamponade and enhanced proliferation.[5] The most frequent complication of the use of silicone oil as an internal tamponade is therefore the persistence or recurrence of inferior RD due to advanced PVR.[6,7,8,9,10] In the 1990s, high-density (> 1.90 g/cm^3) perfluorocarbons and partially fluorinated alkanes were used for RD surgery. However, these fluids were associated with tamponade emulsification, intraocular inflammation, and rises in intraocular pressure (IOP).

At the beginning of the 21st century, the first high-density silicone oils (HDSO) were introduced as endotamponade agents for RD with inferior PVR. HDSOs are a mixture of silicone oil and partially fluorinated alkanes and have a relative density of 1.02–1.06 g/cm^3 at 22°C. The mixtures were developed to decrease postoperative tamponade emulsification, intraocular inflammation, and rises in IOP.

In 2003, a silicone oil–RMN3 mixture, Oxane® HD, which has a density of 1.03 g/cm^3 at 22°C and a viscosity of 3300 centistokes (cSt) at 25°C was introduced. Oxane HD® consists of 11% RMN3 and 89% 5700 cSt silicone (Oxane 5700®), a polydimethylsiloxane (Figure 1A), and RMN3 (Figure 1B). It is a hydrogenated and fluorinated olefin, 1 perfluorooctyl-5-methylhex-2-ene and is soluble in silicone oil. It was followed in 2005 by another HDSO, a silicone oil–perfluorohexyloctane mixture called Densiron® 68, with a density of 1.06 g/cm^3 at 22 °C and a viscosity of 1400 cSt at 25°C. Densiron® 68 comes from a blend of 69.5% 5000 cSt silicone (Siluron 5000®), a polydimethylsiloxane, and 30.5% of perfluorohexyloctane (F6H8®) (Figure 1C).

These HDSOs have shown higher attachment rates in complicated RD.[11,12,13,14,15,16,17] A recent meta-analysis has shown that the complication spectrum of these new-generation HDSOs seems to be similar to that of conventional silicone oil tamponades.[18] These two approved heavier-than-water silicone oil tamponades, Oxane® HD and Densiron® 68, are commonly used in clinical practice.

Densiron® 68 has a higher density than Oxane® HD. Nevertheless, due to its lower viscosity, Densiron® 68 could result

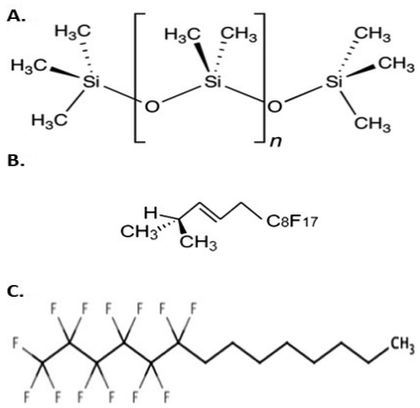


Figure 1. Chemical structure of HDSO components, A. Polydimethylsiloxane, B. RMN3, C. Perfluorohexyloctane

in more tamponade emulsification, intraocular inflammation, and IOP elevation than Oxane® HD. In the present study, we compared the effectiveness and tolerance of Densiron® 68 and Oxane® HD for the management of complicated inferior RD in order to provide a decision-making table for vitreoretinal surgeons for the use of HDSO.

Methods

We retrospectively reviewed the medical records of patients with complicated RD treated using Oxane® HD or Densiron® 68 as an internal tamponade after pars plana vitrectomy (PPV) between September 2014 and June 2016. Prior to surgery, all patients underwent complete ophthalmologic evaluation including detailed slit-lamp and funduscopic examination, assessment of best corrected visual acuity (BCVA), and tonometry. The diagnosis of complicated RD was based on funduscopic examination of the retina. B-scan ultrasonography was performed if RD was difficult to assess using funduscopic examination. Inclusion criteria were: complicated RD, age over 18 years, pseudophakic eye, surgery performed under peribulbar anesthesia, patient able to communicate effectively, and informed consent obtained from the patient. Complicated RD was defined as follows: RD secondary to PVR and to inferior or posterior tears. In addition, recurrent and chronic RD was considered complicated RD. PVR was assessed according to the updated Retina Society Classification. Exclusion criteria were: chronic glaucoma, diabetes with retinopathy or diabetic maculopathy, active periocular or ocular infection, diagnosis of uncontrolled systemic disease, epiretinal membrane, non-French speakers, hallucinations, delirium, and Alzheimer's disorders. All surgeries were carried out by three specialist retinal surgeons at the Centre Hospitalier National d'Ophtalmologie (CHNO) des Quinze-Vingts, Paris, France.

Two HDSO were used: Oxane® HD (Bausch & Lomb, Germany) and Densiron® 68 (Fluoron Gmbh, Germany). The use of Oxane® HD or Densiron® 68 was based on surgeon preference. Both Oxane® HD and Densiron® 68 were used by the three surgeons.

All surgeries consisted of standard three-port 23-gauge pars plana vitrectomy. Membrane peeling, retinotomy, and retinectomies were performed if needed. Retinal breaks were treated by endolaser. In patients with previous injected standard silicone oil, this agent was removed first. PFCL (perfluorocarbon liquid) was used during surgery only if retinotomy was performed. Subconjunctival injection of 4 mg dexamethasone was performed at the end of surgery. Antibiotic–steroid eye drops were applied 4 times daily for 1 month after surgery. HDSO was removed by active aspiration using an 18-gauge cannula and two 23-gauge ports for endoillumination probe and infusion.

Patients were examined at 1 week and at 1, 3, and 6 months postoperatively. Functional outcomes such as anatomical success under HDSO and after HDSO removal, BCVA, IOP changes, emulsification, intraocular inflammation scored with ocular inflammation grading scale (Table 1) and complications

during and after endotamponade removal were documented at each follow-up visit. Functional outcomes were assessed via funduscopic examination and intraocular inflammation was assessed using slit-lamp examination.

Collected data included patient demographics, indication for pars plana vitrectomy, procedure performed, type of HDSO, and duration of follow-up.

The primary endpoints were anatomical success defined as a completely attached retina under HDSO, time under HDSO, rate of RD recurrence under HDSO tamponade in the Oxane® HD and Densiron® 68 groups, and mean BCVA at postoperative 6 months. In addition, data were compared between the Oxane® HD and Densiron® 68 groups during the same period in our hospital. Secondary endpoints were rate of RD recurrence after HDSO removal, mean duration to RD recurrence after HDSO removal, IOP changes, emulsification, intraocular inflammation, and endophthalmitis.

Statistical Analysis

BVCA values were converted into logMAR units. Primary and secondary endpoints were evaluated using chi-square and Mann–Whitney U tests, with $p < 0.05$ considered statistically significant. The nonparametric Mann–Whitney test is widely used to test treatment effects by comparing the outcome distributions between two groups. Source apportionments of elements were carried out using MS Excel 2010®. Data were analyzed using XLSTAT® software. The Quinze-Vingts ethics committee approved this study.

Results

Twenty-three eyes of 21 patients were included: 16 eyes treated with Densiron® 68 tamponade and 7 eyes with Oxane® HD tamponade. Two patients with glaucoma were excluded (Figure 2). Analysis of the patient demographics (Table 2) showed that the average age was 65 ± 12 years (mean ± standard deviation). No significant difference in age was observed between the Densiron® 68 and Oxane® HD groups. In addition, no differences were found for any of the patient demographics, such as age or ethnicity, nor for anesthesia (Table 2). The indications for HDSO tamponade were similar for both groups and included: RD secondary to PVR with inferior breaks. The mean follow-up time was similar for both groups: 9 ± 4 months.

The prevalence of macular detachment before surgery was approximately 80% in both the Densiron® 68 and the Oxane® HD group (Table 2). Two patients in the Densiron® 68 group were under standard silicone oil tamponade before inclusion. Four patients had undergone vitrectomy with gas endotamponade

Table 1. Ocular inflammation grading scale

	Anterior Chamber
Grade	**Flare count**
0	Complete absence
1	Very slight (barely detectable)
2	Moderate (iris and lens clear)
3	Marked (iris and lens hazy)
4	Intense (fibrin clot)

Table 2. Study population characteristics

	Densiron 68	**Oxane HD**	
Gender (%)			
Male	43.7*	42.8*	
Female	56.2*	57.1*	
Age (years), mean (SD)	66.2 (12.8)	64.7 (12.9)	
Ethnicity (%)			
Europe	93.7*	100	
North Africa	6.2*	0	
Eye (%)			
Right	68.7	85.7	
Left	31.3	14.3	
Anesthesia (%)			
Peribulbar	100	100	
General	0	0	
PVR (%)			
Yes	87.4	71.4	
No	12.6	28.6	
PVR grade (%)			
A	9	20	
B	54.6	20	
C	36.4	60	
Retinotomy RD (%)	75	71.4	
Location of RD (%)			
Inferior	75	85.7	
Superior	18.7	0	
Total	6.3	14.3	
Macular detachment (%)			
ON	25	14.3	
OFF	75	85.7	
BVCA before surgery (logMAR), mean (SD)	1.48 (0.78)	1.97 (0.48)	p=0.20
Recurrent and chronic RD, n (%)	9 (56.2%)	3 (42.8%)	
RD under standard silicone	2	0	
RD after gas endotamponade	3	2	
Chronic RD with no personal history of vitrectomy	4	1	
Lifestyle habits (%)			
Smoking	87.5	85.7	
Alcohol	12.5	14.3	

SD: Standard deviation, RD: Retinal detachment, PVR: Proliferative vitreoretinopathy, p: P value, n: Number
*Percentages are rounded and may not sum to 100

(three in the Densiron® 68 group and two in the Oxane® HD group). No eyes in either group had phacoemulsification before vitrectomy. All eyes already had an intraocular lens (IOL) before surgery. Retinectomies and retinotomies were only performed on patients with PVR. The rate of retinotomy was similar in both groups (Table 2). No statistically significantly difference in BVCA was observed between the Densiron® 68 group and the Oxane® HD group prior to surgery (p = 0.20) (Table 2).

Anatomical Success and RD Recurrence Under HDSO

Anatomical success under HDSO was significantly higher in the Densiron® 68 group (100%) than in the Oxane® HD group (42.8%) (p = 0.0455). Of the 7 eyes treated using Oxane® HD, 3 (42.8%) showed recurrent RD with macular detachment under HDSO. All of these detachment events occurred in the inferior retinal quadrants. None of the 16 eyes in the Densiron® 68 group showed recurrent RD under HDSO. Anatomical success after HDSO removal was also significantly higher in the Densiron® 68 group (81.3%) than in the Oxane® HD group (48%) (p = 0.001). In the Densiron® 68 group, the mean duration until silicon oil removal was 4.18 ± 2.56 months compared with 3.50 ± 2.20 months in the Oxane® HD group. The mean duration until silicon oil removal was shorter in the Oxane® HD group due to recurrent RD which occurred after 1 month in 2 eyes and only 1 week in 1 eye in this group (Table 3).

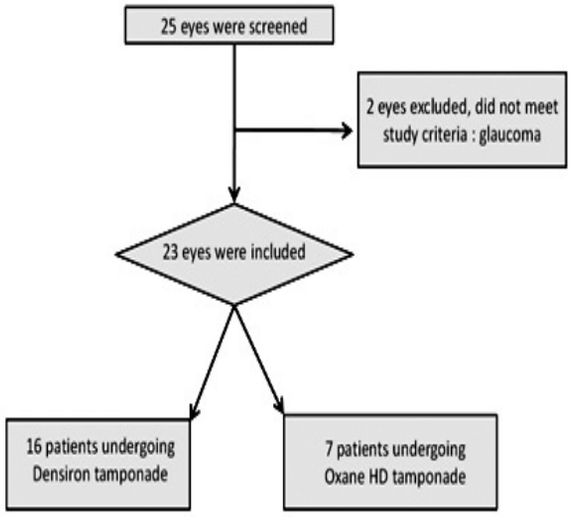


Figure 2. Study flowchart

Rate of RD Recurrence After HDSO Removal

Concerning the secondary endpoints, of the 16 eyes in the Densiron® 68 group, 3 (18.7%) displayed recurrent RD with macular detachment following HDSO removal. All of these detachment events occurred in the inferior retinal quadrants. The mean duration until recurrent RD was 5 months after Densiron® 68 removal. In the Oxane® HD group, 3 of the 7 eyes displayed RD under HDSO. Recurrent RD was higher in the Oxane® HD group than in the Densiron® 68 group after HDSO removal (Table 3).

BVCA at Postoperative 6 Months

Concerning the primary endpoints, mean BVCA at postoperative 6 months was 0.83 ± 0.62 logMAR in the Densiron® 68 group and 1.81 ± 0.65 logMAR units in the Oxane® HD group (Table 4). BVCA at 6 months was significantly better in the Densiron® 68 group than in the Oxane® HD group (p = 0.006) (Table 4). The Densiron® 68 group showed a significant improvement in BVCA at postoperative 6 months compared to before surgery (0.83 ± 0.62 logMAR vs. 1.48 ± 0.78 logMAR; p = 0.01), while the postoperative change in BCVA was not statistically significant in the Oxane® HD group (1.97 ± 0.48 logMAR vs. 1.81 ± 0.65 logMAR; p = 0.80) (Table 4).

Tolerance Under HDSO

The Densiron® 68 and Oxane® HD groups were compared in terms of IOP changes, emulsification, and intraocular inflammation (Table 5). No significant differences were observed between the two groups. Densiron® 68 was well tolerated with the exception of one patient who developed chronic glaucoma.

Table 3. Anatomical success and retinal detachment recurrence under HDSO

	Densiron 68	Oxane HD	p value
Anatomical success 6 months after HDSO removal (%)	81.3	42.8	0.0455
RD recurrence under HDSO (%)	0	42.8	0.001
RD recurrence after HDSO removal (%)	18.7	42	0.317
Time to RD recurrence after HDSO removal (months), mean (SD)	4.18 (2.56)	3.50 (2.08)	

SD: Standard deviation, RD: Retinal detachment, HDSO: High-density silicone oil
* Statistically significant result p<0.05

Table 4. Best corrected visual acuity before and 6 months after surgery

	Densiron 68	Oxane HD	p value (Densiron 68 vs. Oxane HD)
Preoperative BVCA (logMAR), mean (SD)	1.48 (0.78)	1.97 (0.48)	0.20
Postoperative 6-month BVCA (logMAR), mean (SD)	0.83 (0.62)	1.81 (0.65)	0.006*
p value (preoperative vs. postoperative)	0.01*	0.80	

BCVA: Best corrected visual acuity, SD: Standard deviation
* Statistically significant result p<0.05

Both HDSOs induced intraocular inflammation, but only in a few patients, about 10% in both groups. All patients that had inflammation were assessed as grade 2 on the ocular inflammation grading scale. Several cases of HDSO emulsification were observed: 25% in Densiron® 68 group and 16% in Oxane® HD group after 1 month (Figures 3 and 4). No significant differences were observed between the two groups for emulsification. No cases of endophthalmitis were noted in either group.

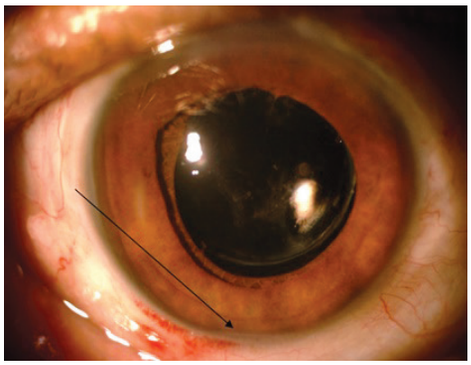


Figure 3. Inferior emulsification under Densiron® 68 tamponade in anterior chamber (black arrow)

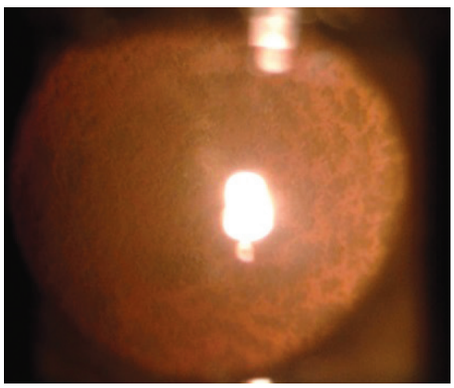


Figure 4. Retrocapsular emulsification under Densiron® 68 tamponade

Table 5. Tolerance under HDSO

	Densiron 68	Oxane HD	p value
Tolerance under HDSO at week 1			
IOP mean (SD)	15.1 (8.7)	12.1 (2.5)	Ns
Emulsification (%)	12.5	14.3	
Intraocular inflammation (%)	6.3	14.3	
Tolerance under HDSO at month 1			
IOP mean (SD)	14.3 (4.6)	15.5 (7.1)	Ns
Emulsification (%)	25	16.6	
Intraocular inflammation (%)	12.5	14.3	
Tolerance under HDSO at month 3			
IOP mean (SD)	15.1 (4.1)	14.6 (5.5)	Ns
Emulsification (%)	25	16.6	
Intraocular inflammation (%)	12.5	14.3	

SD: Standard deviation, HDSO: High-density silicone oil, IOP: Intraocular pressure, ns: Not significant

Surgeon Use of HDSOs

Use of Densiron® 68 and Oxane® HD was similar for all of the surgeons. In addition, RD recurrence after HDSO removal was similar for each surgeon (Table 6).

Discussion

The use of HDSO is required for internal tamponades when the duration of the tamponade is greater than one month and when there is a significant risk of recurrent RD without internal tamponade. The use of HDSO is therefore strongly indicated for patients with complex retinal detachments, as all patients under Densiron® 68 had complete anatomical success.

In this study, we compared the effectiveness and tolerance of Densiron® 68 and Oxane® HD for the management of complicated RD. To the best of our knowledge, no studies have yet compared these two HDSOs.

We found a statistically significant difference between the Densiron® 68 and Oxane® HD groups in terms of anatomical and functional success rates. Our final 81.3% success rate for primary reattachment at least 6 months after Densiron® 68 removal is consistent with the results of other studies.[19,20] Only 48% of patients had anatomical success after Oxane® HD removal. This suggests that Densiron® 68 provided better support for the inferior retina than Oxane® HD. Densiron® 68 is a mixture of 30.5% perfluorohexyloctane (F6H8) and 69.5% polydimethylsiloxane (SiO) (vol/vol). The specific gravity of Densiron® 68 (1.06 g/cm^3 at 25°C) is higher than that of Oxane® HD (1.03 g/cm^3 at 25°C). Because a heavy intraocular tamponade is needed for the management of complicated RD, the greater density of Densiron® 68 could explain the lower rate of retinal redetachment under Densiron® 68 compared with Oxane® HD.

In addition, our result of 81.3% anatomical success under Densiron® 68 HD is similar to other studies.[21]

All redetachment events were observed in the inferior retina. Densiron® 68 and Oxane® HD could also be effective

Table 6. Use of HDSO for each surgeon

	Surgeon 1	Surgeon 2	Surgeon 3
Use of Densiron (%)	31.2	31.2	37.6
Use of Oxane HD (%)	28.5	28.5	43
RD recurrence after HDSO removal in Densiron group (%)	6.25	6.25	6.25
RD recurrence after HDSO removal in Oxane HD group (%)	14.3	14.3	14.3

RD: Retinal detachment

in providing support for the superior retina, as no superior RD events or tears were observed following HDSO removal.

In addition, patients who received an endotamponade with Densiron® 68 showed more favorable functional outcomes, with mean postoperative 6-month BCVA that was significantly better compared to preoperative BCVA (p = 0.01) and the postoperative 6-month BCVA in patients treated with Oxane® HD (p = 0.006). The rate of functional success was disappointing in patients who received an endotamponade with Oxane® HD because of anatomical failure due to the high RD recurrence rate (42.8%).

In the present study, the mean time to Densiron® 68 removal was 4.18 ± 2.56 months, which is relatively short. This could probably be explained by the fact that surgeons wanted to avoid potential complications associated with Densiron® 68, especially emulsification. In the Densiron® 68 group of this retrospective study, recurrent RD was observed in 18.7% eyes following HDSO removal. However, given the low complication rate in patients undergoing tamponade with Densiron® 68, it is possible that a longer tamponade duration, for example 6 months, could decrease the RD recurrence rate following HDSO removal despite the general consensus that the timing of silicone oil removal has no impact on redetachment rate.[22]

Both groups showed similar complications, such as a rise in IOP, inflammatory reactions, and emulsification of HDSO, and complication rates did not differ significantly between the two groups. Similar complications have been observed in previous reports on the use of Densiron® 68.[23,24,25] One patient in the Densiron® 68 group developed chronic glaucoma. Apart from this single case, Densiron® 68 was well tolerated. Previous studies have reported that the use of Densiron® 68 results in higher IOP levels, and more cases of inflammatory reaction and emulsification than Oxane® HD because of its lower viscosity (1400 cSt for Densiron® 68 vs. 3300 cSt for Oxane® HD at 25°C.[26,27,28] Nevertheless, in our study Densiron® 68 and Oxane® HD had similar, low complication rates. Two steps of the procedure could explain these low complication rates: first, all patients received a subconjunctival injection of 4 mg dexamethasone at the end of surgery, which reduces postoperative inflammation, and second, the ocular cavity was completely filled with HDSO. The importance of completely filling the ocular cavity with silicone oil has previously been demonstrated because the presence of an incomplete bubble promotes emulsification.[29] In addition, the lower viscosity of Densiron® 68 makes both injection and removal easier. Recently, Densiron® Xtra has been produced. It has a lower viscosity (1200 cSt) than Densiron® 68, allowing easy injection, especially with 25-gauge systems. It also allows easy removal and has a low emulsification rate.[30]

Many studies have studied retinal and corneal toxicity. No histological changes have been reported in rabbit or pig. Some lesions have been observed on optical microscopy, including minor mononuclear inflammatory reaction, some disorganization of the intercellular space between photoreceptors, nuclear densification in the outer nuclear layer, irregularities in the external limiting membrane, and intracellular edema in the outer retinal layers. In electron microscopy, intercellular edema at the level of the outer layer and disorganization of the inter-photoreceptor space have been well described, while the structure of the photoreceptor segments remained normal.[31,32,33,34,35]

Limitations of the present study are the lack of a randomized procedure and the small number of patients in the Oxane® HD group. Surgical steps during the procedure were similar for the two groups, which reduces bias in evaluating success after surgery. This study is retrospective with low-level evidence; however, our results for anatomical success and mean BVCA in patients after HDSO tamponade could guide future statistical considerations if a randomized controlled study is to be conducted. The use of Oxane® HD or Densiron® 68 was based on surgeon preference, which is another source of bias.

