ISSN 2149-8695

www.oftalmoloji.org

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

Turkish Journal of Ophthalmology

Vol: 47 Issue: 1 January-February 2017 Page: 1-62

Original Articles

Review

Case Reports

January
February
2017
47 Volume
Issue 1

galenos

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

galenos yayınevi

Publishing House

Molla Gürani Mah. Kaçamak Sokak No: 21,
34093 Fındıkzade-İstanbul-Turkey

Phone: +90 212 621 99 25 **Fax:** +90 212 621 99 27

E-mail: info@galenos.com.tr

Printed at: Doğa Basım İleri Matbaacılık San. ve Tic. Ltd. Şti.
İ.O.S.B. Turgut Özal Cd. Çelik Yenal İş Mrk.
No:117/2A-2B İkitelli / İstanbul / Turkey

Phone: +90 212 407 09 00 **Fax:** +90 212 407 09 02

Date of printing: January 2017

International scientific journal published bimonthly.

ISSN: 2149-8695

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

T. Reha Ersöz,

Çukurova University Faculty of Medicine, Department of Ophthalmology, Adana, 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 Central (PMC), Web of Science-Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), Gale/Cengage Learning, Index Copernicus, EBSCO Database, Scopus, Turkish Medline-National Citation Index, Turk Medline, Cinahl, Proquest, TUBITAK/ULAKBIM and Turkish Citation Index** databases.

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 published 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/v3/sozluk/default.asp) 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 printing, 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 [copyright transfer]. 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 2008) (http://www.wma.net/en/30publications/10policies/b3/). 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. 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.

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

www.oftalmoloji.org

INSTRUCTIONS TO AUTHORS

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, keywords 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 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
Adress: 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

Original Articles

Review

Case Reports

DOI: 10.4274/tjo.92593
Turk J Ophthalmol 2017;47:1-4

Original Article

Comparison of Intraocular Pressure Measurements in Healthy Pediatric Patients using Three Types of Tonometers

Muhsin Eraslan, Eren Çerman, Sena Sümmen
Marmara University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: This study aimed to compare intraocular pressure (IOP) measurements in healthy pediatric patients using three types of tonometers.

Materials and Methods: Seventy-eight eyes of 78 patients under the age of 18 who underwent a routine ophthalmologic examination were included in the study. IOP was measured using Tono-Pen (TP) tonometry, Goldmann applanation tonometry (GAT), and non-contact tonometry (NCT), consecutively. IOP was adjusted based on central corneal thickness (CCT). Patients with any ocular disorders other than a limited refractive error were excluded from the study.

Results: The study consisted of 46 girls and 32 boys. The mean age was 12.6±2.7 (range: 5-17) years. The mean CCT was 559.3±35.3 µm. The mean refractive error was -0.50±1.70. The mean level of visual acuity was 0.98±0.1 (range: 0.3-1.0) using the Snellen chart. Significant differences were found between the measurement results of each of the three tonometric methods. Mean IOP was 12.1±2.2 mmHg for TP, 15.7±2.5 mmHg for GAT, and 17.1±3.1 mmHg for NCT. The correlations between measurement methods revealed that the highest correlation was between NCT and GAT ($p<0.001$, $r=0.670$). The second highest correlation was between NCT and TP ($p<0.001$, $r=0.477$). The lowest correlation was between GAT and TP ($p<0.001$, $r=0.403$). A positive correlation was found between CCT and each IOP measurement method.

Conclusion: In pediatric patients, TP and NCT measurements were found to be positively correlated with GAT measurements. Because TP measurements were lower than GAT measurements and NCT measurements were higher than GAT measurements, patient follow-ups, treatment strategies, and surgery plans must be organized taking these differences into consideration.

Keywords: Pediatric intraocular pressure, Tono-Pen tonometry, Goldmann applanation tonometry, non-contact tonometry, central corneal thickness

Introduction

Despite the important role of cornea and optic nerve appearance in the diagnosis of pediatric glaucoma, intraocular pressure (IOP) measurement is still the primary diagnostic method. In addition, IOP remains the only risk factor that can be altered in glaucoma therapy and these modifications have been proven to be able to prevent disease progression.[1] This makes the accurate measurement of IOP particularly important. The evaluation of IOP in pediatric cases may vary depending on patient cooperation. Stress caused by devices which contact the cornea may cause the patient to cry, leading to the Valsava maneuver and increasing systemic venous pressure and IOP.[2] It is therefore recommended to conduct the examination under general anesthesia in patients with suspected glaucoma. However, IOP measurements conducted in the outpatient clinic setting can are informative when deciding which patients to examine under general anesthesia.

Previous studies have demonstrated that measurements made using Schiotz tonometry may lead to inaccurate results due to factors such as corneal curvature incompatibility and corneal diameter.[3] For this reason, the Goldmann applanation tonometer (GAT) is currently accepted as the gold standard tonometer. Unfortunately, measuring with the GAT is not possible with pediatric patients of all ages. Although some studies have demonstrated good agreement between measurements made with the Tono-Pen (TP), GAT and non-contact tonometer

Address for Correspondence: Muhsin Eraslan MD, Marmara University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 532 545 94 54 E-mail: muhsineraslan@hotmail.com **Received:** 09.12.2015 **Accepted:** 22.04.2016

(NCT),[4,5] in clinical practice these instruments can yield very different results. This can have an impact on treatment decisions and in some cases even surgery decisions. Because IOP assessment may lead to legal issues in certain situations, it is critical to evaluate measurement reliability and determine the factors affecting measurement.

The aim of this study was to compare IOP measurements made in outpatient clinic conditions with TP, GAT and NCT in pediatric patients amenable to IOP measurement in a sitting position.

Materials and Methods

Seventy-eight eyes of 78 patients examined in our ophthalmology clinic between April and June 2015 were included in the study. Only the patients' right eyes were included. Patients had no ocular disease other than refractive errors. Exclusion criteria included: hypermetropia or myopia greater than 4 diopters (D); corneal astigmatism greater than 2.5 D; any known ocular disease or suspicion of glaucoma (history of high IOP, deep or large optic pit, family history, etc.); history of ocular surgery; periocular steroid use during or within 3 months prior to the study; use of any systemic or ophthalmic drugs which may affect IOP; and inability to comply with any of the assessment methods utilized in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local clinical research ethics committee. Informed consent was obtained from the patients' legal guardians before each procedure.

IOP measurements were conducted using the TP (Tono-Pen Avia, Reichert, USA), GAT (Haag-Streit, Switzerland) and NCT (Nidek NT 530, Japan). The same tonometers were used throughout the study. As recommended by the manufacturers, the TP and GAT were calibrated daily and the NCT was calibrated once a month. Measurements were performed by the same physician before dilating the pupil, instilling a topical anesthetic (Alcaine proparacaine hydrochloride; Alcon, Fort Worth, Texas, USA), and fluorescein stain (Norvatis fluorescein; Norvatis, Basel, Switzerland) for GAT. Measurements were taken at 5-minute intervals, and the average of 3 measurements was taken for each device. All measurements were done with the patient in a seated position. Measurements were taken with the three instruments in the following order: TP, GAT, NCT. This was followed by central corneal thickness (CCT) measurement using the Pachymeter SP-3000 (Tomey, USA) pachymetry instrument, then a corrected IOP value was calculated based on the CCT value: corrected IOP=Measured IOP-(CCT-545)/50x2.5 mmHg.[6]

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) software package was used for statistical analyses. P values less than 0.05 were accepted as statistically significant. Independent samples t-test was used for intergroup comparisons. Pearson's test was used to determine the presence of correlations. Differences of 1.96 standard deviations from the mean were used when calculating the limits of agreement. Associations between differences and means were analyzed using Bland-Altman plots.

Results

A total of 78 subjects were included in the study; 18 were later excluded due to noncompliance with at least 1 of the measurement techniques.

Of the subjects included in the study, 46 were female and 32 were male. The mean age was 12.6±2.7 (range, 5-17) years. Mean CCT was 559.3±35.3 µm and mean refraction value was -0.50±1.70 D. Visual acuity on Snellen chart was 0.98±0.1 (range, 0.3-1.0).

Mean IOP was measured as 12.1±2.2 mmHg with TP, 15.7±2.5 mmHg with GAT and 17.1±3.1 mmHg with NCT. The differences and 95% confidence intervals between these mean values are shown in the Bland-Altman plots in Figures 1 and 2.