One of the main advantages of using HDSOs is that patients are not required to lie face-down after surgery, a position that can be difficult to maintain, especially with older patients.

In this study, all retinal surgeries were performed by three surgeons, which could have introduced bias. However, the procedures were similar and both Oxane® HD and Densiron® 68 were used by the three surgeons, so any bias should be minimal. Moreover, RD recurrence after HDSO removal was similar for each surgeon (Table 6).

Our study suggests that Densiron® 68 is a better endotamponade agent than Oxane® HD for treating complicated inferior RD due to its higher density. Thus, we propose a decision-making table for the management of complicated inferior RD (Table 7).

Table 7. Proposition for management of inferior RD with HDSO

	High density silicone oils	
	Densiron 68	**Oxane HD**
Viscosity (cSt) at 25°C	1400	3300
Density (g/cm^3) at 22°C	1.06	1.03
Indications	RD with inferior dehiscence and difficult postoperative face down positioning RD with small inferior retinotomy	Long time tamponade without inferior dehiscence

RD: Retinal detachment

Conclusion

In summary, Densiron® 68 seems to be more effective for endotamponade than Oxane® HD to manage complex RD associated with PVR. Densiron® 68 provides high anatomical and functional success rates. The rate of complications with Densiron® 68 is low with adapted postoperative management. A controlled, randomized interventional study is now required to further investigate the advantages of Densiron® 68 and demonstrate its superiority.

Ethics

Ethics Committee Approval: CHNO committee, approval number 32154

Informed Consent: Obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S. Ayello-Scheer, R. Ores, C. Keilani, Concept: C. Keilani, S. Ayello-Scheer, Design: C. Keilani, S. Ayello-Scheer, JA. Sahel, Data Collection or Processing: C. Keilani, E. Augstburger, M. Robin, A. Beaugrand, Analysis or Interpretation: C. Keilani, E. Augstburger, M. Robin, A. Beaugrand, Literature Search: C. Keilani, S. Ayello-Scheer, R. Ores, JA. Sahel, Writing: C. Keilani, E. Augstburger, M. Robin, A. Beaugrand

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

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

Declarations: Availability of data and materials: data and materials are available on https://osf.io/hk67p/

Acknowledgments

Pr. M. PAQUES, H. KEILANI

References

1. McCuen BW 3 rd, de Juan E Jr, Machemer R. Silicone oil in vitreoretinal surgery. Part I. Surgical techniques. Retina. 1985;5:189-197.
2. McCuen BW 2nd, de Juan E Jr, Landers MB 3rd, Machemer R. Silicone oil in vitreoretinal surgery. Part 2: Results and complications. Retina. 1985;5:198-205.
3. Sell CH, McCuen BW 2nd, Landers MB 3rd, Machemer R. Long-term results of successful vitrectomy with silicone oil for advanced proliferative vitreoretinopathy. Am J Ophthalmol. 1987;103:24-28.
4. Hammer ME, Rinder DF, Hicks EL, Yang CH, Hornung CA. Tolerance of perfluorocarbons, fluorosilicone and silicone liquids in the vitreous. In: Freeman HM, Tolentino FI, eds. Proliferative Vitreoretinopathy. New York: Springer-Verlag; 1988:156-161.
5. Petersen J. The physical and surgical aspects of silicone oil the vitreous cavity. Graefes Arch Clin Exp Ophthalmol. 1987;225: 452-456.
6. Sharma T, Gopal L, Shanmugam MP, Bhende PS, Agrawal R, Badrinath SS, Samanta TK. Management of recurrent retinal detachment in silicone oil-filled eyes. Retina. 2002;22:153-157.
7. Falkner CI, Binder S, Kruger A. Outcome after silicone oil removal. Br J Ophthalmol. 2001;85:1324-1327.
8. Zilis JD, McCuen BW 2nd, de Juan E Jr, Stefansson E, Machemer R. Results of silicone oil removal in advanced proliferative vitreoretinopathy. Am J Ophthalmol. 1989;108:15-21.
9. Riedel KG, Gabel VP, Neubauer L, Kampik A, Lund OE. Intravitreal silicone injection: complications and treatment of 415 consecutive patients. Graefes Arch Clin Exp Ophthalmol. 1990;228 :19-23.
10. Abrams GW, Azen SP, McCuen BW II, Flynn HW Jr, Lai MY, Ryan SJ. Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. Silicone Study report 11. Arch Ophthalmol. 1997;115:335-344.
11. Scheer S, Boni S, Barale PO, Bourhis A, Bonnel S, Tuil E, Girmens JF, Buil O, Baudouin C, Laroche L, Nordmann JP, Poisson F, Warnet JM, Sahel JA. Heavy silicone oil as internal tamponade for retinal detachment: efficacy and tolerance. J Fr Ophtalmol. 2006;29:129-135.
12. Pagot-Mathis V, Benouaich X, Mathis A, Rico-Lattes I, Dumoulin A. Management of complicated retinal detachment using a heavy silicon oil as temporary tamponade. J Fr Ophtalmol. 2006;29:137-145
13. Sandner D, Engelmann K. First experiences with high-density silicone oil (Densiron) as an intraocular tamponade in complex retinal detachment. Graefes Arch Clin Exp Ophthalmol. 2006;244:609-619.
14. Sandner D, Herbrig E, Engelmann K. High-density silicone oil (Densiron) as a primary intraocular tamponade: 12-month follow up. Graefes Arch Clin Exp Ophthalmol. 2007;245:1097-1105.
15. Boscia F, Furino C, Recchimurzo N, Besozzi G, Sborgia G, Sborgia C. Oxane HD vs silicone oil and scleral buckle in retinal detachment with proliferative vitreoretinopathy and inferior retinal breaks. Graefes Arch Clin Exp Ophthalmol. 2008;246:943-948.
16. Ang GS, Murphy AL, Ng WS, Atta HR. Oxane HD and retinal detachment surgery in routine clinical practice. Ophthalmologica. 2010;224:347-353.
17. Hussain RN, Banerjee S. Densiron 68 as an intraocular tamponade for complex inferior retinal detachments. Clin Ophthalmol. 2011;5:603-607.
18. Russo A, Morescalchi F, Donati S, Gambicorti E, Azzolini C, Costagliola C, Semeraro F. Heavy and standard silicone oil: intraocular inflammation. Int Ophthalmol. 2018;38:855-867.
19. Tognetto D, Minutola D, Sanguinetti G, Ravalico G. Anatomical and functional out comes after heavy silicone oil tamponade in vitreoretinal surgery for complicated retinal detachment: a pilot study. Ophtahalmology. 2005;112:1574
20. Prazeres J, Magalhães O Jr, Lucatto LF, Navarro RM, Moraes NS, Farah ME, Maia A, Maia M. Heavy Silicone Oil as a Long-Term Endotamponade Agent for Complicated Retinal Detachments. Biomed Res Int. 2014;2014:136031.
21. Caporossi T, Franco F, Finocchio L, Barca F, Giansanti F, Tartaro R, Virgili G, Rizzo S. Densiron 68 heavy silicone oil in the management of inferior retinal detachment recurrence: analysis on functional and anatomical outcomes and complications. Int J Ophthalmol. 2019;12:615-620.
22. Er H. Primary heavy silicone oil usage in inferior rhegmatogenous retinal detachment. Ophthalmologica. 2010;224:122-125.
23. Wong D, Van Meurs JC, Stappler T, Groenewald C, Pearce IA, McGalliard JN, Manousakis E, Herbert EN. A pilot study on the use of a perfluorohexyloctane/silicone oil solution as a heavier than water internal tamponade agent. Br J Ophthalmol. 2005;89:662-665.
24. Li W, Zheng J, Zheng Q, Wu R, Wang X, Xu M. Clinical complications of Densiron 68 intraocular tamponade for complicated retinal detachment. Eye (Lond). 2010;24:21-28.
25. Majid MA, Hussin HM, Biswas S, Haynes RJ, Mayer EJ, Dick AD. Emulsification of Densiron 68 used in inferior retinal detachment surgery. Eye (Lond). 2008;22:152-157.
26. Ozdek S, Yuksel N, Gurelik G, Hasanreisoglu B. High-density silicone oil as an intraocular tamponade in complex retinal detachments. Can J Ophthalmol. 2011;46:51-55.
27. Joussen AM, Rizzo S, Kirchhof B, Schrage N, Li X, Lente C, Hilgers RD ; HSO-Study Group. Heavy silicone oil versus standard silicone oil in as vitreous tamponade in inferior PVR (HSO Study): interim analysis. Acta Ophthalmol. 2011;89:483-489.

28. Semeraro F, Russo A, Morescalchi F, Gambicorti E, Vezzoli S, Parmeggiani F, Romano MR, Costagliola C. Comparative assessment of intraocular inflammation following standard or heavy silicone oil tamponade: a prospective study. Acta Ophthalmol. 2019;97:97-102.
29. Nakamura K, Refojo MF, Crabtree DV. Factors contributing to the emulsification of intraocular silicone and fluorosilicone oils. Invest Ophthalmol Vis Sci. 1990;31:647-656.
30. Caramoy A, Schröder S, Fauser S, Kirchhof B. In vitro emulsification assessment of new silicone oils. Br J Ophthalmol. 2010;94:509-512.
31. Chang S, Sparrow JR, Iwamoto T, Gershbein A, Ross R, Ortiz R. Experimental studies of tolerance to intravitreal perfluoro-n-octane liquid. Retina. 1991;11:367-374.
32. Eckardt C, Nicolai U, Winter M, Knop E. Experimental intraocular tolerance to liquid perfluorooctane and perfluoropolyether. Retina. 1991;11:375-384.
33. Rizzo S, Genovesi-Ebert F, Belting C, Vento A, Cresti F. A pilot study on the use of silicone oil-RMN3 as heavier-than-water endotamponade agent. Graefes Arch Clin Exp Ophthalmol. 2005 ;243:153-157.
34. Rico-Lattes I, Quintyn JC, Pagot-Mathis V, Benouaich X, Mathis A. Chapter 9 - Fluorinated Molecules in Eye Surgery: Experimental and Clinical Benefit of a Heavy Silicone Oil Oxane Hd® (Mixture of Silicone Oil and RMN3 Fluorine Olefin) in the Treatment of Retinal Detachment. In: Fluorine and Health; Tressaud A, Ed. Elsevier Science B. V: Amsterdam ; 2008;2 :407-420.
35. Cecutti C, Rico I, Lattes A, Novelli A, Rico A, Marion G, Graciaa A, Lachaise J. New formulation of blood substitutes : optimization of novel fluorinated microemulsions Nouvelle strate´gie dans la formulation de substituts du sang: optimisation de nouvelles microe´mulsions fluore´es. Eur J Med Chem. 1989;24: 485-492.

DOI: 10.4274/tjo.galenos.2019.22844
Turk J Ophthalmol 2019;49:342-346

Original Article

Demarcation Laser Photocoagulation for Subclinical Retinal Detachment: Can Progression to Retinal Detachment Be Prevented?

Nilüfer Koçak*, Mahmut Kaya*, Taylan Öztürk*, Volkan Bolluk**, Süleyman Kaynak*

*Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
**Kadirli State Hospital, Clinic of Ophthalmology, Osmaniye, Turkey

Abstract

Objectives: To describe results of demarcation laser photocoagulation in preventing progression of subclinical retinal detachment (SCRD).

Materials and Methods: Twenty-one eyes of 20 patients with SCRD were included. All patients underwent a complete ophthalmological examination, spectral-domain optical coherence tomography, and color fundus photography. Ages at initial diagnosis ranged between 18 and 75 years (mean: 57.3±16.2 years). Patients followed for at least 6 months were included in the study. Periodic retinal examinations were performed over follow-up periods of 6-55 months using Goldmann three-mirror contact lens and sometimes semilunar mirror lens with scleral indentation.

Results: Twelve patients (60%) were female, eight (40%) were male. The mean follow-up period was 24.3±15.2 months (6-55 months). Three (14.3%) eyes were pseudophakic. One patient was affected bilaterally, with both eyes each containing two separate areas of involvement. The SCRD was in the upper quadrant of 18 eyes (85.7%) and the lower quadrant in 3 eyes (14.3%), and was located in the temporal region 10 eyes (47.6%), the nasal quadrant in 4 eyes (19.1%), and in the upper quadrant (temporal-nasal) in 7 eyes (33.3%). Six eyes (28.6%) were found to have myopia greater than -3.0 diopters. Progression to clinical retinal detachment was observed in 4/21 SCRD eyes (19%). All eyes showing progression to clinical retinal detachment had >-3.0 diopter myopia and multiple retinal tears located in the upper quadrant.

Conclusion: Demarcation laser photocoagulation should be kept in mind as a first-line treatment for eyes with SCRD. Laser photocoagulation is vital in preventing progression to rhegmatogenous retinal detachment in most patients. After this treatment, these patients should be followed closely.

Keywords: Clinical retinal detachment, first-line treatment, laser photocoagulation, subclinical retinal detachment

Introduction

There is no clear or sufficiently broad consensus among ophthalmologists regarding the term "subclinical retinal detachment" (SCRD). At present, SCRD is defined as rhegmatogenous retinal detachment that causes no change in visual acuity or visual field.[1] Another commonly used definition is the presence of subretinal fluid that extends at least one disc diameter from the nearest break and no more than two disc diameters posterior to the equator.[2,3,4] The real incidence and natural history of SCRD are unknown, as most patients are clinically asymptomatic. In the literature, clinical progression is reported in up to 50% of SCRDs.[5] Therefore, these patients

Address for Correspondence: Mahmut Kaya MD, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey
Phone:+90 505 525 22 16 E-mail: mahmutkaya78@yahoo.com **ORCID-ID:** orcid.org/0000-0002-2728-9858
Received: 28.01.2019 **Accepted:** 18.06.2019

Cite this article as: Koçak N, Kaya M, Öztürk T, Bolluk V, Kaynak S. Demarcation Laser Photocoagulation for Subclinical Retinal Detachment: Can Progression to Retinal Detachment Be Prevented?. Turk J Ophthalmol. 2019;49:342-346

should be treated. If eyes with SCRD are left untreated, regular examination is imperative. SCRD may also lead to epiretinal membrane and/or cystoid macular edema.

Our main objective in this study was to evaluate the safety and effectiveness of demarcation laser photocoagulation in preventing the progression of SCRD to clinical retinal detachment. The secondary aim of the study was to investigate the presence of epiretinal membrane and/or cystoid macular edema in SCRD patients treated with demarcation laser photocoagulation.

Materials and Methods

The study included 21 eyes of 20 patients who were followed for SCRD in the Retina Unit of the Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology between October 2014 and May 2018 and had not previously received any treatment. The patients included in the study presented to the outpatient clinic due to refractive error and were diagnosed with SCRD upon fundus examination. The study was approved by Dokuz Eylül University Faculty of Medicine Ethics Committee (2018/29-35) and conducted in accordance with the accepted principles in the Declaration of Helsinki. All patients who volunteered to participate were informed in detail about the study and laser photocoagulation, and their written informed consent was obtained. Inclusion criteria were undergoing 360º laser photocoagulation for SCRD and being followed for at least 6 months after treatment. Exclusion criteria were reduced visual acuity or visual field loss associated with detachment upon initial examination, detachment that could not be encircled by 360° laser photocoagulation, history of other retinal surgery, and myopia greater than -8.0 D. The medical records of the patients included in the study were examined in detail and the data were recorded in full in SPSS.

All patients underwent a detailed eye examination prior to treatment. Best corrected visual acuity (BCVA) was measured by Snellen chart. Slit-lamp examination was performed and intraocular pressure was measured with Goldmann applanation tonometer. Fundus examination was performed on both affected and unaffected eyes with a Goldmann three-mirror contact lens. Color fundus photographs and spectral domain optical coherence tomography (SD-OCT) scans (Heidelberg HRA-OCT Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) of the posterior segment were acquired for all patients prior to treatment.

Argon laser photocoagulation was performed using the 360° demarcation technique surrounding the SCRD using a Goldmann three-mirror contact lens and, when necessary, a contact lens with scleral indentation (Figures 1 and 2). Additional laser photocoagulation was performed as necessary during follow-up. The argon green wavelength (514 µm) of the Zeiss Argon Laser system was used for photocoagulation. After instilling proparacaine hydrochloride 0.5% (Alcaine®) for topical anesthesia, the laser procedure was performed using a Goldmann three-mirror contact lens. Pulses were delivered with 200-micron spot diameter and 0.2-s duration, starting at energy of 180 mW and increasing the power when necessary.

Follow-up examinations were performed at 1, 3, and 6 weeks after laser photocoagulation, followed by monthly follow-ups for the remainder of the first 6 months. At all follow-up visits, patients underwent BCVA assessment with Snellen chart, anterior segment examination, intraocular pressure measurement, and detailed fundus examination using a Goldmann three-mirrored contact lens. Posterior segment color fundus photographs and SD-OCT scans were also acquired but not routinely at each visit.

Statistical Analysis

The data obtained were recorded in SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Means and standard deviations were calculated for all the data.

Results

The patients' demographic data, ophthalmic findings, and follow-up times are summarized in Table 1. Of the 20 patients with SCRD, 12 (60%) were female and 8 (40%) were male. The mean age was 57.3±16.2 years (18-75 years) and mean follow-up time was 24.3±15.2 months (6-55 months). Three eyes (14.3%) were pseudophakic. Axial length of the eyes was 22-27 mm. Of the 21 affected eyes, 11 (52%) were right eyes and 10 (48%) were left eyes. One patient (patient: 9, Table 1) had bilateral involvement, with two separate areas affected in each eye. In terms of retinal quadrants affected, SCRD was in the upper quadrant in 18 eyes (85.7%) and the lower quadrant

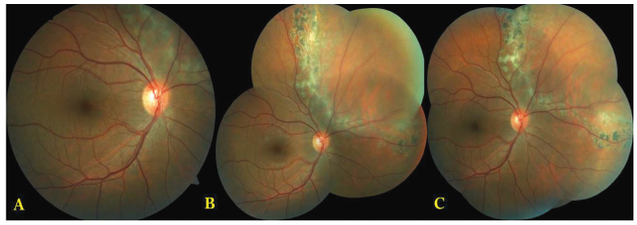


Figure 1. A) Color fundus photographs from a 19-year-old male patient (Patient 4) show subclinical retinal detachment secondary to a retinal tear in the peripheral upper nasal area of the right eye, B) appearance 1 month after demarcation laser photocoagulation, and C) appearance 6 months after demarcation laser photocoagulation. The entire SCRD and 360° laser demarcation could not be shown due to the difficulty of obtaining fundus photographs of the peripheral retina

SRCD: Subclinical retinal detachment

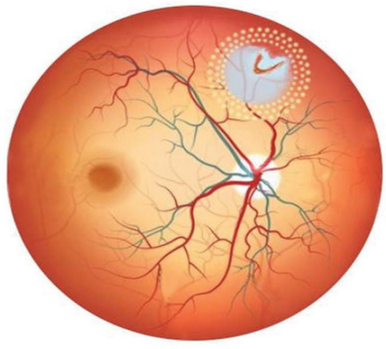


Figure 2. Schematic showing subclinical retinal detachment secondary to horseshoe retinal tear in the peripheral upper nasal area of the right eye and the 360° laser photocoagulation procedure

Table 1. Demographic data, ocular findings, and follow-up periods of the patients

Patient no	Age (years)	Sex	Eye	Spheric equivalent	Tear location	Number of tears	ERM/CME	PPV	Follow-up time (months)
1	74	F	R	-1.75	Superotemporal	1	-	-	42
2	37	M	L	-1.24	Superotemporal	1	-	-	21
3	70	F	R	-0.78	Superior	2	-	-	16
4	19	M	R	-3.22	Superonasal	1	-	-	6
5	61	F	L	+0.78	Superotemporal	1	-	-	7
6	54	M	L	-1.45	Superotemporal	1	+	-	9
7	68	M	L	-0.56	Superior	1	+	-	14
8	64	F	R	-4.25	Superior	2	+	+	28
9	71	F	R	-4.76	Superotemporal	2	+	+	26
			L	-5.32	Superior	2	+	+	
10	57	F	L	-2.36	Superior	2	+	-	24
11	75	M	R	-1.56	Inferotemporal	1	-	-	50
12	60	F	L	+0.58	Superotemporal	1	+	-	36
13	67	M	R	-1.46	Superotemporal	1	+	-	55
14	59	F	R	-0.86	Inferonasal	1	-	-	18
15	46	F	R	-6.34	Superonasal	2	-	+	9
16	61	F	L	+0.38	Inferonasal	1	-	-	29
17	18	M	R	-1.12	Superior	1	-	-	35
18	68	F	L	-0.26	Superotemporal	1	-	-	7
19	57	M	L	-2.46	Superior	1	-	-	6
20	46	F	R	-3.68	Superotemporal	1	-	-	46

ERM: Epiretinal membrane, CME: Cystoid macular edema, PPV: Pars plana vitrectomy, F: Female, M: Male, R: Right, L: Left

in 3 eyes (14.3%), and was located in the temporal quadrant in 10 eyes (47.6%), the nasal quadrant in 4 eyes (19.1%), and both the temporal and nasal quadrants in 7 eyes (33.3%). Etiology of SCRD was secondary to lattice degeneration in 16 eyes, secondary to posterior vitreous detachment (horseshoe tear) in 4 eyes, and secondary to an atrophic hole in 1 eye.

Myopia greater than -3.0 D was detected in 6 (28.6%) of the eyes with SCRD. Epiretinal membrane and/or cystoid macular edema occurred in 8 (38%) of the eyes included in the study (Table 1). In the 3 eyes (14.3%) that developed cystoid macular edema, complete regression was observed with topical nepafenac 3 times a day used for a mean of 3 months. Progression to clinical retinal detachment was observed in 4 (19%) of the 21 eyes during follow-up, and these patients underwent pars plana vitrectomy (PPV). All of the eyes with progression to clinical retinal detachment had greater than -3.0 D myopia and multiple retinal breaks in the upper quadrant. No recurrence was observed in the eyes that underwent PPV. No major complications related to demarcation laser photocoagulation were observed.

Discussion

The term SCRD was first used in 1952 by Schepens[6] to describe cases in which a diagnosis of clinical retinal detachment could not be established using the usual investigation methods. The methods available at that time included direct ophthalmoscopy and sometimes slit-lamp biomicroscopy and visual field examination. In 1958, Schepens[1] defined SCRD as retinal detachment that does not cause changes in the patient's visual field or visual acuity. The criterion used in this second definition formed the basis of the term SCRD as currently used. In 1973, Davis[7] described SCRD in anatomical terms, delimiting and thus substantially refining its definition. At present, there is no complete consensus regarding the term SCRD.

Detachments that do not cause visual field defects or reduce visual acuity may not be noticed by patients. In such cases, the retinal detachment is either self-limited to the demarcation line or progresses to clinical retinal detachment. Because patients with SCRD are asymptomatic and do not receive medical treatment, the real incidence or natural history of SCRD cannot be determined. There are few studies in the literature reporting the natural course of SCRD. In a study by Byer[8] including 17 eyes with asymptomatic retinal tears and long-term follow-up, 18 SCRD areas were monitored without treatment. In the natural course of SCRD in these eyes, 11% progressed from SCRD to clinical retinal detachment. In the same study, 59% of the SCRD areas were in the lower retinal quadrants and 90.9% of the eyes had involvement in the temporal half of the retina.

This localization may have contributed to SCRD being preserved as subclinical and remaining asymptomatic in terms of visual field defects. Brod et al.[9] followed 31 eyes of 28 patients with asymptomatic rhegmatogenous retinal detachment for a mean of 3.4 years and observed progression of detachment in only 6% of the eyes.

The literature is not clear regarding how to approach SCRD or the necessity of treatment.[8,9,10,11,12] Although these detachments exhibit different clinical states during their natural course, they may progress to a symptomatic condition. In symptomatic detachments that develop from SCRD, the former detachment line is seen in most patients.[9] Because there is insufficient data on the natural course of SCRD, the risk of their progression to symptomatic retinal detachment is not fully known. When deciding whether or not to treat a patient, treatment should be considered in patients who need to be physically active; those who have superiorly located, horseshoe, or multiple retinal tears; and most importantly, those who develop symptomatic retinal detachment.[5] Intraocular surgery to treat SCRD carries the risk of postoperative decrease in vision. As many patients with SCRD have ≥0.8 (Snellen) visual acuity, substantial reductions in visual acuity may be observed following surgery.

Since the development of microincision approaches (23-, 25-, and 27-gauge), wide-angle imaging systems, high-speed cutters, and better illumination methods, PPV is now preferred for the treatment of retinal detachment.[13] Scleral buckling surgery (cerclage band), a minimal surgical method, can also yield successful outcomes in suitable patients. However, this procedure is less preferred because some surgeons working in this field have poor command of the indirect ophthalmoscope, and there is a lack of time and training programs for cerclage training.[14] Different therapeutic approaches to SCRD and clinical retinal detachment can be observed among physicians. The decision to pursue invasive treatment or to monitor SCRD is not urgent, and surgical interventions may not be necessary in primary treatment as long as there is no clinical retinal detachment in the patient's fellow eye. We preferred demarcation laser photocoagulation as a more conservative therapeutic approach in our SCRD patients and achieved successful outcomes with this noninvasive treatment.

There is evidence that adhesion between the neural retina and retinal pigment epithelium begins to develop 24 hours after the treatment of laser photocoagulation.[15] However, it takes 3 to 14 days to reach maximum strength.[16] If laser photocoagulation can be successfully applied in 360° surrounding the detachment, it is a non-invasive, simple, and effective treatment option. In all of our patients, the detachments were encircled with 3-4 rows of 360° laser photocoagulation and monitored closely. Epiretinal membrane and/or cystoid macular edema was detected in 38% of the eyes, but none of the eyes required surgical treatment for epiretinal membrane. The 3 eyes (14.3%) that developed cystoid macular edema, were treated with topical nepafenac 3 times a day, and regression was observed within an average of 3 months. SCRD progression to clinical retinal detachment occurred in 19% (4 eyes) during the long-term follow-up of our patients. We noted that the eyes in our study that progressed to clinical retinal detachment and underwent PPV had multiple (≥2) retinal tears and SCRD located in the upper quadrant.

In patients with SCRD, demarcation laser photocoagulation should be kept in mind as a primary treatment to avoid the possible complications of intraocular surgery. Demarcation laser photocoagulation is of great importance in preventing progression to clinical retinal detachment in most patients. Patients should be monitored closely after demarcation laser photocoagulation therapy. The patient group most at risk for progression to clinical retinal detachment includes those with multiple retinal tears, upper quadrant involvement, and extensive subretinal fluid, and these patients should therefore be monitored more closely and carefully.

Ethics

Ethics Committee Approval: The study was approved by Dokuz Eylül University Faculty of Medicine Ethics Committee (2018/29-35).

Informed Consent: All patients who volunteered to participate were informed in detail about the study and laser photocoagulation, and their written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nilüfer Koçak, Mahmut Kaya, Concept: Nilüfer Koçak, Mahmut Kaya, Süleyman Kaynak, Design: Nilüfer Koçak, Mahmut Kaya, Süleyman Kaynak, Data Collection or Processing: Mahmut Kaya, Taylan Öztürk, Volkan Bolluk, Analysis or Interpretation: Mahmut Kaya, Taylan Öztürk, Nilüfer Koçak, Literature Search: Mahmut Kaya, Taylan Öztürk, Volkan Bolluk, Writing: Nilüfer Koçak, Mahmut Kaya, Süleyman Kaynak.

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. Schepens CL. Preventive treatment of idiopathic and secondary retinal detachment. Acta XVIII Concilium Ophthalmologicum Belgica. 1958;1:1019-1027.
2. Aylward GW. Optimal procedures for retinal detachments repair. In: Ryan SJ, ed. Retina. Los Angeles: Elsevier Mosby;2012.
3. Cohen SM. Natural history of asymptomatic clinical retinal detachments. Am J Ophthalmol. 2005;139:777-779.
4. Davis MD. The natural history of retinal breaks without detachment. Trans Am Ophthalmol Soc. 1973;71:343-372.
5. Garcia-Arumi J, Boixadera A, Martinez-Castillo V, Zapata MA. Subclinical Retinal Detachment. In: Kırchhof B, Wong D, eds. Vitreo-retinal surgery (1st ed). New York; Springer Berlin Heidelberg; 2007;11:133-142.
6. Schepens CL. Subclinical retinal detachments. Ama Arch Ophthalmol. 1952;47:593-606.

7. Davis MD. The natural history of retinal breaks without detachment. Trans Am Ophthalmol Soc. 1973;71:343-372.
8. Byer NE. Subclinical retinal detachment resulting from asymptomatic retinal breaks: prognosis for progression and regression. Ophthalmology. 2001;108:1499-1503.
9. Brod RD, Flynn HW, Lightman DA. Asymptomatic rhegmatogenous retinal detachments. Arch Ophthalmol. 1995;113:1030-1032.
10. Byer NE. The natural history of asymptomatic retinal breaks. Ophthalmology. 1982;89:1033-1039.
11. Byer NE. Spontaneous regression and disappearance of subclinical rhegmatogenous retinal detachment. Am J Ophthalmol. 2001;131:269-270.
12. Greven CM, Wall AB, Slusher MM. Anatomic and visual results in asymptomatic clinical rhegmatogenous retinal detachment repaired by scleral buckling. Am J Ophthalmol. 1999;128:618-620.
13. Shah GK, Ahmad B, Kiss S. Controversies in Vitreoretinal Surgery: Is Scleral Buckling an Important Mainstay in the Treatment of Retinal Detachment in 2014?. Retina Today. 2014:45-50.
14. Adelman RA, Parnes AJ, Ducournau D; European Vitreo-Retinal Society (EVRS) Retinal Detachment Study Group. Strategy for the management of uncomplicated retinal detachments: the European vitreo-retinal society retinal detachment study report 1. Ophthalmology. 2013;120:1804-1808.
15. Folk JC, Sneed SR, Folberg R, Coonan P, Pulido JS. Early adhesion from laser photocoagulation. Ophthalmology. 1989;96:1523-1525.
16. Yoon YH, Marmor MF. Rapid enhancement of retinal adhesion by laser photocoagulation. Ophthalmology. 1988;95:1385-1388.

DOI: 10.4274/tjo.galenos.2019.28828
Turk J Ophthalmol 2019;49:347-355

Review

Update in Genetics and Surgical Management of Primary Congenital Glaucoma

Mehmet C Mocan, Amy A Mehta, Ahmad A Aref

University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences, Chicago, USA

Abstract

Primary congenital glaucoma (PCG) continues to be an important cause of visual impairment in children despite advances in medical and surgical treatment options. The progressive and blinding nature of the disease, together with the long lifespan of the affected population, necessitates a thorough understanding of the pathophysiology of PCG and the development of long-lasting treatment options.

The first part of this review discusses the genetic features and makeup of this disorder, including all currently identified genetic loci (GLC3A, GLC3B, GLC3C and GLC3D) and relevant protein targets important for trabecular and Schlemm canal dysgenesis. These target molecules primarily include CYP1B1, LTBP2, and TEK/Tie2 proteins. Their potential roles in PCG pathogenesis are discussed with the purpose of bringing the readers up to date on the molecular genetics aspect of this disorder. Special emphasis is placed on functional implications of reported genetic mutations in the setting of PCG. The second part of the review focuses on various modifications and refinements to the traditional surgical approaches performed to treat PCG, including advances in goniotomy and trabeculotomy ab externo techniques, glaucoma drainage implant surgery and cyclodiode photocoagulation techniques that ultimately provide safer surgical approaches and more effective intraocular pressure control in the 21st century.

Keywords: Primary congenital glaucoma, genetics, angle surgery, glaucoma drainage implants

Introduction

Primary congenital glaucoma (PCG) (OMIM 231300) is a potentially blinding ocular disease that occurs secondary to a developmental anomaly of the anterior chamber angle and which results in high intraocular pressure (IOP) with its resultant devastating consequences.[1,2] It is an important global cause of pediatric visual impairment and leads to legal blindness, even with treatment.[3,4,5] The underlying mechanism in PCG is trabecular dysgenesis with or without varying degrees of associated iridodysgenesis including arrested posterior migration of the peripheral iris tissue and maldeveloped trabecular angle meshwork with or without dysgenesis of the Schlemm's canal (SC).[1] Current evidence suggests that trabecular dysgenesis occurs due to mutations that impair normal trabecular meshwork development.[6,7,8] However, the mechanisms through which these genes act to induce trabecular dysgenesis is not, as of yet, clearly elucidated.

Current treatment strategies for PCG revolve around surgical methods that target the abnormal trabecular angle.[9] These options include goniotomy and trabeculotomy ab externo, and variations thereof, that are performed as primary procedures in patients with PCG.[9,10,11,12] Many patients require more than one surgery and, in some cases, drainage procedures if these angle-based procedures do not lower the IOP to a safe level to halt glaucomatous optic neuropathy.[9,13,14] Patients with PCG also frequently require adjunctive topical hypotensive medications in their postoperative course.[2,4]

Address for Correspondence: Cem Mocan MD, University of Illinois at Chicago, Department of Ophthalmology and Visual Sciences, Chicago, USA
Phone:+90 532 685 63 12 E-mail: mocancem@gmail.com **ORCID-ID:** orcid.org/0000-0002-3419-9105
Received: 14.03.2019 **Accepted:** 10.06.2019

Cite this article as: Mocan MC, Mehta AA, Aref AA. Update in Genetics and Surgical Management of Primary Congenital Glaucoma. Turk J Ophthalmol. 2019;49:347-355

The purpose of this review is to provide an update on the genetic basis of PCG and to summarize the current surgical options for treatment of this condition.

Genetics of Primary Congenital Glaucoma

PCG is a genetic disorder with either sporadic or familial pattern of inheritance.[15] Around 10-40% of cases are familial and transmitted in an autosomal recessive manner with variable penetrance.[15,16] It is an uncommon disease with variable prevalence rates for PCG ranging between 1:2,500 to 1:10,000 depending on the population studied (i.e., Saudi Arabia, Middle Eastern countries) and seen much more frequently in populations where consanguinity is common.[8,15]

To date, four distinct genetic loci, namely GLC3A on chromosomal region 2p21, GLC3B on 1p36, GLC3C on 14q24, and GLC3D also on 14q24 have been found to be associated with PCG (Table 1).[6,7,17,18] GLC3A was the first locus to be identified in association with PCG in a study involving 17 Turkish families.[6] The GLC3A locus was localized to the chromosome 2p21 region and was later shown to harbor the *CYP1B1* gene.[6,19] Subsequently, another locus was identified on chromosome 1p36 in 1996 in 8 families (7 of Turkish and 1 of Canadian nationality) including 37 offspring, 17 of whom had PCG.[7] None of the patients in this cohort had genetic linkage to the GLC3A locus. Additionally, two other loci on chromosome 14q24 (GLC3C and GLC3D) have been reported in association of PCG.[17,18] It has been hypothesized that GLC3D locus may be related to the *LTBP2* (latent transforming growth factor-beta binding protein 2) gene.[20] Although no specific gene has been linked to the GLC3B locus at 1p36.2, a probable candidate is the *CDT6/ANGPTL7* gene at this (1p36.22) location, the protein product of which is an angiopoietin-like molecule (angiopoietin-like factor 7) and was found to be expressed in significant amounts in the human trabecular meshwork region.[21]

Recently, mutations in the angiopoietin receptor TEK (Tie2) have been found to be associated in 10 out of 189 families with PCG.[22] Unlike *CYP1B1*, TEK mutations that result in PCG appear to be transmitted in an autosomal dominant mode of inheritance with variable expression.[22]

Although myocilin gene mutations have been found to be associated with juvenile and adult onset open angle glaucoma, they have also been reported in PCG patients in association with heterozygous *CYP1B1* mutations, suggesting a potential digenic involvement of myocilin gene mutations with PCG.[23,24] However, other studies have not been able to find myocilin mutations in the setting of PCG and it appears that myocilin mutations do not appear to be directly responsible for development of PCG.[25,26]

Overall, five different loci have been implicated in PCG in different geographic locations globally. Although the involved genes for all these mutations are not yet identified, three protein products associated with these loci, namely CYP1B1, LTBP2, and Tie2, appear to regulate anterior segment development and seem to be likely candidate genes for the development of PCG (Table 1).

Cytochrome P450 1B1

Cytochrome P450 1B1 protein is member of heme-binding monoxygenases of the CYP450 superfamily that is localized to the endoplasmic reticulum.[27,28] It is a dioxin inducible oxidoreductase and is involved in steroid containing molecules as well as retinols and is involved in cell signaling.[27] It is encoded by the *CYP1B1* gene located in the 2p22.2 locus and has been associated with PCG.[8] Over 100 mutations of CYP1B1 have been found to be associated with PCG and mutations of this gene alone appear to be responsible for the majority of PCG cases in certain geographic regions, such as Saudi Arabia.[29] However, it appears to be responsible for only a minority of PCG cases in other parts of the world such as the United States (14.9%), Brazil (23.5%) and China (17.2%).[24,25,30] CYP1B1 is expressed in the anterior segment in non-pigmented ciliary epithelium, corneal epithelium, and retina and is thought to have a role in proper development of the outflow pathways through metabolism of essential endogenous steroid substrates.[31] CYP1B1 expression has also been demonstrated in the human trabecular meshwork.[19,21] The findings of irregular collagen architecture together with increased markers for oxidative stress in the trabecular meshwork of double knock-out CYP1B1 (*Cyp1b1*$^{-/-}$) mice suggest that CYP1B1 is involved in the proper development of the fetal trabecular meshwork.[32]

Latent Transforming Growth Factor (TGF)-beta Binding Protein 2 (LTBP2)

Homozygous mutations of the *LTBP2* gene at the chromosomal 14q24 locus have been shown to be present in members of families diagnosed with PCG in separate studies.[20,33,34] Similar to *CYP1B1* mutations, *LTBP2* mutations are expressed in an autosomal recessive manner in these patients and are more frequently seen in consanguineous families.[8]

LTBP2 gene product acts to interact with fibrillin-1 and is involved in various aspects of extracellular matrix organization

Table 1. Various genetic loci associated with or implicated in the pathogenesis of primary congenital glaucoma

Locus (year identified)	Chromosomal region	Gene product	Function
GLC3A (1995)	2p21	CYP1B1	Endogenous steroid metabolism
GLC3B (1996)	1p36	CDT6/ANGPTL7*	Extracellular matrix organization and formation
GLC3C (2002)	14q24	Unknown	Unknown
GLC3D (2008)	14q24	LTBP2	Extracellular matrix organization
Undesignated (2016)	9p21	TEK/Tie2	Formation and homeostasis of Schlemm's canal

*Implicated in PCG pathogenesis

including assembly of elastic fibers, and as a structural component of microfibrils under physiologic conditions.[35,36] As such, it is postulated that null mutations in the *LTBP2* gene may result in altered elastic and structural mechanics of the trabecular meshwork, ultimately giving rise to PCG.[20] LTBP2 also is involved in ciliary zonule formation and anterior chamber differentiation, and its mutations have been found in cases with lens structural abnormalities as well as those with lens dislocations.[37,38] Homozygous mutations of the p.R299X mutation in the Roma/gypsy population have been found to confer a poorer prognosis with a more severe PCG phenotype.[34] Thus, LTBP2 appears to be a distinct protein involved in anterior segment differentiation and functioning, the mutations of which are associated with PCG.

Angiopoietin Receptor Tyrosine Endothelial Cell Kinase (TEK)

The angiopoietin receptor TEK, also known as tunica interna endothelial cell kinase, is involved in normal vascular development and homeostasis in humans and other mammalian species via interaction with its two ligands, angiopoietin-1 and angiopoietin-2.[39,40] Recently, angiopoietin receptor *TEK* gene (Tie2) mutations localizing to 9p21.2 have been reported in PCG patients who did not have mutations of the *CYP1B1*, *LTBP2*, myocilin, or *FOXC1* genes, suggesting mutation of this receptor tyrosine kinase could be involved in PCG pathogenesis.[22] Tie2 is expressed in the human SC endothelium and the Tie2-angiopoietin pathway plays an important role in SC formation and homeostasis.[41] In addition, induced mutations of the *Tie2* gene has been shown to be associated with SC malformation with induce ocular hypertension and retinal ganglion cells in experimental animal models.[42] Unlike the *CYP1B1* gene, which appears to indirectly affect trabecular meshwork development through ligand metabolism, the *Tie2* gene likely has a more direct role in SC, and even 50% reduction in the activity of this tyrosine kinase leads to abnormal SC and impaired aqueous outflow facility.[8,22]

Update on Surgical Treatments for PCG

Managing congenital glaucoma is challenging both diagnostically and therapeutically. The definite treatment for PCG is surgical management, using medical management as a bridge.[13] Various modifications to the traditional angle- and non-angle-based surgical procedures have been introduced in the last three decades to increase the efficacy and safety of these interventions in the pediatric population (Table 2). As life expectancy is longer in the pediatric population, the longevity of treatment choice is crucial. The literature on current practices include angle surgery such as goniotomy or trabeculotomy, trabeculectomy, glaucoma drainage implants (GDIs), and/or laser cyclophotocoagulation (CPC).[9,10,11,12,13]

Angle Surgery

Angle surgery is frequently the primary procedure in PCG as it directly addresses the underlying outflow abnormality and restores a physiologic outflow of the aqueous humor from the anterior chamber to the SC.[3,5,9] Two angle procedures currently employed are goniotomy and trabeculotomy ab externo, both of which appear to achieve similar rates of successful outcomes.[1,3,5,9,10,11,12,13] In addition, these angle procedures appear to have better outcomes in patients with PCG presenting between 1-24 months of age and have a worse prognosis in neonatal-onset PCG and in those with late-onset disease.[10,43,44]

Goniotomy

Modern angle surgery for the treatment of PCG was developed and popularized by Otto Barkan,[45] who coined the term goniotomy for this procedure in 1938. This procedure has proven to be highly effective by allowing the aqueous humor to flow into the SC and collector channels using an incision of the trabecular meshwork under direct gonioscopic visualization.[45] Although the procedure was initially developed to remove embryologically abnormal tissue overlying the trabecular meshwork, the exact mechanisms as to how it lowers IOP in PCG are not clearly identified, and it has also been shown to effectively lower IOP in non-PCG forms of childhood glaucomas.[10,45,46]

Table 2. Modifications for surgical interventions for primary congenital glaucoma

Standard procedure	Modifications
Goniotomy	(1) Two-site goniotomy[51] (2) Viscogoniotomy[52] (3) Specialized blade assisted goniotomy[53] (4) Endoscopic goniotomy[50]
Trabeculotomy	(1) 360-degree suture trabeculotomy[11] (2) Illuminated microcatheter assisted circumferential trabeculotomy (IMCT)[65] (3) Viscotrabeculotomy[60]
Trabeculectomy	(1) Combined trabeculotomy-trabeculectomy[68] (2) Mitomycin-C augmented trabeculectomy[14,73]
Glaucoma drainage implantation	(1) May consider smaller implant plate designs (2) Plan for possible tube repositioning or extension over the patient's lifetime[85]
Cyclophotocoagulation	Endoscopic cyclophotocoagulation[87]

Goniotomy requires a clear cornea for proper visualization of the angle structures and targets around 120 degrees of the angle when performed in one quadrant through a single incision, as is most common in clinical practice.[47] Its advantages include a short operating time, its conjunctiva-sparing nature, potential for repeatability in another quadrant, and relatively low incidence of complications when performed by a specialist who has experience with this procedure. The reported success outcomes vary between 60-90% with one or more goniotomies.[4,48,49,50] Infants who present in the first month of life and those who initially require more than one goniotomy are at higher risk of relapse and may need further surgical interventions.[50]

One important limitation of goniotomy is that it cannot be performed in infants with corneal opacification. An endoscopic goniotomy technique that can potentially overcome limited corneal clarity has been reported and initial results have been encouraging.[51] Although this modification requires sophisticated instrumentation, a wide-angle goniotomy can be achieved using this approach using two separate incisions, thus allowing for more effective IOP lowering.

A simultaneous two-incision site that would allow for wider extent of angle treatment has been put forward.[52] However, the 1-year results of this modified procedure were not found to be significantly better compared to single-incision goniotomy.[52]

Currently, goniotomy continues to be practiced with essentially the same technique developed by Barkan[45] seven decades ago with minor modifications and improvements. These modifications include the use of better goniolenses, anterior chamber maintainers, and utilization of viscolelastics for even safer surgery in eyes with PCG.[10,53]

Despite its shortcomings, goniotomy is an excellent surgical option for the treatment of PCG as it allows for IOP lowering with an acceptable level of risk and is performed without disturbing the conjunctiva. Further improvements in this technique will likely focus on treating a wider angle of trabeculum through a single incision and the development of incisional tools that will allow for more refined tactile feedback. One such instrument is the recently introduced Kahook dual blade, which enables controlled excision of the trabecular meshwork with an ab interno approach and is specifically designed to allow for a more controlled depth of trabecular incision and decrease the rate of underlying ciliary body image that may be observed with the use of sharper MVR blades.[54,55]

Trabeculotomy ab externo

Trabeculotomy ab externo is an intervention for the treatment of PCG wherein the SC is cannulated and trabecular meshwork torn towards the anterior chamber in a controlled manner using an external approach with a scleral cut-down.[9,56,57] This procedure was developed in the 1960s thorough the works of Smith[56] and Burian[57], who independently cannulated the SC using a nylon suture and a metal probe, respectively. Thorough a single scleral cut-down site, about one-third of the angle can be accessed and fistulized with the anterior chamber, thus creating an outflow of aqueous humor through the maldeveloped anterior chamber angle. Trabeculotomy is a highly effective procedure with reported success rates ranging from 70-100% with one or more interventions, although loss of IOP control with time also occurs with this type of angle surgery.[58,59,60] The use of viscoelastic devices appears to lower the incidence of postoperative hyphema and improve overall success rates in trabeculotomy.[61]

A 360-degree circumferential trabeculotomy procedure was introduced by Beck and Lynch[11] to increase the extent of abnormal angle treated by the traditional trabeculotomy approach. In this modification, a 6-0 polypropylene suture is used to access the SC instead of a rigid metal probe and propagate the suture around the limbus to open the entire angle with a single cut-down underneath a partial thickness scleral flap.[11] The advantage of this approach is that in a single session, the entire abnormal angle can be bypassed and the need for a second angle procedure would be obviated. The 360-degree trabeculotomy has been shown to be associated with a higher success rate over both standard trabeculotomy procedure (85.7% vs. 58.4% with 1-year of follow up) and traditional goniotomy (92.0% vs. 60% at the end of a 6-year follow-up).[62,63] In another study, circumferential trabeculotomy was associated with a much higher rate of successful outcome (81% vs. 31%) compared to conventional angle procedure in the form of either trabeculotomy or goniotomy with a follow-up of 7-8 years.[64] Creation of a false passage into the suprachoroidal space with resultant damage to fovea or ciliary body as well as hyphema and iris prolapse are potential complications of this procedure.[11,65]

In order to better visualize the course of the probe during 360-degree trabeculotomy, a microcatheter attached to a light source has been used to cannulate the SC (iTRACK 250A; iScience Interventional, Menlo Park, CA).[66] The rationale of illuminated microcatheter assisted circumferential trabeculotomy (IMCT) has been to visualize the probe during cannulation and prevent misdirection of the probe into the suprachoroidal space. A subsequent study demonstrated that illuminated microcatheter assisted 360-degree trabeculotomy was associated with significantly higher success rate compared to standard goniotomy (83.3% versus 53.8%) over the course of 12 months.[12] A recent study demonstrated that this procedure had an 80% complete success rate (IOP≤18 mmHg without medications) and 100% qualified success rate (IOP≤18 mmHg with medications) in 20 previously non-operated eyes of patients with PCG.[67] IMCT also appeared to outperform conventional trabeculotomy in a recent study, with higher percentage of patients achieving successful outcomes with the former technique (90% vs. 70% qualified success) over the course of 12 months.[68] In this study, complete cannulation could not be achieved in 20% of cases undergoing the procedure.[68]

Combining trabeculotomy with trabeculotomy as an initial procedure to achieve long-term IOP control in patients with early (i.e., neonatal-onset) and more severe PCG has been advocated by some authors.[69,70] The results of this modification have been encouraging, with >90% success rate at 1 year, decreasing to around 60% with 6 years of follow-up.[69]

Glaucoma Drainage Implants and Trabeculectomy

Based on the literature, angle surgery and trabeculectomy are considered both safe and effective interventions for congenital or developmental glaucomas.[71,72] However, given the frequency of complications of trabeculectomy and angle surgeries such as hypotony, leakage, scarring, bleb-related infection, and need for frequent follow-up, these procedures are less manageable treatment options in the pediatric population. In addition, examining pediatric patients can prove difficult in an outpatient setting, increasing the challenge of postoperative assessments of these complications.[13,73] Jayaram et al.[74] reported 78% 1-year and 67% 5-year success rate with the use of mitomycin-C (MMC)-augmented trabeculectomy in pediatric patients who had failed primary trabeculotomy in a cohort comprising mainly those with PCG. Although GDIs and CPC are reserved for refractory glaucoma cases, where refractory glaucoma refers to patients that have failed prior medical or surgical therapies, GDI is being more frequently employed following failed angle procedures due to its overall better postoperative safety profile.[14]

When comparing GDIs to the more conventional trabeculectomy with MMC in the pediatric population, GDIs have shown better IOP control than trabeculectomy with MMC, with 1- and 6-year success rates of ~87% and 53% for GDIs versus 36% and 19% for MMC-augmented trabeculectomy, respectively.[14] It has been proposed that the higher rate of failure with trabeculectomy compared to GDIs may be due to the robust healing properties as well as the elasticity and thinness of the sclera in the pediatric population resulting in faster scarring of potentially functioning trabeculectomy. This was demonstrated in a prospective study comparing Ahmed implantation to trabeculectomy with MMC (67% success in Ahmed group versus 40% in MMC trabeculectomy group, and 40% complications in the trabeculectomy group versus 26.7% in the Ahmed group).[74] However, in the previous study comparing GDIs to trabeculectomy with MMC, there was a higher rate of reoperation in the GDI group (45.7%) compared to trabeculectomy (12.5%).[14]

Historically, Molteno, Krupin, Shocket, Baerveldt, and Ahmed implants have been used in the pediatric glaucoma population.[75] Currently, Baerveldt and Ahmed implants are the most common implant used, when GDIs are indicated.[75,76] Without any head-to-head studies to compare the different drainage devices in a pediatric population, studies in adults comparing Ahmed to Baerveldt implants (AVB, ABC trials) have been used as evidence-based practices to determine which implant will provide superior outcomes, longevity, decrease in medication use, and less risk of complications.[77,78] Studies evaluating drainage implants (both Baerveldt and Ahmed) in primary and secondary congenital glaucoma demonstrated high success rate in the first year (~80-90.6%). However, a combination of complications and failures led to dramatic decrease in success to 58.3% at 2 years and ~20% by 5 years.[13,79] In a large-scale study evaluating GDI (Ahmed and Baerveldt) success in 70 eyes (congenital glaucoma and aphakic glaucoma), it was concluded that the Ahmed valve is preferable in patients with congenital glaucoma and Baerveldt implants are preferable in aphakic patients, with results showing 92% and 90% success at 1 year and a decrease to 42% and 55% success at 10 years, respectively.[76] Given their intrinsic valve mechanism, Ahmed implants can avoid hypotony (a common complication with trabeculectomy and Baerveldt implants) with a threshold valve opening pressure of 8 mmHg, providing a more predictable response in the congenital glaucoma population.[76]

An overall comparison of studies on the surgical management of pediatric glaucoma reveals highly variable outcomes. For example, a study looking at Ahmed success reported a low success rate of 31% after 2 years, while another reported 86% success.[80,81] Factors that may contribute to this variability could be the etiology of glaucoma, primary congenital versus secondary glaucoma, age of the patients, other comorbidities, number of prior interventions, and/or size of implant plate. Studies assessing these characteristics as potential risks for failure have come to differing conclusions as well. Some reporting that congenital glaucoma patients have a higher failure rate than secondary pediatric glaucoma, while others found no difference in the failure rate.[82,83] Some studies have looked at the age of patients and tried to correlate success of GDI surgery to age, finding that the age of the patient did not have a clear correlation to success rate, but that complications are seen more in children than in adults.[75] These complications could be the result of the anatomical structure of a pediatric glaucomatous eye [thinner sclera, larger buphthalmic globes, anterior segment agenesis, aphakia (unicameral eyes)]. Another risk factor to consider is any prior surgery and whether this changes the probability of success of subsequent procedures. Studies looking at Ahmed valves did not find a correlation between failure and prior glaucoma surgery, while others reported that eyes with previous glaucoma surgeries showed significantly worse results.[81,83,84,85] Surgical failure may also occur as a result of aqueous shunt tube retraction in a growing pediatric eye. Several techniques, including use of intravenous angiocatheter "bridge" and use of a commercially available Tube Extender (New World Medical, Inc.) have been described to manage this complication. Chiang et al.[86] recently described an innovative "tube-in-tube" technique, which involves threading a new tube element within the lumen of the existing tube. Encouraging results were described in a case series of 3 patients.

The size of the implant is also an important characteristic of glaucoma surgery as pivotal studies have shown the amount of IOP reduction is directly proportional to the end plate size.[87] There are currently two versions of the Ahmed valve, FP8 (96 mm^2) and FP7 (184 mm^2). Although the FP8 is a smaller implant, current practice is to use the larger size (FP7), as it can fit in the pediatric eye unless nanophthalmic. Similarly, the Baerveldt implant has two size versions of 250 mm^2 and 350 mm^2, with a similar common practice of larger plate usage in adults as well as children.

A spectrum of cyclodestructive procedures, transscleral cyclophotocoagulation diode (TSCPC), and endocyclophotocoagulation (ECP) are relied upon for refractory

glaucoma cases.[88] The goal of these procedures is to blunt the production of aqueous humor in attempts to lower the IOP via its inflow mechanism. Although effective at lowering IOP, these procedures have been relegated to severely refractory cases due to complications associated with poor prognosis, such as hypotony, recalcitrant inflammation, retinal detachments, and the possibility of consequent phthisis bulbi.[88,89,90]

The literature to date reports success rates over 50% for TSCPC in refractory pediatric glaucoma cases, and even higher rates (~72%) in patients who have had retreatments with TSCPC.[89,90,91] In a recent study comparing the safety and efficacy of initial trabeculectomy versus initial TSCPC, it was concluded that although safe and effective, difficulties regarding repeatable technique as well as post procedural complications of TSCPC can occur. Transillumination using either a Finhoff (muscle) light or a fiberoptic transilluminator was recommended as a way to correctly identify the ciliary body underneath the sclera.[88] In the TSCPC group, 6 of 17 eyes (35%) required further interventions, whereas 4 of 19 eyes (21%) in the trabeculectomy group were operated on again.[73]

Study Limitations

Limitations included identifying and precisely targeting the ciliary body and titrating the laser energy to adequate uptake, especially in varying anterior segment anatomies. Post procedural complications such as inflammation and overtreatment resulting in irreversible hypotony and phthisis are also increasingly more difficult to manage in a pediatric patient.[89,92]

Most ophthalmologists will reserve TSCPC for patients with a limited visual potential given the adverse effect profile, especially given the potential for retinal detachment (~10%) and irreversible hypotony.[88] Additionally, they will reserve this approach for patients who have glaucoma refractory to prior surgeries, elevated pressure with pain in a blind eye, or if surgical/incisional measures are too risky. Rarer complications that can occur with TSCPC involve scleral thinning, especially when too many audible laser sounds are heard. Limiting the area of ablation per session to no more than 180 degrees appears to confer increased safety to the TSCPC procedure, though the procedure may need to be repeated to achieve target IOPs.[93]

An intraocular procedure that has more recently been utilized in the pediatric population is ECP.[93] Using a 19-23-gauge instrument, one can endoscopically visualize the ciliary body processes and treat with photocoagulation directly to the processes.[94]

Studies reporting results from ECP have been promising, with no sight-threatening complications of severe hypotony, intractable pain, or recalcitrant inflammation.[94] At 3 year follow-ups, 50% of patients had a cumulative success rate of 43%.[94] Considerations for ECP include whether the patient is phakic or aphakic and risks of introducing potential infection, causing suprachoroidal hemorrhages, or IOP spikes.

Given the propensity for glaucoma surgical procedures to fail over time in the pediatric population, secondary and tertiary surgical procedures have to be considered in these patients. Procedures that will function for the longer life expectancy of the pediatric patient are crucial. The decision to perform another tube surgery versus repeated TSCPC has been shown to be equivocal in the results, despite small powers in numbers of patients to evaluate this.[95]

Conclusion

PCG continues to be a challenging disease in the 21st century in that long-lasting IOP control is still difficult to achieve and the visual prognosis is somewhat guarded despite state-of-the-art treatment paradigms.[3,5] Over the course of five decades, several modifications have been introduced to standard angle surgery procedures to improve IOP outcomes, increase safety of the interventions, and decrease the total number of procedures in PCG. There has been a shift away from trabeculectomy and toward GDIs to decrease the frequency of postoperative hypotony and to ensure long-term IOP control. Currently, aqueous drainage devices as well as laser cyclophotocoagulation are successfully used in current practice to lower IOP in PCG, more frequently as a secondary procedure but in select cases as a primary intervention modality. These procedures can provide a pediatric patient longevity of stable IOP and thus preservation of visual function for a longer period of time. Limitations of current studies that provide evidence of safety and efficacy are the power in numbers of patients as well as duration of follow-up. Comparative studies of various procedures are needed to further investigate efficacy, outcomes, and quality of life outcomes.

Categorizing patients as either PCG or secondary congenital glaucoma and then stratifying those with secondary congenital glaucoma by mechanism, such as trauma-related, aphakic glaucoma, or anterior segment dysgenesis-related glaucoma, could help to better understand outcomes of various procedures in these different patient groups. Additionally, the pediatric patient population is reliant on other social risk factors such as caregivers, economic, education, and distance of travel, all factors that can influence time to diagnosis, time to surgery, and postoperative care. When trying to clinically appreciate the outcomes of this literature review, a case-by-case analysis must also be performed to account for these social risk factors prior to determining a management plan for these patients. A better understanding of PCG as a disease, improved diagnostic capacity, together with advances in surgical procedures will continue to improve the outlook for PCG in the future.

Ethics

Ethics Committee Approval: Not applicable per nature of the manuscript (review paper)

Informed Consent: None required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet C Mocan, Ahmad A Aref, Amy A Mehta, Concept: Mehmet C Mocan, Ahmad A Aref, Design: Mehmet C Mocan, Data Collection or Processing: Mehmet C Mocan, Ahmad A Aref, Amy A Mehta, Analysis or Interpretation: Mehmet C Mocan, Ahmad A Aref, Literature

Search: Mehmet C Mocan, Ahmad A Aref, Amy A Mehta, Writing: Mehmet C Mocan, Ahmad A Aref, Amy A Mehta

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. Anderson DR. The development of the trabecular meshwork and its abnormality in primary infantile glaucoma. Trans Am Ophthalmol Soc. 1981;79:458-485.
2. Chang T, Brookes J, Cavuoto K, Bitrian E, Grajewski A. Primary congenital glaucoma and juvenile openangle glaucoma. In: Weinreb R, Grajewski A, Papadopoulos M, Grigg J, Freedman S, eds. Childhood Glaucoma. The 9th Consensus Report of the World Glaucoma Association. Amsterdam: Kugler; 2013:137-153.
3. Alsheikheh A, Klink J, Klink T, Steffen H, Grehn F. Long-term results of surgery in childhood glaucoma. Graefes Arch Clin Exp Ophthalmol. 2007;245:195-203.
4. Taylor RH, Ainsworth JR, Evans AR, Levin AV. The epidemiology of pediatric glaucoma: the Toronto experience. J AAPOS. 1999;3:308-315.
5. Zagora SL, Funnell CL, Martin FJ, Smith JE, Hing S, Billson FA, Veillard AS, Jamieson RV, Grigg JR. Primary congenital glaucoma outcomes: lessons from 23 years of follow-up. Am J Ophthalmol. 2015;159:788-796.
6. Sarfarazi M, Akarsu AN, Hossain A, Turacli ME, Aktan SG, Barsoum-Homsy M, Chevrette L, Sayli BS. Assignment of a locus (GLC3A) for primary congenital glaucoma (Buphthalmos) to 2p21 and evidence for genetic heterogeneity. Genomics. 1995;30:171-177.
7. Akarsu AN, Turacli ME, Aktan SG, Barsoum-Homsy M, Chevrette L, Sayli BS, Sarfarazi M. A second locus (GLC3B) for primary congenital glaucoma (Buphthalmos) maps to the 1p36 region. Hum Mol Genet. 1996;5:1199-1203.
8. Lewis CJ, Hedberg-Buenz A, DeLuca AP, Stone EM, Alward WLM, Fingert JH. Primary congenital and developmental glaucomas. Hum Mol Genet. 2017;26:R28-R36.
9. Chen TC, Chen PP, Francis BA, Junk AK, Smith SD, Singh K, Lin SC. Pediatric glaucoma surgery: a report by the American Academy Of Ophthalmology. Ophthalmology. 2014;121:2107-2115.
10. Papadopoulos M, Edmunds B, Fenerty C, Khaw PT. Childhood glaucoma surgery in the 21st century. Eye (Lond). 2014;28:931-943.
11. Beck AD, Lynch MG. 360 degrees trabeculotomy for primary congenital glaucoma. Archives of Ophthalmology. 1995;113:1200-1202.
12. Girkin CA, Marchase N, Cogen MS. Circumferential trabeculotomy with an illuminated microcatheter in congenital glaucomas. J Glaucoma. 2012;21:160-163.
13. Morales J, Al Shahwan S, Al Odhayb S, Al Jadaan I, Edward DP. Current surgical options for the management of pediatric glaucoma. Journal of Ophthalmology. 2013;1-16.
14. Beck AD, Freedman S, Kammer J, Jin J. Aqueous shunt devices compared with trabeculectomy with Mitomycin-C for children in the first two years of life. Am J Ophthalmol. 2003;136:994-1000.
15. Sarfarazi M, Stoilov I, Schenkman JB. Genetics and biochemistry of primary congenital glaucoma. Ophthalmol Clin North Am. 2003;16:543-554.
16. Ho CL, Walton DS. Primary congenital glaucoma: 2004 update. J Pediatr Ophthalmol Strabismus. 2004;41:271-288.
17. Stoilov, I.R. and Sarfarazi, M. The third genetic locus (GLC3C) for primary congenital glaucoma (PCG) maps to chromosome 14q24.3. Invest. Ophthalmol. Vis. Sci. 2002:43;3015.
18. Firasat S, Riazuddin SA, Hejtmancik JF, Riazuddin S. Primary congenital glaucoma localizes to chromosome 14q24.2-24.3 in two consanguineous Pakistani families. Mol Vis. 2008;14:1659-1665.
19. Stoilov I, Akarsu AN, Sarfarazi M. Identification of three different truncating mutations in cytochrome P4501B1 (CYP1B1) as the principal cause of primary congenital glaucoma (Buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. Hum Mol Genet. 1997;6:641-647.
20. Ali M, McKibbin M, Booth A, Parry DA, Jain P, Riazuddin SA, Hejtmancik JF, Khan SN, Firasat S, Shires M, Gilmour DF, Towns K, Murphy AL, Azmanov D, Tournev I, Cherninkova S, Jafri H, Raashid Y, Toomes C, Craig J, Mackey DA, Kalaydjieva L, Riazuddin S, Inglehearn CF. Null mutations in LTBP2 cause primary congenital glaucoma. Am J Hum Genet. 2009;84:664-671.
21. Tomarev S, Wistow G, Raymond V, Dubois S, Malyukova I. Gene expression profile of the human trabecular meshwork: NEIBank sequence tag analysis. Invest Ophthalmol Vis Sci. 2003;44:2588-2596.
22. Souma T, Tompson SW, Thomson BR, Siggs OM, Kizhatil K, Yamaguchi S, Feng L, Limviphuvadh V, Whisenhunt KN, Maurer-Stroh S, Yanovitch TL, Kalaydjieva L, Azmanov DN, Finzi S, Mauri L, Javadiyan S, Souzeau E, Zhou T, Hewitt AW, Kloss B, Burdon KP, Mackey DA, Allen KF, Ruddle JB, Lim SH, Rozen S, Tran-Viet KN, Liu X, John S, Wiggs JL, Pasutto F, Craig JE, Jin J, Quaggin SE, Young TL. Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity. J Clin Invest. 2016;126:2575-2587.
23. Kaur K, Reddy ABM, Mukhopadhyay A, Mandal AK, Hasnain SE, Ray K, Thomas R, Balasubramanian D, Chakrabarti S. Myocilin gene implicated in primary congenital glaucoma. Clin Genet. 2005;67:335-340.
24. Chen Y, Jiang D, Yu L, Katz B, Zhang K, Wan B, Sun X. CYP1B1 and MYOC mutations in 116 Chinese patients with primary congenital glaucoma. Arch Ophthalmol. 2008;126:1443-1447.
25. Lim SH, Tran-Viet KN, Yanovitch TL, Freedman SF, Klemm T, Call W, Powell C, Ravichandran A, Metlapally R, Nading EB, Rozen S, Young TL. CYP1B1, MYOC, and LTBP2 mutations in primary congenital glaucoma patients in the United States. Am J Ophthalmol. 2013;155:508-517.
26. Do T, Shei W, Chau PT, Trang DL, Yong VH, Ng XY, Chen YM, Aung T, Vithana EN. CYP1B1 and MYOC Mutations in Vietnamese Primary Congenital Glaucoma Patients. J Glaucoma. 2016;25:e491-e498.
27. Faiq MA, Dada R, Sharma R, Saluja D, Dada T. CYP1B1: a unique gene with unique characteristics. Curr Drug Metab. 2014;15:893-914.
28. Zhao Y, Sorenson CM, Sheibani N. Cytochrome P450 1B1 and Primary Congenital Glaucoma. J Ophthalmic Vis Res. 2015;10:60-67.
29. Bejjani BA, Lewis RA, Tomey KF, Anderson KL, Dueker DK, Jabak M, Astle WF, Otterud B, Leppert M, Lupski JR. Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. Am J Hum Genet. 1998;62:325-333.
30. Coêlho REA, Sena DR, Santa Cruz F, Moura BCFS, Han CC, Andrade FN, Lira RPC. CYP1B1 Gene and Phenotypic Correlation in Patients From Northeastern Brazil With Primary Congenital Glaucoma. J Glaucoma. 2019;28:161-164.
31. Doshi M, Marcus C, Bejjani BA, Edward DP. Immunolocalization of CYP1B1 in normal, human, fetal and adult eyes. Exp Eye Res. 2006;82:24-32.
32. Zhao Y, Wang S, Sorenson CM, Teixeira L, Dubielzig RR, Peters DM, Conway SJ, Jefcoate CR, Sheibani N. Cyp1b1 mediates periostin regulation of trabecular meshwork development by suppression of oxidative stress. Mol Cell Biol. 2013;33:4225-4240.
33. Narooie-Nejad M, Paylakhi SH, Shojaee S, Fazlali Z, Rezaei Kanavi M, Nilforushan N, Yazdani S, Babrzadeh F, Suri F, Ronaghi M, Elahi E, Paisán-Ruiz C. Loss of function mutations in the gene encoding latent transforming growth factor beta binding protein 2, LTBP2, cause primary congenital glaucoma. Hum Mol Genet. 2009;18:3969-3977.
34. Azmanov DN, Dimitrova S, Florez L, Cherninkova S, Draganov D, Morar B, Saat R, Juan M, Arostegui JI, Ganguly S, Soodyall H, Chakrabarti S, Padh H, López-Nevot MA, Chernodrinska V, Anguelov B, Majumder P, Angelova L, Kaneva R, Mackey DA, Tournev I, Kalaydjieva L. LTBP2 and CYP1B1 mutations and associated ocular phenotypes in the Roma/Gypsy founder population. Eur J Hum Genet. 2011;19:326-333.
35. Hirai M, Horiguchi M, Ohbayashi T, Kita T, Chien KR, Nakamura T. Latent TGF-beta-binding protein 2 binds to DANCE/fibulin-5 and regulates elastic fiber assembly. EMBO J. 2007;26:3283-3295.
36. Fujikawa Y, Yoshida H, Inoue T, Ohbayashi T, Noda K, von Melchner H, Iwasaka T, Shiojima I, Akama TO, Nakamura T. Latent TGF-β binding protein

2 and 4 have essential overlapping functions in microfibril development. Sci Rep. 2017;7:43714.
37. Haji-Seyed-Javadi R, Jelodari-Mamaghani S, Paylakhi SH, Yazdani S, Nilforushan N, Fan JB, Klotzle B, Mahmoudi MJ, Ebrahimian MJ, Chelich N, Taghiabadi E, Kamyab K, Boileau C, Paisan-Ruiz C, Ronaghi M, Elahi E. LTBP2 mutations cause Weill-Marchesani and Weill-Marchesani-like syndrome and affect disruptions in the extracellular matrix. Hum Mutat. 2012;33:1182-1187.
38. Khan AO, Aldahmesh MA, Alkuraya FS. Congenital megalocornea with zonular weakness and childhood lens-related secondary glaucoma - a distinct phenotype caused by recessive LTBP2 mutations. Mol Vis. 2011;17:2570-2579.
39. Augustin HG, Koh GY, Thurston G, Alitalo K. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. Nat Rev Mol Cell Biol. 2009;10:165-177.
40. Thurston G, Daly C. The complex role of angiopoietin-2 in the angiopoietin-tie signaling pathway. Cold Spring Harb Perspect Med. 2012;2:a006550.
41. Kizhatil K, Ryan M, Marchant JK, Henrich S, John SW. Schlemm's canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process. PLoS Biol. 2014;12:e1001912.
42. Thomson BR, Heinen S, Jeansson M, Ghosh AK, Fatima A, Sung HK, Onay T, Chen H, Yamaguchi S, Economides AN, Flenniken A, Gale NW, Hong YK, Fawzi A, Liu X, Kume T, Quaggin SE. A lymphatic defect causes ocular hypertension and glaucoma in mice. J Clin Invest. 2014;124:4320-4324.
43. Anderson DR. Trabeculotomy compared to goniotomy for glaucoma in children. Ophthalmology. 1983;90:805-806.
44. Hassanein DH, Awadein A, Elhilali H. Factors associated with early and late failure after goniotomy for primary pediatric glaucoma. Eur J Ophthalmol. 2018 Oct 10:1120672118805872.
45. Barkan O. Technique of goniotomy. Arch Ophthalmol. 1938;19:217-221
46. Medical and surgical treatments for childhood glaucomas. In: Allingham RR, Shields MB, eds. Shields Textbook of Glaucoma (6th ed). Philadelphia; Lippincott Williams and Wilkins; 2011:542-564.
47. Shaffer RN. Goniotomy technique in congenital glaucoma. Am J Ophthalmol. 1959;47:90-97.
48. Shaffer RN. Prognosis of goniotomy in primary infantile glaucoma (trabeculodysgenesis). Trans Am Ophthalmol Soc. 1982;80:321-325.
49. Gramer E, Tausch M, Kraemer C. Time of diagnosis, reoperations and long-term results of goniotomy in the treatment of primary congenital glaucoma: a clinical study. Int Ophthalmol. 1996-1997;20:117-123.
50. Russell-Eggitt IM, Rice NS, Jay B, Wyse RK. Relapse following goniotomy for congenital glaucoma due to trabecular dysgenesis. Eye (Lond). 1992;6:197-200.
51. Kulkarni SV, Damji KF, Fournier AV, Pan I, Hodge WG. Endoscopic goniotomy: early clinical experience in congenital glaucoma. J Glaucoma. 2010;19:264-269.
52. Catalano RA, King RA, Calhoun JH, Sargent RA. One versus two simultaneous goniotomies as the initial surgical procedure for primary infantile glaucoma. J Pediatr Ophthalmol Strabismus. 1989;26:9-13.
53. Tamçelik N, Ozkiriş A. A comparison of viscogoniotomy with classical goniotomy in Turkish patients. Jpn J Ophthalmol. 2004;48:404-407.
54. Khouri AS, Wong SH. Ab Interno Trabeculectomy With a Dual Blade: Surgical Technique for Childhood Glaucoma. J Glaucoma. 2017;26:749-751.
55. Harvey MM, Schmitz JW. Use of ab interno Kahook Dual Blade trabeculectomy for treatment of primary congenital glaucoma. Eur J Ophthalmol. 2018;14:1120672118805873.
56. Smith R. A new technique for opening the canal of Schlemm. Preliminary report. Br J Ophthalmol. 1960;44:370-373.
57. Burian HM. A case of Marfan's syndrome with bilateral glaucoma. With description of a new type of operation for developmental glaucoma (trabeculotomy ab externo). Am J Ophthalmol. 1960;50:1187-1192.
58. de Luise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). Surv Ophthalmol. 1983;28:1-19.
59. Luntz MH. Congenital, infantile, and juvenile glaucoma. Ophthalmology. 1979;86:793-802.
60. Yalvac IS, Satana B, Suveren A, Eksioğlu U, Duman S. Success of trabeculotomy in patients with congenital glaucoma operated on within 3 months of birth. Eye (Lond). 2007;21:459-464.
61. Tamcelik N, Ozkiris A. Long-term results of viscotrabeculotomy in congenital glaucoma: comparison to classical trabeculotomy. Br J Ophthalmol. 2008;92:36-39.
62. Lim ME, Neely DE, Wang J, Haider KM, Smith HA, Plager DA. Comparison of 360-degree versus traditional trabeculotomy in pediatric glaucoma. J AAPOS 2015;19:145-149.
63. Mendicino ME, Lynch MG, Drack A, Beck AD, Harbin T, Pollard Z, Vela MA, Lynn MJ. Long-term surgical and visual outcomes in primary congenital glaucoma: 360 degrees trabeculotomy versus goniotomy. Journal of AAPOS. 2000;4:205-210.
64. Neustein RF, Beck AD. Circumferential Trabeculotomy Versus Conventional Angle Surgery: Comparing Long-term Surgical Success and Clinical Outcomes in Children With Primary Congenital Glaucoma. Am J Ophthalmol. 2017;183:17-24.
65. Neely DE. False passage: a complication of 360 degrees suture trabeculotomy. J AAPOS. 2005;9:396-397.
66. Sarkisian SR Jr. An illuminated microcatheter for 360-degree trabeculectomy in congenital glaucoma: a retrospective case series. J AAPOS. 2010;14:412-416.
67. Toshev AP, Much MM, Klink T, Pfeiffer N, Hoffmann EM, Grehn F. Catheter-assisted 360-Degree Trabeculotomy for Congenital Glaucoma. J Glaucoma. 2018;27:572-577.
68. Shakrawal J, Bali S, Sidhu T, Verma S, Sihota R, Dada T. Randomized Trial on Illuminated-Microcatheter Circumferential Trabeculotomy Versus Conventional Trabeculotomy in Congenital Glaucoma. Am J Ophthalmol. 2017;180:158-164.
69. Mandal AK, Bhatia PG, Bhaskar A, Nutheti R. Long-term surgical and visual outcomes in Indian children with developmental glaucoma operated on within 6 months of birth. Ophthalmology. 2004;111:283-290.
70. Jalil A, Au L, Khan I, Ashworth J, Lloyd IC, Biswas S. Combined trabeculotomy trabeculectomy augmented with 5-fluorouracil in paediatric glaucoma. Clin Experiment Ophthalmol. 2011;39:207-214.
71. Sidoti PA, Belmonte SJ, Liebmann JM, Ritch R. Trabeculectomy with mitomycin-C in the treatment of pediatric glaucomas. Ophthalmology. 2000;104:422-429.
72. Giampani J Jr, Borges-Giampani AS, Carani JC, Oltrogge EW, Susanna R Jr. Efficacy and safety of trabeculectomy with mitomycin C for childhood glaucoma: a study of results with long-term follow-up. Clinics. 2008;63:421-426.
73. Fieß A, Shah P, Sii F, Godfrey F, Abbott J, Bowman R, Bauer J, Dithmar S, Philippin H. Trabeculectomy or Transscleral Cyclophotocoagulation as Initial Treatment of Secondary Childhood Glaucoma in Northern Tanzania. J Glaucoma. 2017;26:657-660.
74. Jayaram H, Scawn R, Pooley F, Chiang M, Bunce C, Strouthidis NG, Khaw PT, Papadopoulos M. Long-Term Outcomes of Trabeculectomy Augmented with Mitomycin C Undertaken within the First 2 Years of Life. Ophthalmology. 2015;122:2216-2222.
75. Nassiri N, Kouros NM, Coleman Al. Ahmed glaucoma valve in children: a review. Saudi J Ophthalmol. 2011;25:317-327.
76. Budenz DL, Gedde SJ, Brandt JD, Kira D, Feuer W, Larson E. Baerveldt glaucoma implant in the management of refractory childhood glaucomas. Ophthalmology. 2004;111:2204-2210.
77. O'Malley Schotthoefer E, Yanovitch TL, Freedman SF. Aqueous drainage device surgery in refractory pediatric glaucomas: I. Long-term outcomes. J AAPOS. 2008;12:33-39.
78. Christakis PG, Kalenak JW, Tsai JC, Zurakowski D, Kammer JA, Harasymowycz PJ, Mura JJ, Cantor LB, Ahmed II. The Ahmed Versus Baerveldt Study: Five-Year Treatment Outcomes. Ophthalmology. 2016;123:2093-2102.

79. Christakis PG, Zhang D, Budenz DL, Barton K, Tsai JC, Ahmed IIK; ABC-AVB Study Groups. Five Year Pooled Data Analysis of Ahmed Baerveldt Comparison Study and the Ahmed Versus Baerveldt Study. Am J Ophthalmol. 2017;176:118-126.
80. Englert J, Freedman S, Cox T. The Ahmed Valve in Refractory Pediatric Glaucoma. Am J Ophthalmol. 1999;127:34-42.
81. Al-Mobarak F, Khan AO. Two-year survival of Ahmed valve implantation in the first 2 years of life with and without intraoperative mitomycin-C. Ophthalmology. 2009;116:1862-1865.
82. Morad Y, Donaldson CE, Kim YM, Abdolell M, Levin AV. The Ahmed drainage implant in the treatment of pediatric glaucoma.Am J Ophthalmol. 2003;135:821-829.
83. Coleman AL, Smyth RJ, Wilson MR, Tam M. Initial clinical experience with the Ahmed Glaucoma Valve implant in pediatric patients. Arch Ophthalmol. 1997;115:186-191.
84. Djodeyre MR, Peralta Calvo J, Abelairas Gomez J. Clinical evaluation and risk factors of time to failure of Ahmed Glaucoma Valve implant in pediatric patients. Ophthalmology. 2001;108:614-620.
85. Souza C, Tran DH, Loman J, Law SK, Coleman AL, Caprioli J. Long-term outcomes of Ahmed glaucoma valve implantation in refractory glaucomas. Am J Ophthalmol. 2007;144:893-900.
86. Chiang MY, Camuglia JE, Khaw PT. A Novel Method of Extending Glaucoma Drainage Tube: "Tube-in-Tube" Technique. J Glaucoma. 2017;26:93-95.
87. Britt MT, LaBree LD, Lloyd MA, Minckler DS, Heuer DK, Baerveldt G, Varma R. Randomized clinical trial of the 350-mm2 versus the 500-mm2 Baerveldt implant: longer term results: is bigger better? Ophthalmology. 1999;106:2312-2318.
88. Bock CJ, Freedman SF, Buckley EG, Shields MB. Transscleral diode laser cyclophotocoagulation for refractory pediatric glaucomas. J Pediatr Ophthalmol Strabismus. 1997;34:235-239.
89. Schlote T, Grub M, Kynigopoulos M. Long-term results after transscleral diode laser cyclophotocoagulation in refractory posttraumatic glaucoma and glaucoma in aphakia. Graefes Arch Clin Exp Ophthalmol. 2008;246:405-410.
90. Wagle NS, Freedman SF, Buckley EG, Davis JS, Biglan AW. Long-term outcome of cyclocryotherapy for refractory pediatric glaucoma. Ophthalmology. 1998;105:1921-1927.
91. Kirwan JF, Shah P, Khaw PT. Diode laser cyclophotocoagulation: role in the management of refractory pediatric glaucomas. Ophthalmology. 2002;109:316-323.
92. Hamard P, May F, Quesnot S, Hamard H. Trans-scleral diode laser cyclophotocoagulation of the treatment of refractory pediatric glaucoma. J Fr Ophthalmol. 2000;23:773-780.
93. Bezci Aygün F, Mocan MC, Kocabeyoğlu S, İrkeç M. Efficacy of 180° Cyclodiode Transscleral Photocoagulation for Refractory Glaucoma. Turk J Ophthalmol. 2018;48:299-303.
94. Neely DE, Plager DA. Endocyclophotocoagulation for management of difficult pediatric glaucomas. J AAPOS. 2001;5:221-229.
95. Sood S, Beck A. Cyclophotocoagulation versus sequential tube shunt as a secondary intervention following primary tube shunt failure in pediatric glaucoma. J AAPOS. 2009;13:379-383.

DOI: 10.4274/tjo.galenos.2019.13333
Turk J Ophthalmol 2019;49:356-360

Case Report

Sutureless Amniotic Membrane Transplantation in a Pediatric Patient with Acute Toxic Epidermal Necrolysis

Zeynep Baş, Ömür Uçakhan Gündüz

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

Abstract

The purpose of this case report is to describe a new surgical method for sutureless placement of the amniotic membrane with a symblepharon ring in a pediatric patient with acute toxic epidermal necrolysis (TEN). A 1-year-old girl developed severe ocular surface inflammation with large corneal and conjunctival epithelial defects secondary to TEN. She was treated by applying a large (4 cm x 4 cm) amniotic membrane graft and non-sterile symblepharon ring under sedoanalgesia at bedside in the intensive care unit. The ocular surface was completely epithelized by post-treatment week 6 in the right and week 8 in the left eye. Two years after amniotic membrane transplantation, both eyes were quiet with no symblepharon, scar formation, or limbal stem cell deficiency. Performing bilateral amniotic membrane transplantation under a symblepharon ring at bedside provided sufficient acute coverage of the ocular surface and led to excellent clinical outcomes by reducing inflammation and protecting the ocular surface.

Keywords: Amniotic membrane transplantation, dry eye, ocular surface, toxic epidermal necrolysis

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are severe adverse drug reactions that predominantly involve the skin and mucous membranes. They are considered to be two ends of the same spectrum, differing only by their extent of skin detachment. Both are rare diseases, with an approximate incidence of 1 to 2 per 1,000,000 annually.[1] SJS and TEN are both immune-mediated diseases caused by cytotoxic CD8+T lymphocyte response. The histopathology of SJS/TEN lesions shows that T cells respond via interferong and Fas ligand pathway, leading to keratinocyte apoptosis. Drugs are identified as the main cause of SJS and TEN in most cases, but *Mycoplasma pneumoniae* and herpes simplex virus infections are also well documented causes. Genetic background may also have an impact on risk of developing SJS/TEN. Recently, associations between HLA genotypes and drug hypersensitivity have been demonstrated in various ethnic groups.[2] Chung et al.[3] described strong relationships between HLA-B1502 and carbamazepine, HLA-B5801, and allopurinol.

SJS and TEN are severe and life-threatening diseases with an estimated mortality rate of 1-5% for SJS and 25-35% for TEN.[4] Clinical findings include a prodromal symptom of fever and malaise, followed by the development of generalized, tender cutaneous eruptions. Common ocular manifestations of TEN include conjunctivitis, as well as conjunctival and corneal

Address for Correspondence: Zeynep Baş MD, Ankara University, Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone:+90 543 449 88 97 E-mail: zeynepbs2003@yahoo.com **ORCID-ID:** orcid.org/0000-0002-8172-0477
Received: 20.06.2018 **Accepted:** 10.09.2019

Cite this article as: Baş Z, Uçakhan Gündüz Ö. Sutureless Amniotic Membrane Transplantation in a Pediatric Patient with Acute Toxic Epidermal Necrolysis. Turk J Ophthalmol. 2019;49:356-360

epithelial defects and ulcerations secondary to conjunctival inflammation. Goblet cells, lacrimal ducts, and meibomian glands may be damaged.[5] If left untreated, these acute changes may ultimately lead to recurrent or persistent corneal epithelial defects and symblepharon formation. Severe dry eye and limbal stem cell deficiency may subsequently develop in the chronic stage.[6] The ongoing inflammatory process on the ocular surface tends to be relentless and prolonged even after the patients are discharged from the hospital.[7] Although intervention in the acute stage has more favorable ocular outcomes, treatments also exist for the chronic sequelae of SJS and TEN. Patients with SJS/TEN are poor candidates for traditional penetrating keratoplasty due to the development of cicatrizing lid disorders and severe ocular surface diseases. For these patients, limbal allografting and Boston keratoprosthesis may provide some visual recovery despite limbal stem cell deficiency and corneal conjunctivalization.[8]

Early evaluation and treatment of patients with SJS and TEN are critical. Recent literature data show that amniotic membrane transplantation (AMT) can suppress inflammation and facilitate healing if done in the acute phase of TEN.[7,9,10] The amnion has immunomodulatory effects and promotes epithelialization. The amnion's anti-inflammatory mechanism of action may be due to downregulation of inflammatory cytokines released by activated lymphocytes and promotion of leukocyte apoptosis.[11]

Various AMT techniques have been described previously, as traditional AMT is a time-consuming and a laborious surgery that is difficult to perform on patients who are unstable for surgical interventions because of systemic complications. It should also be taken into account that extensive eyelid sloughing in these patients makes the surgical area unfit for traditional AMT, and multiple surgeries are needed. Recently, a sutureless amniotic membrane fixation method was described, which utilized different materials to secure the membrane in the fornices. Ma et al.[12] described a technique for sutureless application of amniotic membrane in SJS patients using sterile intravenous tubing. Kara.[13] utilized a feeding tube to make a modified ocular surface ring in a chemical ocular surface burn patient.

In this case report, we describe a method for sutureless placement of amniotic membrane on the bulbar and palpebral conjunctiva that has been previously used for acute ocular burns but is novel in the setting of ocular TEN.[14] To the best of our knowledge this is the first report documenting the use of this novel technique in a TEN patient.

Case Report

A 1-year-old girl was admitted to the Ankara University Pediatric Emergency Department with the suspicion of TEN. Her history revealed that she had received a measles, mumps, and rubella vaccine 13 days before admission. The day after vaccination, she developed seizures and was transferred to another pediatric emergency department. Under suspicion of febrile convulsion, she was treated with phenobarbital, levetiracetam, and cefuroxime. Seizure did not recur, and on day 9 she was discharged from the hospital. Three days after initiation of treatment, the patient developed a raised, maculopapular rash on her body, together with mucosal involvement. She was admitted to the Ankara University Pediatric Infection Unit with suspected Stevens-Johnson Syndrome. Upon admission, the anticonvulsant medications were discontinued and she was started on intravenous (IV) prednisolone 2 mg/kg/day and IV immunoglobulin 2 g/kg/day. On her second day in hospital, she was evaluated by the ophthalmology unit. On examination at bedside, the patient was observed to have severe bilateral bulbar and palpebral conjunctival inflammation, desquamation, and epithelial defects. The corneal epithelial defects measured 1x1 mm in the right eye and 7x8 mm in the left eye (Figure 1). The patient was started on aggressive lubrication with preservative-free artificial tears, as well as cyclosporine ophthalmic emulsion 0.05% (Restasisâ, Allergan, Ireland) and loteprednol ophthalmic suspension 0.5% (Lotemaxâ, Bausch&Lomb, USA) 4 times a day to both eyes.

The patient remained in critical condition, which prevented her from leaving the pediatric unit for surgery. During this period, it was noted that her systemic condition was worsening despite systemic treatment, so she was treated with infliximab (Remicadeâ, Essex GmbH, Germany) 5 mg/kg as single-shot therapy. The patient's severe clinical condition, intense laryngeal desquamation, and edema precluded her from receiving general anesthesia. On post-admission day 3, it was decided to perform AMT at bedside under sedoanalgesia. The placenta was retrieved intact and processed under sterile conditions. The chorioamnion was stripped from the placenta, and following antibiotic decontamination, the amniotic membrane was separated from the chorion, cut into 4-cm squares and mounted on nitrocellulose backing paper as previously described.[15] After instilling 1 drop of proparacaine (Alcaine®, Alcon, USA), the amniotic membrane was spread onto the ocular surface epithelial side up. Since there was severe epidermal desquamation, we had difficulty even holding the eyelids open and instead of securing the amniotic membrane with sutures, a symblepharon ring was gently placed on the ocular surface in the superior and inferior fornix. The symblepharon ring (open fornix conformer) was chosen according to the height of palpebral apertures and was big

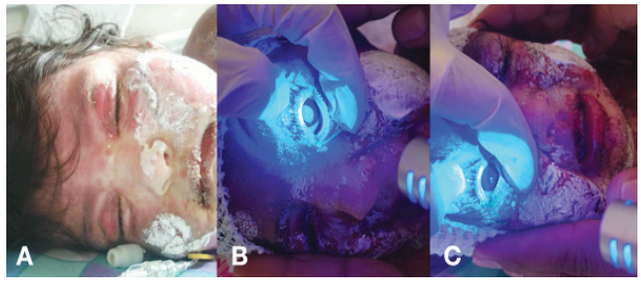


Figure 1. Ocular manifestations of acute toxic epidermal necrolysis: A) Sloughing and erythema on eyelid skin; B) Fluorescein-stained corneal epithelial defect; C) Eyelid margin sloughing and conjunctival injection

enough to safely sit in the fornices. It was made of polymethyl methacrylate and had a diameter of 18 mm (IMKA, Ankara, Turkey) (Figure 2). The rest of the membrane was tucked into the palpebral conjunctiva using forceps and the excess was trimmed with Westcott scissors. The same procedure was performed on the contralateral eye. Postoperatively, moxifloxacin 0.5% (Vigamox®, Alcon, USA) 4 times a day and tacrolimus ointment 0.03% (Protopic®, Astellas, USA) 2 times a day were added to topical treatment.

On postoperative day 3, the amniotic membranes and symblepharon rings were still in place (Figure 3). Disintegration of the amniotic membrane was noticed and the procedure was repeated on both eyes on day 7 (Figure 4). The patient was seen 1 month later. Her systemic condition was stable, so she was examined under general anesthesia. Examination of her right eye on day 37 showed the corneal defect was healed and the tarsal conjunctiva was epithelized, and a bandage contact lens (Pure Vision, Bausch & Lomb, USA) was applied. In the left eye, the symblepharon ring and the old disintegrated membrane were removed, and a 7x7 mm persistent corneal epithelial defect was observed. Peripheral keratectomy was performed and a new amniotic membrane was sutured onto the cornea using 10-0 nylon sutures, and a bandage contact lens was placed (Figure 5). The corneal defect in the left eye was healed on day 53 and remained that way through the remainder of the follow-up. The patient was kept on cyclosporine, tacrolimus, artificial tears and ointments for 3 months, followed by tapering of all medications. At postoperative 6 months, there was no ectropion and the conjunctival fornices were preserved without residual inflammation in both eyes. There was mild corneal haze in left eye (Figure 6). At 2-year follow-up, both corneas were clear with no residual scars (Figure 7). No other scarring sequelae occurred.

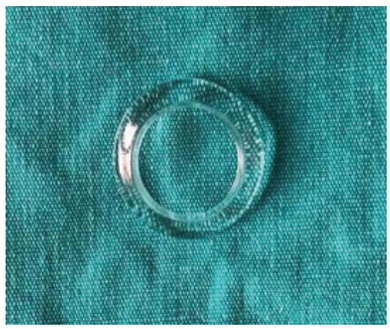


Figure 2. Small non-sterile symblepharon ring, size 18 mm, polymethyl methacrylate (IMKA, Ankara, Turkey)

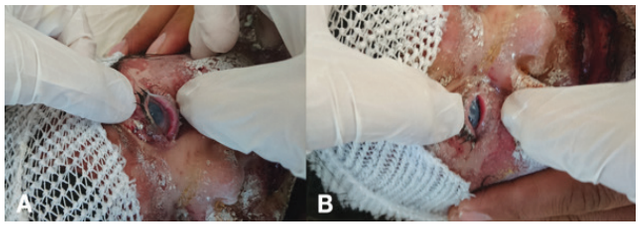


Figure 3. Postoperative day 3: Amniotic membranes wrapped around a symblepharon ring in the A) Right eye and B) Left eye

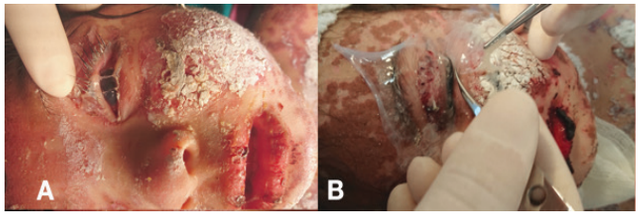


Figure 4. Postoperative day 7: A) Amniotic membrane has begun to erode on the left side; B) Amniotic membrane transplantation was repeated at bedside with the same procedure on both eyes

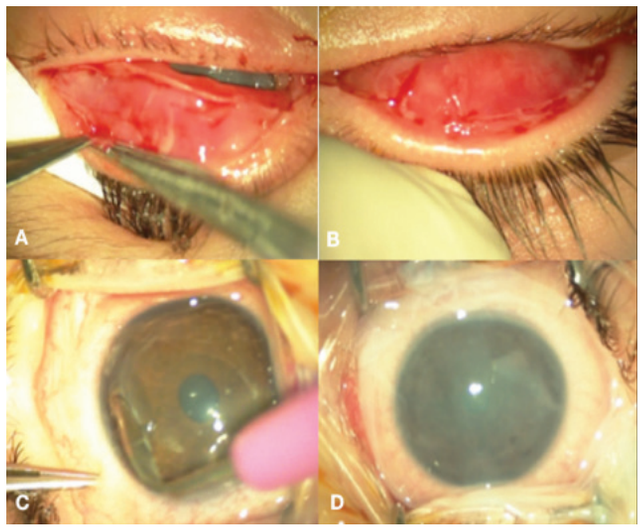


Figure 5. Postoperative 1 month, examination under general anesthesia: Epithelization has begun on the A) left and B) right palpebral conjunctiva. In the left eye, C) peripheral keratectomy was performed and D) amniotic membrane transplantation was repeated for the third time, this time under general anesthesia

Figure 6. At 6-month follow up, the patient had grade 1 corneal haze in her left eye

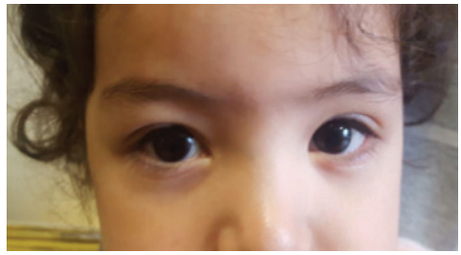


Figure 7. At 2-year follow-up, the patient exhibited no corneal haze or other sequelae

Discussion

Toxic epidermal necrolysis is a severe immunologic dermatobullous condition with high morbidity and mortality. It is characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes. It exists on the same spectrum as SJS, but is characterized by more than 30% body surface area detachment.[16] It is believed that drugs or metabolites, acting as receptors, bind to surface of keratinocytes and cause them to become antigenic and stimulate cytotoxic CD8+T cell response.[17] In our case, the immune reaction was considered to be triggered by the use of phenobarbital. SJS and TEN have long been associated with the administration of barbiturates, with the greatest risk occurring within the first two months of treatment.[4]

The incidence of TEN is very low but the ocular sequelae can be blinding. Rapid recognition and prompt withdrawal of the offending drug is essential. The main clinical presentations are conjunctival inflammation, keratinization of the ocular surface, and symblepharon formation. Recent literature data indicate that early intervention with AMT in the hyperacute phase gives better long-term results in terms of ocular surface and forniceal stability.[7,10] Amniotic membrane suppresses inflammation, prevents ulcer formation, and promotes healing of the ocular surface.[11] A delay in the treatment may result in corneal stem cell deficiency and sight-threatening cicatricial complications.[18] However, securing the amniotic membrane onto the ocular surface with sutures at bedside in intensive care units is technically difficult and poses several challenges.[7] Anchoring the amniotic membrane requires complex and time-consuming suturing of multiple amnion pieces to the eyelids, fornix, and limbus that requires bolsters and stitch removal from the patient's eyelids and ocular surface. In order to address some of these problems, sutureless techniques in SJS patients have been published recently by Shay et al.[7], Pruet et al.[9], Cheung et al.,[10] and Ma et al.[12] Cheung et al.[10] used specially made symblepharon rings that are not commercially available and hard to find, possibly causing operations to be delayed. Shay et al.[7] utilized ProKera rings, but the diameter of the ProKera only covers the cornea and perilimbal conjunctiva, thus making the fornices vulnerable to symblepharon formation.[19] Ma et al.[12] employed an intravenous tube, but the circular shape of the tube may not be an adequate fit for the oval contour of the fornices.

Our technique minimized symblepharon formation because of increased coverage of the amnion membrane thanks to the broad shape of the symblepharon rings. Symblepharon rings are effective in keeping the fornices intact in conjunctival cicatricial diseases. The ring prevents adhesions and forniceal contractures without touching the cornea. Liang et al.[14] used a similar sutureless technique on burn patients and reported higher reepithelialization rates, shorter operation time, and lower symblepharon rates in the sutureless AMT group. To our knowledge, this technique was never performed in patients with SJS/TEN.

Patients with acute TEN often do not receive AMT during the hyperacute phase because of the lack of standardized protocol, high mortality risk associated with general anesthesia, and difficulty in performing this extensive surgery. Our technique can be performed at the bedside without the need for general anesthesia or operating room conditions. This minimizes the delay in AMT and is less invasive for the patient. In addition, amniotic membrane coverage of the entire conjunctival surface is crucial to maximizing benefit; therefore, patients undergoing traditional AMT only to the bulbar conjunctiva may still develop chronic sequelae of SJS and TEN. A possible disadvantage is that the amniotic membrane and ring may come loose from the fornices. However, the simplicity of the method allows easy manipulation of the membrane.

In the absence of banked cryopreserved amnion and due to the pressing nature of the patient's condition, we decided to use fresh amniotic membrane. There may be a number of disadvantages to this, the most important being the theoretical risk of disease transmission. Another difficulty is the need to find a suitable donor fast enough in advance of surgery to allow processing and testing and coordination with the obstetrics and gynecology department.[15] No such problems arose in our case.

The use of a symblepharon ring with amniotic membrane to cover the ocular surface and fornices without the use of sutures or tissue glue as described herein is fast, nontraumatic, technically easy, and seems to yield final outcomes comparable to those achieved with conventional AMT methods. The results of this study are in agreement with recently published reports that AMT performed in the acute phase of TEN is vital to prevent sight-threatening cicatrizing sequelae associated with ocular manifestations of the disease.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zeynep Baş, Ömür Uçakhan Gündüz, Concept: Zeynep Baş, Ömür Uçakhan Gündüz, Design: Zeynep Baş, Ömür Uçakhan Gündüz, Data Collection or Processing: Zeynep Baş, Ömür Uçakhan Gündüz, Analysis or Interpretation: Zeynep Baş, Ömür Uçakhan Gündüz, Literature Search: Zeynep Baş, Ömür Uçakhan Gündüz, Writing: Zeynep Baş, Ömür Uçakhan Gündüz,

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. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010;5:39.
2. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, Bouwes-Bavinck JN, Sidoroff A, de Toma C, Schumacher M, Roujeau JC, Hovnanian A, Mockenhaupt M; RegiSCAR study group. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics. 2008;18:99-107.

3. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004;428:486.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272-1285.
5. Di Pascuale MA, Espana EM, Liu DT, Kawakita T, Li W, Gao YY, Baradaran-Rafii A, Elizondo A, Raju VK, Tseng SC. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. Ophthalmology. 2005;112:904-912.
6. Catt CJ, Hamilton GM, Fish J, Mireskandari K, Ali A. Ocular Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children. Am J Ophthalmol. 2016;166:68-75.
7. Shay E, Khadem JJ, Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrolysis. Cornea. 2010;29:359-361.
8. Sayegh RR, Ang LP, Foster CS, Dohlman CH. The Boston keratoprosthesis in Stevens-Johnson syndrome. Am J Ophthalmol. 2008;145:438-444.
9. Pruet CM, Queen JH, Kim G. Amnion doughnut: a novel method for sutureless fixation of amniotic membrane to the bulbar and palpebral conjunctiva in acute ocular-involving Stevens-Johnson syndrome. Cornea. 2014;33:1240-1244.
10. Cheung CS, Ali A, Chew HF. Successful Treatment of Acute Ocular-Involving Toxic Epidermal Necrolysis Using Amniotic Membrane Suture Fixated to Custom Designed Symblepharon Rings. Cornea. 2016;35:578-581.
11. Park CY, Kohanim S, Zhu L, Gehlbach PL, Chuck RS. Immunosuppressive property of dried human amniotic membrane. Ophthalmic Res. 2009;41:112-113.
12. Ma KN, Thanos A, Chodosh J, Shah AS, Mantagos IS. A Novel Technique for Amniotic Membrane Transplantation in Patients with Acute Stevens-Johnson Syndrome. Ocul Surf. 2016;14:31-36.
13. Kara N. Sutureless amniotic membrane transplantation with a modified ocular surface ring. Can J Ophthalmol. 2018;53:46-48.
14. Liang X, Liu Z, Lin Y, Li N, Huang M, Wang Z. A modified symblepharon ring for sutureless amniotic membrane patch to treat acute ocular surface burns. J Burn Care Res. 2012;33:32-38.
15. Adds PJ, Hunt CJ, Dart JK. Amniotic membrane grafts, «fresh» or frozen? A clinical and in vitro comparison. Br J Ophthalmol. 2001;85:905-907.
16. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. Allergol Int. 2006;55:9-16.
17. Abe R. Immunological response in Stevens-Johnson syndrome and toxic epidermal necrolysis. J Dermatol. 2015;42:42-48.
18. Tomlins PJ, Parulekar MV, Rauz S. «Triple-TEN» in the treatment of acute ocular complications from toxic epidermal necrolysis. Cornea. 2013;32:365-369.
19. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. Ophthalmology. 2011;118:908-914.

DOI: 10.4274/tjo.galenos.2019.55889
Turk J Ophthalmol 2019;49:361-363

Case Report

Tuberculosis: A Cunning Disease Presenting with Endopericarditis-Associated Bilateral Uveitis

Gholam Hossein Yaghoubi*, Farshid Abedi**, Masoud Ziaee**, Amir Norouzpour***

*Birjand University of Medical Sciences, Department of Ophthalmology, Birjand, Iran
**Birjand University of Medical Sciences, Department of Infectious Diseases, Birjand, Iran
***Shiraz University of Medical Sciences, Poostchi Ophthalmology Research Center, Shiraz, Iran

Abstract

Mycobacterium tuberculosis can spread through the entire body but rarely involves the eye. We report a patient with endophthalmitis in one eye and simultaneous retinal vasculitis in the fellow eye. Systemic work-up suggested infective endopericarditis. Polymerase chain reaction analyses of the vitreous and pericardial fluid were positive for *M. tuberculosis*. We initiated a four-drug antituberculous treatment regimen (isoniazid, ethambutol, pyrazinamide, and rifampin). After two weeks, we discontinued all the medications due to drug-induced hepatitis. We restarted isoniazid and rifampin, but hepatitis recurred. Finally, we chose isoniazid/ethambutol combination for 18 months, and also administered short-term systemic corticosteroid. His vision improved considerably with no recurrence of hepatitis or tuberculosis for 3 years after completion of treatment. Ocular tuberculosis can masquerade as other causes of intraocular inflammation, and a medical team consisting of an ophthalmologist and an infectious disease specialist might be needed for the diagnosis and management.

Keywords: Tuberculosis, endophthalmitis, endocarditis, pericarditis, polymerase chain reaction (PCR)

Introduction

Tuberculosis (TB) is a noticeable public health problem with an increasing incidence in recent years. TB can either be restricted to one organ, most commonly the lung, or spread throughout the body, involving multiple organs.[1] Ocular TB is a rare presentation of extrapulmonary TB which accounts for 0.2-18% of TB cases, depending on the geographic area.[2] Almost all parts of the eye can be involved, but the most common manifestations are chronic uveitis, choroiditis, and keratitis.[3] It occasionally mimics intraocular malignancies or other causes of ocular inflammation.[4] It needs a high clinical suspicion to be diagnosed as early as possible before any permanent visual loss occurs. In this case report, we present a patient with endogenous endophthalmitis in one eye and retinal vasculitis in the fellow eye, most probably resulting from *Mycobacterium tuberculosis*-induced infective endopericarditis.

Case Report

A 45-year-old man presented to our hospital with subacute low-grade fever, malaise, and myalgia. A few days after admission for sepsis work-up, the vision in both his eyes gradually blurred within a few days of each other. His medical and ocular history was unremarkable. Visual acuity was 20/400 in his right eye and 20/630 in the left eye. The right eye had moderate

Address for Correspondence: Asst. Prof. Amir Norouzpour, M.D., Shiraz University of Medical Sciences, Poostchi Ophthalmology Research Center, Shiraz, Iran
Phone:0901 250 9856 E-mail: anorouzpour@gmail.com **ORCID-ID**: orcid.org/0000-0002-7175-1536
Received: 15.05.2019 **Accepted:** 19.08.2019

Cite this article as: Yaghoubi GH, Abedi F, Ziaee M, Norouzpour A. Tuberculosis: A Cunning Disease Presenting with Endopericarditis-Associated Bilateral Uveitis. Turk J Ophthalmol. 2019;49:361-363

nuclear sclerosis, retinal vasculitis, and Roth spots (Figure 1a). The left eye had ciliary injection of the conjunctiva, corneal stromal edema, dense cells and flare in the anterior chamber, and posterior synechiae (Figure 1b). The vitreous was hazy, and a blurred view of the fundus without retinal detachment was obtained. Endogenous endophthalmitis in the left eye was suspected; therefore, vitreous aspiration as well as intravitreal vancomycin (1 mg/0.1 mL) and amikacin (0.4 mg/0.1 mL) injection were performed. Vitreous, blood, and urine cultures were all negative, but vitreous polymerase chain reaction (PCR) analysis was positive for *M. tuberculosis* (Figure 1c). The results from a complete systemic work-up were positive for an elevated erythrocyte sedimentation rate and C-reactive protein, but negative for HIV infection. A chest roentgenogram showed no significant pathologic changes at initial presentation. Whole-body bone scintigraphy was noncontributory other than mild right sternoclavicular arthritis. Echocardiography showed a large (15x15 mm) mobile mass in the left atrial side of the mitral valve with severe mitral regurgitation. Infective endocarditis was suspected, and mitral valve replacement surgery was performed. Pericardial fluid had high levels of lactate dehydrogenase and adenosine deaminase with normal levels of protein and glucose. Pericardial fluid PCR was positive for *M. tuberculosis,* but culture was negative. Pericardial biopsy showed chronic fibrohistiocytic reaction with no dysplastic changes. A four-drug antituberculous treatment regimen (isoniazid, ethambutol, pyrazinamide, and rifampin) was started. After two weeks, the patient exhibited clinical signs of hepatitis, and serum aspartate aminotransferase and alanine aminotransferase levels were elevated up to four times higher than normal. We discontinued all the anti-TB medications, after which the hepatitis resolved. We restarted only isoniazid and rifampin, but the hepatitis recurred. We discontinued the medications again until hepatic enzyme levels returned to within normal range. Serology for viral hepatitis was negative. We then chose the combined isoniazid/ethambutol regimen. There was no recurrence of hepatitis this time, and liver enzyme levels remained within normal range. We administered short-term systemic corticosteroid to reduce the risk of mortality and prevent progression to constrictive pericarditis. His vision returned to 20/25 in the right eye and 20/32 in the left eye two months after the treatment was initiated. The two-drug regimen was continued for 18 months. No systemic relapse has occurred during the intervening 3-year follow-up period, and his vision has remained unchanged.

Discussion

M. tuberculosis can involve any organ, but most commonly affects the lung. It can also involve any part of the eye. TB can invade the eye either as a primary or secondary infection. Primary infection is usually limited to the conjunctiva and cornea, but secondary infection is more widespread, resulting from either contiguous spread from an adjacent tissue or hematogenous spread. The most common ocular manifestations in secondary infections are chronic uveitis, choroiditis, and keratitis.[3] Panophthalmitis, endophthalmitis, and vitritis have also been reported.[5] Here, we presented a case with endophthalmitis in one eye and simultaneous retinal vasculitis in the fellow eye.

Diagnosis of ocular TB is a challenging issue for ophthalmologists.[2] A negative smear for acid-fast bacilli, failure to culture the bacilli, and lack of necrotizing granulomas on histopathology specimen do not, however, exclude the diagnosis of TB. The tuberculin skin test, interferon gamma release assays, and chest roentgenograms might not be helpful for diagnosis of ocular TB.[6] PCR has been a robust diagnostic technique particularly for ocular TB since it requires only a small sample with no need for the cells to be viable.[7] Although vitreous culture was negative in our case, vitreous PCR was positive for *M. tuberculosis*.

TB endophthalmitis is a rare intraocular inflammation which usually results from hematologic spread of a lung or central nervous system infection.[5] However, the pulmonary foci might not be clear clinically or radiographically. It has been reported that even up to 60% of extrapulmonary TB might not have pulmonary disease.[8] In our case, we did not find a primary source for TB infection other than the heart. Serial chest roentgenograms did not show any remarkable changes typical

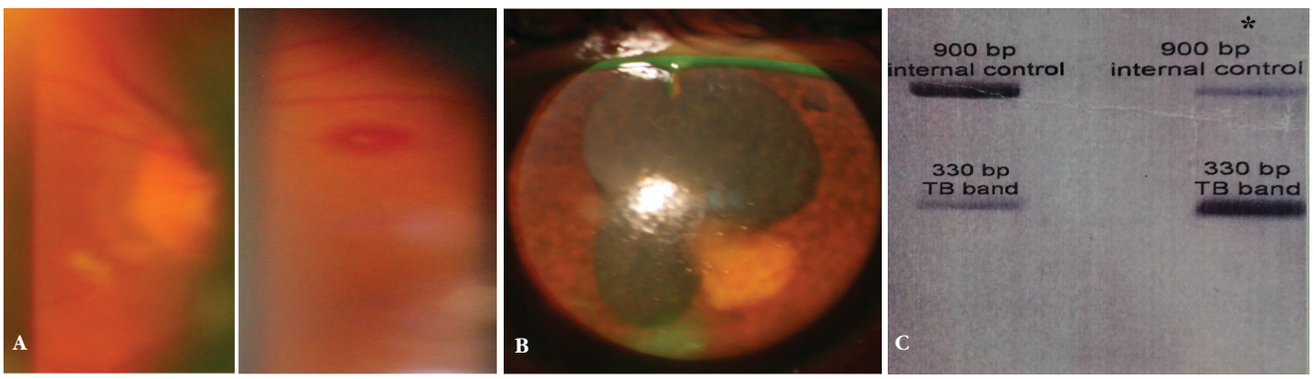


Figure 1. Clinical examination findings and polymerase chain reaction (PCR) results of the patient. **A)** Fundus examination of the right eye shows retinal vasculitis and a Roth spot which are distributed over the entire retina. **B)** Slit-lamp biomicroscopy of the left eye shows corneal stromal edema, intense anterior chamber reaction, posterior synechiae, and an iris granuloma close to the posterior synechia. **C)** PCR result from vitreous tap was positive for *M. tuberculosis*. The positive control is in the right column, shown with an asterisk sign (*)

of TB infection other than mild pulmonary edema with pleural effusion. Pleural as well as cerebrospinal fluid PCR analyses were negative for *M. tuberculosis*. On the other hand, TB has been reported to affect the pericardium,[9] myocardium,[10] endocardium, and valvular structures.[11] In our case, the ocular manifestations were most probably secondary to hematologic spread of infective endopericarditis. Pericardial fluid PCR was positive for *M. tuberculosis*, supporting our hypothesis.

The main therapeutic challenges in TB infections are patient compliance and the increasing incidence of drug resistance. Because TB is endemic in Iran, the prevalence of drug resistance might be high. A bacteriologic sensitivity test could help us to find the most appropriate therapeutic regimen for our case; however, we empirically chose the four-drug regimen (isoniazid, ethambutol, pyrazinamide, and rifampin) for the initial phase. This antibiotic combination has been effective in most TB cases in our general hospital. Systemic corticosteroid administration to patients with presumed ocular TB or tuberculous pericardial effusion remains controversial.[9] It may reduce mortality in HIV-negative patients, but it might lead to recurrence of ocular inflammation,[12] and the effects on preventing progression to constrictive pericarditis remain obscure.[13] We administered short-term systemic corticosteroid to our patient and obtained a favorable clinical response with no recurrence for 3 years after completion of treatment.

Response to treatment as well as drug toxicity are monitored clinically and sometimes using laboratory techniques. Our patient showed clinical improvement in the first 2 weeks after the initial regimen was started, but the occurrence of hepatitis did not allow us to continue the quadruple regimen. Hepatotoxicity is the most common adverse effect of anti-TB medications. Serum liver enzyme levels and liver function should be monitored, and the patients should be educated about the symptoms and signs of the hepatotoxicity. Isoniazid, pyrazinamide, and ethambutol are potentially hepatotoxic. They are all metabolized in the liver and might interact with each other as well as other drugs, leading to a higher risk of hepatotoxicity. In our case, hepatotoxicity was resolved after discontinuation of all the anti-TB medications. Pyrazinamide seems to be the most hepatotoxic agent in the quadruple regimen we chose, while the risk of isoniazid-induced hepatitis seems to be lower than previously thought.[14] We restarted isoniazid/rifampin, but hepatitis recurred. After the resolution of hepatitis, we empirically started the combined isoniazid/ethambutol regimen. Hepatitis did not recur with this new regimen, and we continued it for 18 months. Rifampin or isoniazid/rifampin combination was suspected as the cause of hepatitis in our patient. Clinical response to the combined isoniazid/ethambutol regimen was favorable and his vision was considerably improved two months after initiating the treatment.

Conclusion

Ocular TB is a great mimicker of various forms of intraocular inflammation. Our case showed that we should suspect TB in any case with intraocular inflammation, particularly in TB-endemic areas. Systemic signs and symptoms encourage us to search for a primary source of TB, whether pulmonary or extrapulmonary. A medical team consisting of an ophthalmologist and an infectious disease specialist might be needed for the diagnosis and management of ocular TB.

Ethics

Informed Consent: İnformed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Gholam Hossein Yaghoubi, Farshid Abedi, Masoud Ziaee, Concept: Gholam Hossein Yaghoubi, Farshid Abedi, Design: Gholam Hossein Yaghoubi, Farshid Abedi, Data Collection or Processing: Amir Norouzpour, Analysis or Interpretation: Amir Norouzpour, Literature Search: Amir Norouzpour, Writing: Amir Norouzpour

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. Raviglione MC, O'Brien RJ. Tuberculosis. In: Fauci AS, Braunwald E, Isselbacher KJ, (eds). Harrison's Principle of Internal Medicine (14th ed). New York: McGraw-Hill; 1998:1004-1014.
2. Alvarez GG, Roth VR, Hodge W. Ocular tuberculosis: diagnostic and treatment challenges. Int J Infect Dis. 2009;13:432-435.
3. Shakarchi FI. Ocular tuberculosis: current perspectives. Clin Ophthalmol. 2015;9:2223-2227.
4. Demirci H, Shields CL, Shields JA, Eagle RC Jr. Ocular Tuberculosis Masquerading As Ocular Tumors. Surv Ophthalmol. 2004;49:78-89.
5. Sheu SJ, Shyu JS, Chen LM, Chen YY, Chirn SC, Wang JS. Ocular Manifestations of Tuberculosis. Ophthalmology. 2001;108:1580-1585.
6. Venkatesh P. Retina and the tubercle Bacillus: Four decades of our journey and current understanding. Indian J Ophthalmol. 2017;65:122-127.
7. Mehta PK, Raj A, Singh N, Khuller GK. Diagnosis of extrapulmonary tuberculosis by PCR. FEMS Immunol Med Microbiol. 2012;66:20-36.
8. Alvarez S, McCabe WR. Extrapulmonary tuberculosis revisited: a review of experience at Boston City and other hospitals. Medicine (Baltimore). 1984;63:25-55.
9. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous Pericarditis. Circulation. 2005;112:3608-3616.
10. Silingardi E, Rivasi F, Santunione AL, Garagnani L. Sudden death from tubercular myocarditis. J Forensic Sci. 2006;51:667-669.
11. Liu A, Nicol E, Hu Y, Coates A. Tuberculous Endocarditis. Int J Cardiol. 2013;167:640-645.
12. Gupta V, Gupta A, Arora S, Bambery P, Dogra MR, Agarwal A. Presumed tubercular serpiginous like choroiditis: clinical presentation and management. Ophthalmology. 2003;110:1744-1749.
13. Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, Pandie S, Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2017;9:CD000526.
14. Arbex MA, Varella Mde C, Siqueira HR, Mello FA. Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 1: First-line drugs. J Bras Pneumol. 2010;36:626-640.

DOI: 10.4274/tjo.galenos.2019.50460
Turk J Ophthalmol 2019;49:364-366

Case Report

The Relationship Between Vasoproliferative Tumor and Uveitis in a Multiple Sclerosis Patient: A Case Report and Review of the Literature

Onur Özalp, Eray Atalay, Mustafa Değer Bilgeç, Nazmiye Erol, Nilgün Yıldırım

Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey

Abstract

Vasoproliferative retinal tumor (VPRT) is a rare, benign lesion with a variable clinical course depending on the individual. Favorable outcomes are obtained with early diagnosis and treatment of patients with VPRT. In this case report, we present a case of concomitant VPRT and multiple sclerosis along with our management of uveitis and secondary glaucoma that presumably developed following cryotherapy for VPRT.

Keywords: Vasoproliferative tumor, cryotherapy, uveitis, multiple sclerosis

Introduction

Vasoproliferative retinal tumors (VPRTs) are rare, benign tumoral lesions whose pathogenesis has not been fully explained.[1] These lesions, which appear as elevated, yellowish-pink, vascularized masses on fundus examination, are frequently located in the pre-equatorial or equatorial region of the inferior retina, especially in the 5-7 o'clock segment.[2]

VPRTs can occur as primary (74%) or secondary (26%) tumors, whit primary tumors usually being solitary while secondary tumors may be multiple.[1] Secondary tumors may occur in ocular pathologies such as intermediate uveitis, retinitis pigmentosa, Coats disease, neurofibromatosis, retinopathy of prematurity, and familial exudative vitreoretinopathy.[1,3]

VPRTs can cause intraretinal or subretinal hemorrhage, vitreous hemorrhage, intraretinal or subretinal exudation, and hyperpigmentation of the retinal pigment epithelium.[2] These sight-limiting conditions can be prevented with early diagnosis of VPRT and appropriate treatment.[2]

The purpose of this article is to present a case report of concomitant VPRT and multiple sclerosis along with our management of uveitis and secondary glaucoma that presumably developed following cryotherapy for VPRT.

Case Report

A 33-year-old man who presented with low vision in his right eye lasting 6 days was referred to our clinic from another center with the suspicion of serous retinal detachment. His history revealed that he had been diagnosed with MS 7 years earlier and had been treated with intramuscular interferon beta 1a therapy [Avonex®, 30 µg (6 million IU) once a week] for 2 years at another center. After developing side effects to the drug, he was followed without medical treatment. His best corrected visual acuity (BCVA) was measured as 0.1 in the right eye and

Address for Correspondence: Nilgün Yıldırım, Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
Phone:+90 542 422 39 09 E-mail: nyyildirim@yahoo.com **ORCID-ID:** orcid.org/0000-0001-8198-2605
Received: 03.07.2019 **Accepted:** 09.08.2019

Cite this article as: Özalp O, Atalay E, Bilgeç MD, Erol N, Yıldırım N. The Relationship Between Vasoproliferative Tumor and Uveitis in a Multiple Sclerosis Patient: A Case Report and Review of the Literature. Turk J Ophthalmol. 2019;49:364-366

1.0 in the left eye with Snellen chart. The anterior segment was normal in both eyes on slit-lamp examination. Intraocular pressure (IOP) was measured as 14 mmHg bilaterally using a pneumotonometer. Fundus examination revealed a raised pink mass and severe exudation in the inferior retina of the right eye and sporadic atrophic chorioretinal areas in the left eye (Figure 1A). Optical coherence tomography (OCT) revealed serous detachment, brush border pattern, and an epiretinal membrane over the fovea. Fundus fluorescein angiography showed a hyperfluorescent area in the inferotemporal periphery consistent with the raised lesion base, ponding associated with exudative detachment extending to the macula, leakage of the peripheral vessels, and hyperfluorescence of the optic disc in the right eye, while the left eye appeared normal (Figure 1B). The patient was diagnosed with VPRT and underwent cryotherapy using the double freeze technique. His BCVA 3 months after cryotherapy was counting fingers (CF) from 3 meters. Fundus examination revealed hard exudates and a mass in the inferior temporal region (Figure 2A) and OCT revealed subretinal fluid. As additional treatment, he underwent triple-freeze cryotherapy with simultaneous intravitreal anti-VEGF injection. At follow-up 3 months after treatment, his BCVA had improved to 0.1, fundus examination revealed that the mass had shrunk (Figure 2B), and OCT showed that the epiretinal membrane persisted but the subretinal fluid had resolved.

At 6 months after the last cryotherapy, the patient presented to the emergency department with pain in his right eye. His BCVA was again CF at 3 m in the right eye and 1.0 in the left eye. Slit-lamp examination revealed ciliary injection, cells in the anterior chamber (+++), iris bombe seclusio pupillae, and corneal edema in the right eye (Figure 3). The anterior segment of the left eye was normal. IOP measured by applanation tonometry was 35 mmHg in the right eye and 15 mmHg in the left eye. The patient was hospitalized with the suspicion of secondary angle-closure glaucoma. Two peripheral laser iridotomies were performed at the 1 and 11 o'clock positions. Topical mydriatic, antiglaucomatous, corticosteroid drops along with oral acetazolamide were initiated. Due to persistently elevated IOP during follow-up, trabeculectomy with 5-fluorouracil was performed. After 1 week, his IOP was 30 mmHg, so argon laser suturolysis was performed. The next day, his IOP was decreased to 20 mmHg. In his follow-up visit 2 months after trabeculectomy, visual acuity in the right eye was CF at 3 m, IOP was 20 mmHg, and slit-lamp examination revealed a functioning bleb, clear cornea, and deepened anterior chamber.

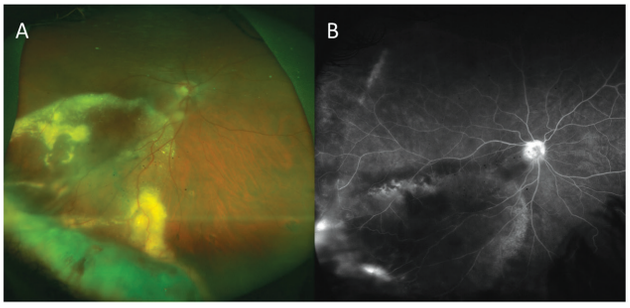


Figure 1. From the patient's initial presentation: **A)** color fundus photograph shows vasoproliferative retinal tumor and exudation; **B)** fundus fluorescein angiography reveals a hyperfluorescent area in the region corresponding to the raised lesion field in the inferotemporal region, leakage from peripheral vessels, and hyperfluorescence at the optic discs

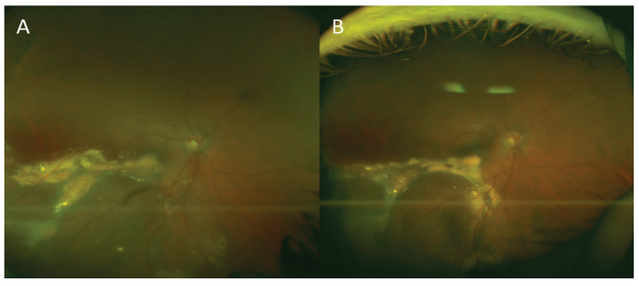


Figure 2. A) Appearance of vasoproliferative retinal tumor in color fundus photograph taken 3 months after the first cryotherapy; **B)** color fundus photograph at 3 months after the second cryotherapy shows the vasoproliferative retinal tumor is reduced in size

Discussion

Although it has no pathognomonic finding, suspicion of VPRT should arouse when a solitary mass with yellowish-pink appearance and vascularization is observed on fundus examination.[2] It is commonly observed between the ages of 40 and 60 years, with no significant difference in prevalence between men and women.[1] In a retrospective study, it was observed that VPRTs were most commonly located in the inferotemporal (42%) segment, followed by inferior (21%) and temporal (15%).[1]

It has been reported that primary VPRTs emerge at a later age, are often solitary and unilateral, and cause fewer symptoms.[4] In a retrospective study by Shields et al.[1], secondary VPRTs were most commonly associated with intermediate uveitis (28%), retinitis pigmentosa (21%), toxoplasma retinitis (7%), toxocariasis (7%), and traumatic chorioretinopathy (7%). When pediatric patients were evaluated, secondary VPRTs were again most often associated with intermediate uveitis.[5]

Intermediate uveitis is an ocular inflammatory syndrome characterized by minimal anterior segment reaction and

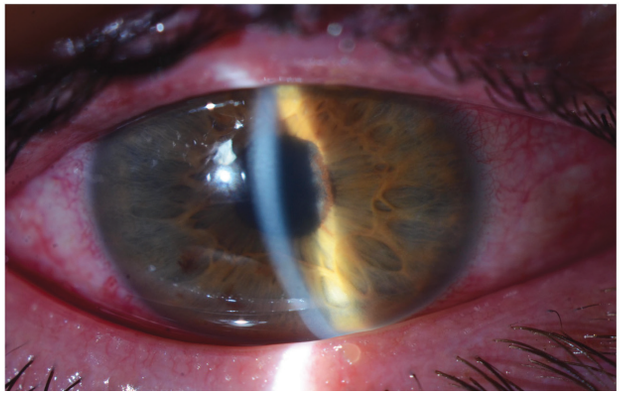


Figure 3. Anterior segment photograph of the patient at presentation for uveitic glaucoma shows ciliary injection, iris bombe, seclusio pupillae, and corneal edema

inflammatory cells and debris in the vitreous, and is often observed in children and young adults.[6] In a study by Ness et al.[7] including 159 cases of intermediate uveitis, most cases were idiopathic (58.5%), while MS was the leading known cause (19.5%). Other studies have also examined systemic diseases in patients with intermediate uveitis, with the prevalence of MS reported as 7% by Boskovich et al.[8] and 11% by Raja et al.[9] The relationship between MS and uveitis remains unclear; in one study evaluating MS patients, the prevalence of uveitis was found to be 0.52%, with intermediate and panuveitis being common forms.[10] In the same study, evaluation of complications in patients with intermediate uveitis showed that cataracts were most common, and glaucoma and retinal neovascularization were also observed.[10] In another study of patients with intermediate uveitis, the most common complications were cystoid macular edema, cataracts, and posterior synechia, and glaucoma was also noted.[11]

The pathogenesis of secondary VPRT associated with intermediate uveitis is believed to involve a reactive process against factors released into the environment with the emergence of uncontrolled proliferation of fibrous tissue and angiogenesis in the retina secondary to disruption of the blood-retina barrier.[2] On the other hand, it has also been suggested that the presence of intraocular inflammation and uveitis may be due to a reactive, or "spillover" phenomenon in which inflammatory cells leak from tumoral lesion vessels into the vitreous.[2]

If VPRTs are asymptomatic, they can be monitored without treatment. In symptomatic cases, treatment may involve photocoagulation, cryotherapy, laser brachytherapy, radiotherapy, photodynamic therapy, or anti-VEGF therapy. Vitreoretinal surgery can be performed in patients with vitreous hemorrhage.[1,3,12,13,14,15]

Of 160 patients with retinal detachment who underwent simultaneous cryotherapy and detachment surgery, 19 (12%) developed postoperative pigment shedding, while 7 (12%) of the 60 patients who did not undergo subretinal fluid drainage developed postoperative uveitis.[16] The same study reported that post-cryotherapy uveitis occurred in an average of 5-8 days.[16] Although our patient presented with uveitis 6 months after the last cryotherapy, we do not rule out the possibility that uveitis may have developed as a complication of cryotherapy.

In conclusion, although VPRTs can occur secondary to uveitis, they may also be a cause of uveitis. However, it should be kept in mind that cryotherapy for VPRT may also be associated with uveitis and the complications of uveitis. Optic neuritis and retinal periphlebitis, which are among the most important signs of MS uveitis, are sometimes the findings that lead to a diagnosis.[17,18] The leakage from the peripheral retinal vessels and optic disc staining initially observed in our patient may have been associated with his existing MS. However, the subsequent, more pronounced presentation of uveitis is believed to have been associated with cryotherapy. MS should be kept in mind with young patients for whom other causes of secondary VPRT cannot be established.

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nilgün Yıldırım, Nazmiye Erol, Concept: Nilgün Yıldırım, Nazmiye Erol, Design: Eray Atalay, Mustafa Değer Bilgeç, Data Collection or Processing: Onur Özalp, Eray Atalay, Mustafa Değer Bilgeç, Analysis or Interpretation: Nazmiye Erol, Nilgün Yıldırım, Literature Search: Onur Özalp, Eray Atalay, Nilgün Yıldırım, Writing: Onur Özalp, Eray Atalay, Nilgün Yıldırım

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. Shields CL, Shields JA, Barrett J, De Potter P. Vasoproliferative tumors of the ocular fundus. Classification and clinical manifestations in 103 patients. Arch Ophthalmol. 1995;113:615-623.
2. Heimann H, Bornfeld N, Vij O, Coupland SE, Bechrakis NE, Kellner U, Foerster MH. Vasoproliferative tumours of the retina. Br J Ophthalmol. 2000;84:1162-1169.
3. Shields JA, Shields CL, Honavar SG, Demirci H. Clinical variations and complications of Coats disease in 150 cases: the 2000 Sanford Gifford Memorial Lecture. Am J Ophthalmol. 2001;131:561-571.
4. Shields CL, Kaliki S, Al-Dahmash S, Rojanaporn D, Shukla SY, Reilly B, Shields JA. Retinal vasoproliferative tumors: comparative clinical features of primary vs secondary tumors in 334 cases. JAMA Ophthalmol. 2013;131:328-334.
5. Shields JA, Reichstein D, Mashayekhi A, Shields CL. Retinal vasoproliferative tumors in ocular conditions of childhood. J AAPOS 2012;16:6-9.
6. Pollack AL, McDonald HR, Johnson RN, Ai E, Irvine AR, Lahey JM, Lewis H, Rodriguez A, Ryan EH Jr, Shields CL. Peripheral retinoschisis and exudative retinal detachment in pars planitis. Retina. 2002;22:719-724.
7. Ness TT, Boehringer D, Heinzelmann S. Intermediate uveitis: pattern of etiology, complications, treatment and outcome in a tertiary academic center. Orphanet J Rare Dis. 2017;12:81.
8. Boskovich SA, Lowder CY, Meisler DM, Gutman FA. Systemic diseases associated with intermediate uveitis. Cleve Clin J Med. 1993;60:460-465.
9. Raja SC, Jabs DA, Dunn JP, Fekrat S, Machan CH, Marsh MJ, Bressler NM. Pars planitis: clinical features and class II HLA associations. Ophthalmology. 1999;106:594-599.
10. Kaya D, Kaya M, Ozakbas S, Idiman E. Uveitis associated with multiple sclerosis: complications and visual prognosis. Int J Ophthalmol 2014;7:1010-1013.
11. Sancho L, Kramer M, Koriat A, Eiger-Moscovich M, Sharon Y, Amer R. Complications in Intermediate Uveitis: Prevalence, Time of Onset, and Effects on Vision in Short-Term and Long-Term Follow-Up. Ocul Immunol Inflamm. 2019;27:447-455.
12. Damato B. Vasoproliferative retinal tumour. Br J Ophthalmol. 2006;90:399-400.
13. Garcia-Arumi J, Distefano LN, Fonollosa A, Quijano C, Corcostegui B. Management of Vision-Threatening Complications of Vasoproliferative Tumors of the Retina. Ophthalmic Res. 2015;54:34-40.
14. Chan RP, Lai TY. Photodynamic therapy with verteporfin for vasoproliferative tumour of the retina. Acta Ophthalmol. 2010;88:711-712.
15. Rogers C, Damato B, Kumar I, Heimann H. Intravitreal bevacizumab in the treatment of vasoproliferative retinal tumours. Eye (Lond) 2014;28:968-973.
16. Chignell AH, Clemett RS, Revie IH. Pigment fallout and uveitis after cryotherapy. Br J Ophthalmol. 1973;57:156-165.
17. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. Ocul Immunol Inflamm. 2004;12:137-142.
18. Jouve L, Benrabah R, Heron E, Bodaghi B, Le Hoang P, Touitou V. Multiple Sclerosis-related Uveitis: Does MS Treatment Affect Uveitis Course? Ocul Immunol Inflamm. 2017;25:302-307.

DOI: 10.4274/tjo.galenos.2019.92255
Turk J Ophthalmol 2019;49:367-369

Case Report

Atypical Presentation of Choroidal Folds: Steroid-induced Central Serous Chorioretinopathy-like Maculopathy

Cumali Değirmenci, Filiz Afrashi, Serhad Nalçacı, Serap Bilge Çeper

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

Abstract

This article reports a case of choroidal folds and central serous chorioretinopathy-like maculopathy induced by corticosteroid treatment. The patient was a 70-year-old woman who presented with decreased visual acuity in the right eye. She had a history of rheumatoid arthritis and was prescribed 20 mg leflunomide and 16 mg corticosteroid daily. Fundoscopy indicated bilateral macular edema and the presence of choroidal folds. Retinal imaging supported choroidal folds and central serous chorioretinopathy-like maculopathy. Corticosteroid therapy was discontinued, and the patient was followed up. Complete regression of the maculopathy was observed at 8-month follow-up examination.

Keywords: Corticosteroid, choroidal folds, rheumatoid arthritis, central serous chorioretinopathy-like maculopathy

Introduction

Choroidal folds, or chorioretinal folds, are defined as undulations of the retina and choroid. Anatomically, they include the inner choroid, Bruch's membrane, and the retinal pigment epithelium (RPE). On fundus examination, they are seen mostly outside the macular area and appear as pigmentary changes with yellow and dark streaks. Occasionally RPE atrophy occurs, which angiographically resembles an angioid streak.[1,2]

Known causes of choroidal folds are retrobulbar masses, thyroid eye disease, posterior scleritis, acquired hypermetropia, uveal effusion syndrome, ocular surgery, hypotony, and optic neuropathy.[2,3] Cases with unknown etiology are defined as idiopathic. Visual acuity can be affected if the folds involve the macula. Although the pathogenic mechanism of choroidal folds is still unclear, two different theories have been suggested. The first theory postulates that the pathogenicity of the folds results from a close relationship between the choriocapillaris and Bruch's membrane such that choroidal expansion can cause folds in Bruch's membrane. The second theory suggests that the relationship between stress and strain that arises from the sclera and choroid may cause choroidal folds.[1]

The aim of this study is to present clinical data obtained at the first visit and follow up examination of a patient presenting with choroidal folds, central serous retinopathy (CSR)-like maculopathy, and hypermetropia.

Case Report

A 70-year-old woman presented with decreased visual acuity in the right eye that started 4 days earlier. She had undergone

Address for Correspondence: Cumali Değirmenci MD, 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: 01.04.2019 **Accepted:** 30.09.2019

Cite this article as: Değirmenci C, Afrashi F, Nalçacı S, Çeper SB. Atypical Presentation of Choroidal Folds: Steroid-induced Central Serous Chorioretinopathy-like Maculopathy. Turk J Ophthalmol. 2019;49:367-369

cataract surgery 4 years ago and had a history of rheumatoid arthritis and hypertension. She had been prescribed oral 20 mg leflunomide (Arava, Sanofi Sağlık Ürünleri, İstanbul) and 16 mg corticosteroid (Prednol, Mustafa Nevzat İlaç, İstanbul) daily 1.5 months earlier for rheumatoid arthritis. The patient underwent a complete ophthalmic examination. Her best corrected visual acuity (BCVA) was 0.2 in the right eye (+7.00 -2.00 α70) and 0.5 (+5.00 -2.50 α100) in the left eye. Intraocular pressure (IOP) measured with Goldman applanation tonometer was 18 mmHg in the right eye and 19 mmHg in left eye. Anterior segment examination showed posterior chamber intraocular lenses. Fundoscopy indicated bilateral macular edema up to the optic nerve and the presence of choroidal folds. Fluorescein angiography demonstrated leakage in the peripapillary region and fundus autofluorescence showed hyperfluorescence in the foveal area (Figure 1). Optical coherence tomography (OCT) revealed intraretinal and subretinal fluid accumulation in the right eye and intraretinal fluid accumulation in the left eye. Additionally, OCT showed the presence of chorioretinal undulation in both eyes (Figure 2). Corticosteroid therapy was discontinued and the patient was followed up. The patient's axial length was measured as 19.26 mm in the right eye and 20.01 mm in the left eye. BCVA, IOP, anterior and posterior segment examination, and OCT were carried out in the follow-up period. At the 8 month examination, BCVA was 0.7 in the right eye and 0.6 in the left eye, IOP was within normal limits (14 mmHg bilaterally), the anterior segment was unchanged, and the posterior segment showed RPE changes in the macular area and peripheral retina in addition to the chorioretinal folds. OCT indicated the absence of intraretinal or subretinal fluid bilaterally. Fluorescein angiography and fundus autofluorescence findings indicated the regression of pathology (Figure 3).

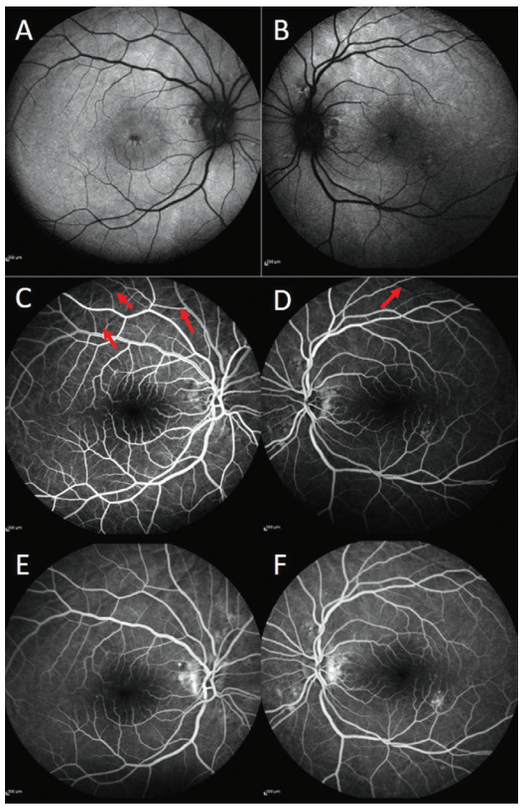


Figure 1. A,B) Fundus autofluorescence of the patient at initial examination showed central hypoautofluorescence related to macular edema; **C,D)** early phase of fluorescein angiography demonstrated choroidal folds (red arrows); **E,F)** late phase of fluorescein angiography showed points of leakage in the peripapillary and left inferotemporal areas

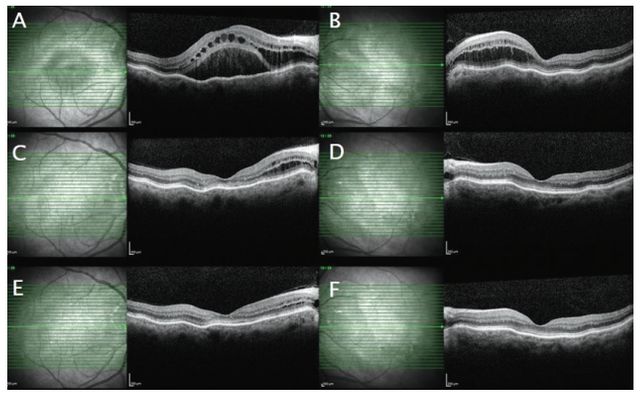


Figure 2. A, B) Optical coherence tomography at initial examination showed significant intraretinal and subretinal fluid; **C, D)** significant regression was observed at 4 months; **E, F)** complete regression was observed at 8 months

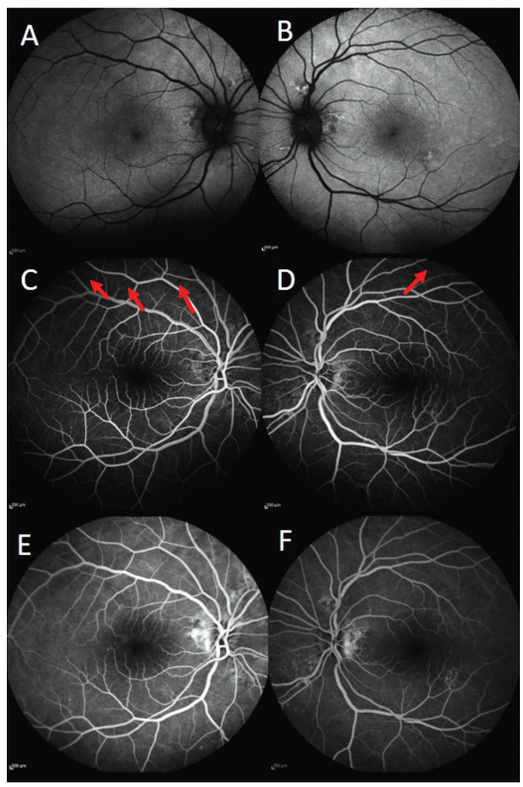


Figure 3. A, B) Fundus autofluorescence at 8 months showed regression of central hypoautofluorescence; **C, D)** early phase of fluorescein angiography demonstrated persistence of the choroidal folds (red arrows); **E, F)** late phase of fluorescein angiography showed no points of leakage

Discussion

Choroidal folds are defined as wrinkles of the RPE and choroid, and in the neural retina secondary to these. Choroidal folds should be carefully investigated clinically because of the underlying pathology. They are associated with inflammatory, neoplastic, and infectious diseases.[1,2] Visual acuity, fundus examination, OCT, fluorescein angiography, indocyanine green angiography, ophthalmic ultrasonography, and magnetic resonance imaging are the tools that have diagnostic importance. In the present study, a 70-year-old female presented with choroidal folds, axial hypermetropia, and CSR-like maculopathy induced by corticosteroid use.

Olsen et al.[2] defined three angiographic stages for choroidal folds. Stage 1 was described as alternating bands of hyperfluorescence and hypofluorescence, stage 2 as a breakdown of RPE along with the breaks in the Bruch's membrane, and stage 3 as occult choroidal neovascularization. RPE atrophy may be seen in the valleys of these bands.[4] In the present study, we observed the presence of alternating bands due to pigmentary changes in the chorioretinal folds and angioid streak-like lesions around the optic disc (Figure 2, 3). Therefore, we thought that the patient may have stage 2 choroidal folds.

The etiology of choroidal folds can be manifold. One of the most important etiologic causes is hypermetropia. In reporting the demographic characteristics of their patient group, Olsen et al.[2] indicated that 18 of 25 patients with known etiology had hypermetropia. Saoji et al.[3] presented a case with axial hypermetropia, choroidal folds, and subretinal fluid. The patient had short axial length and therefore was at risk of disease development.

Choroidal folds are generally not associated with subretinal or intraretinal fluid, with very few studies reporting this. One mechanism suggested for the accumulation of subretinal or intraretinal fluid is localized capillary and venous congestion along the folds leading to capillary hyperpermeability. It has also been suggested that choroidal folds can affect the function of the RPE and cause fluid accumulation.[3,5,6,7] Our patient had CSR-like maculopathy and was taking systemic corticosteroids concurrently for the previous 2 months. Corticosteroid treatment may have contributed to the development of maculopathy in our patient, who already had choroidal congestion due to the presence of chorioretinal folds.

The relationship between corticosteroid intake and CSR is well defined. CSR is characterized by neurosensory retinal detachment and subretinal fluid accumulation. Although intraretinal fluid accumulation may occur, particularly in chronic cases, it is not typical for all cases. In previous reports, intraretinal and/or subretinal fluid accumulation with choroidal folds was annotated as CSR-like maculopathy or chorioretinal folds-related maculopathy. There are only a few case reports about this condition in the literature.[3,6,7,8] In the present study, the patient was observed to have choroidal folds and a short axial length. Therefore, the patient was already at risk for developing CSR-like maculopathy, which may have been exacerbated by corticosteroid treatment. To our knowledge, this is the first report of a patient who had CSR-like maculopathy with choroidal folds who was also concurrently treated with corticosteroids.

We present a patient with choroidal folds and atypical retinal findings that resembled CSR. The etiology for the development of choroidal folds should be closely investigated. In the present case, the patient had short axial length, rheumatoid arthritis, and was taking corticosteroids, which most likely contributed to the pathology. The clinician should therefore be aware of additional systemic diseases and the corresponding treatments, as these may contribute to the etiology in atypical cases.

Ethics

Informed Consent: İnformed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Filiz Afrashi, Serhad Nalçacı, Concept: Filiz Afrashi, Cumali Değirmenci, Design: Cumali Değirmenci, Data Collection or Processing: Serap Bilge Çeper, Analysis or Interpretation: Filiz Afrashi, Literature Search: Cumali Değirmenci, Serap Bilge Çeper, Writing: Cumali Değirmenci.

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. Corvi F, Capuano V, Benatti L, Bandello F, Souied E, Querques G. Atypical Presentation of Chorioretinal Folds-Related Maculopathy. Optom Vis Sci. 2016;93:1304-1314.
2. Olsen TW, Palejwala NV, Lee LB, Bergstrom CS, Yeh S. Chorioretinal folds: associated disorders and a related maculopathy. Am J Ophthalmol. 2014;157:1038-1047.
3. Saoji K, Trehan HS, Gupta A. Association of neurosensory detachment with choroidal folds in a hypermetrope: An unusual presentation. Med J Armed Forces India. 2016;72(Suppl 1):87-90.
4. Shields JA, Shields CL, Rashid RC. Clinicopathologic correlation of choroidal folds: Secondary to massive cranioorbital hemangiopericytoma. Ophthalmic Plast Reconstr Surg. 1992;8:62-68.
5. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol. 1996;121:26-34.
6. Xirou T, Kabanarou SA, Gkizis I, Garnavou-Xirou C, Velissaris S, Theodossiadis P, Chatziralli I. Chronic central serous chorioretinopathy-like maculopathy as atypical presentation of chorioretinal folds. Case Rep Ophthalmol. 2017;8:568-573.
7. Goel N, Kumar V, Raina UK, Ghosh B. An unusual pattern of idiopathic choroidal folds. Oman J Ophthalmol. 2012;5:126-127.
8. Nicholson BP, Atchison E, Idris AA, Bakri SJ. Central serous chorioretinopathy and glucocorticoids: an update on evidence for association. Surv Ophthalmol. 2018;63:1-8.

www.oftalmoloji.org

TÜRK OFTALMOLOJİ DERGİSİ

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

Dear Reviewers

We would like to thank you for your contributions in "Turkısh Journal of Ophthalmology" by being as a reviewer and interest to our journal.

We wish you every success in your academic career.

Sincerely

2019 Referee Index

Abdulbaki Mudun
Afsun Şahin
Ahmet Akman
Ahmet Murat Sarıcı
Ali Bülent Çankaya
Ali Hakan Durukan
Ali Osman Saatci
Alp Alaluf
Altuğ Çetinkaya
Anıl Kubaloğlu
Ayça Sarı
Ayça Yılmaz
Ayşe Burcu
Ayşe Öner
Ayşe Yağcı
Aysel Pelit
Banu Bozkurt
Banu Coşar
Banu Şatana
Banu Turgut Öztürk
Barış Sönmez
Bekir Sıtkı Aslan
Bengü Ekinci Köktekir
Bora Eldem
Bülent Yazıcı
Canan Aslı Utine
Canan Gürdal
Cemil Kadri Apaydın
Defne Kalaycı
Didar Uçar
Dilaver Ersanli
Dilek Dursun Altınörs
Doğan Ceyhan
Elif Demirkılınç Biler
Erdal Yüzbaşıoğlu
Ertuğrul Mirza
Esat Çınar
Esin Başer
Fatih Çakır Gündoğan
Fevzi Şentürk
Feyza Önder
Figen Batıoğlu
Filiz Afrashi
Firdevs Örnek
Gökhan Gürelik
Gölge Acaroğlu
Gürsel Yılmaz
Güzin Iskeleli
H Zeki Büyükyıldız
Hakan Özdemir
Halil Ateş
Halil Özgür Artunay
Halit Oğuz
Hande Taylan Şekeroğlu
Hasan Ali Bayhan
Hatice Elvin Yıldız
Haydar Erdoğan
Hayyam Kıratlı
Hikmet Başmak
Huban Atilla
Hülya Gökmen Soysal
İbrahim Erbağcı
Ilgaz Yalvaç
İlknur Tugal Tutkun
İmren Akkoyun
Jale Menteş
Kaan Gündüz
Kadriye Erkan Turan
Kıvanç Güngör
Lale Közer Bilgin
M Sinan Sarıcaoğlu
Mehmet Akif Acar
Mehmet Ali Şekeroğlu
Mehmet Baykara
Mehmet Cem Mocan
Mehmet Özgür Zengin
Melda Nursal Yenerel
Melih Ünal
Melis Palamar Onay
Meltem Yağmur
Merih Soylu
Muhittin Taskapılı
Murat Hasanreisoğlu
Murat Karaçorlu
Murat Tunç
Müslime Akbaba
Nazife Sefi Yurdakul
Nazmiye Erol
Nihal Demircan
Nilgün Yıldırım
Nilüfer Berker
Nilüfer Koçak
Nilüfer Yalçındağ
Nur Kır
Nuray Akyol
Nurşen Yüksel
Nurten Ünlü
Ömür Gündüz
Önder Üretmen
Öner Gelişken
Onur Konuk
Osman Şevki Arslan
Oya Tekeli
Özcan Kayıkçıoğlu
Özcan Ocakoğlu
Özge Saraç
Özlem Barut Selver
Özlem Evren Kemer
Özlem Şahin
Pelin Kaynak
Pınar Çakar Özdal
Raciha Beril Küçümen
Rana Altan Yaycıoğlu
Reha Ersöz
Remzi Avcı
Samuray Tuncer
Şansal Gedik
Selçuk Sızmaz
Selim Doğanay
Şengül Özdek
Sibel Çalışkan Kadayıfçılar
Sibel Demirel
Sibel Kocabeyoğlu
Sibel Oto
Sinan Emre
Sinan Tatlıpınar
Solmaz Akar
Süleyman Kaynak
Suzan Güven Yılmaz
Tongabay Cumurcu
Tülay Şimşek
Ufuk Elgin
Uğur Keklikçi
Ümit Aykan
Umut Aslı Dinç
Üzeyir Günenç
Volkan Hürmeriç
Yavuz Bardak
Yılmaz Özyazgan
Yonca Aydın Akova
Yusuf Akar
Ziya Kapran
Zuhal Özen Tunay
Züleyha Yalnız Akkaya

2019 Author Index

2019 Author Index

2019 Author Index

2019 Subject Index

2019 Subject Index

2019 Subject Index