CCT positively correlated with measured IOP measurements obtained from all of the devices (TP: r=0.305, p=0.007; GAT: r=0.355, p=<0.001; NCT: r=0.471, p<0.001).

A weak negative correlation emerged between age and the difference between NCT and GAT values (r=-0.225, p=0.048), while there was no significant relationship between age and the difference between TP and GAT values (r=0.126, p=0.271).

Moderate correlations were observed between all of the measurement methods (TP-GAT: r=0.403, p<0.001; NCT-GAT: r=0.670, p<0.001; NCT-TP: r=0.477, p<0.001).

CCT values were not significantly correlated with the amount of deviation of TP and NCT measurements from GAT measurements (p>0.05).

There was a moderate positive correlation between the TP-GAT difference and significantly rising mean IOP values

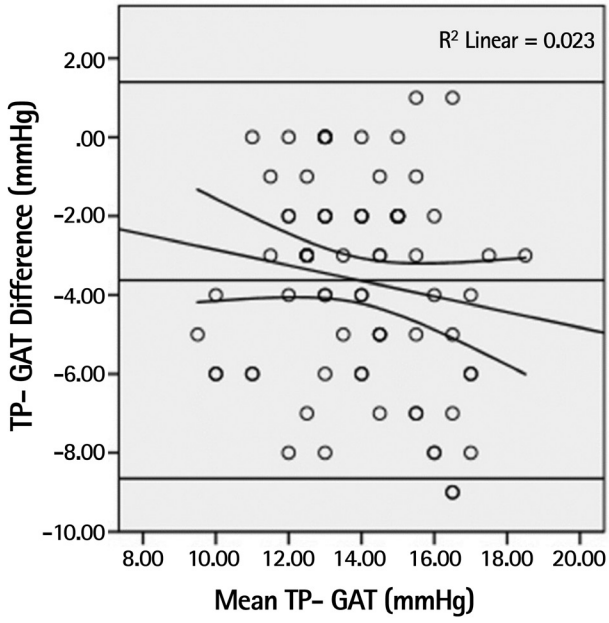

Figure 1. Bland-Altman scatter plot showing the errors in intraocular pressure measurements obtained with the Tono-Pen compared to Goldmann applanation tonometry results
TP: Tono-Pen, GAT: Goldmann applanation tonometry

(r=0.459, p<0.001), whereas a weak negative correlation was observed between the NCT-GAT difference and significantly rising mean IOP values (r=-0.260, p=0.021) (Figure 3).

The Cronbach alpha reliability coefficient of the measurements made with the 3 different instruments was 0.762. The reliability coefficient between TP and GAT was 0.571, indicating low reliability; the Cronbach's alpha of 0.793 between NCT and GAT showed sufficiently reliable agreement.

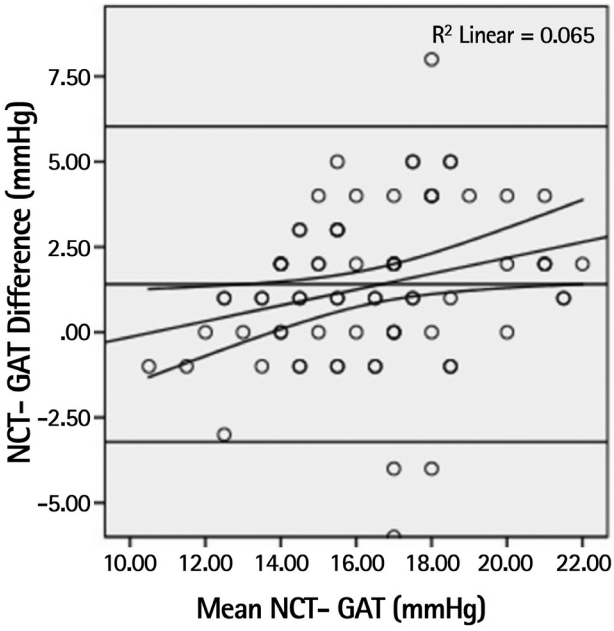

Figure 2. Bland-Altman scatter plot showing the errors in intraocular pressure measurements obtained with non-contact tonometer compared to Goldmann applanation tonometry results
NCT: Non-contact tonometer, GAT: Goldmann applanation tonometry

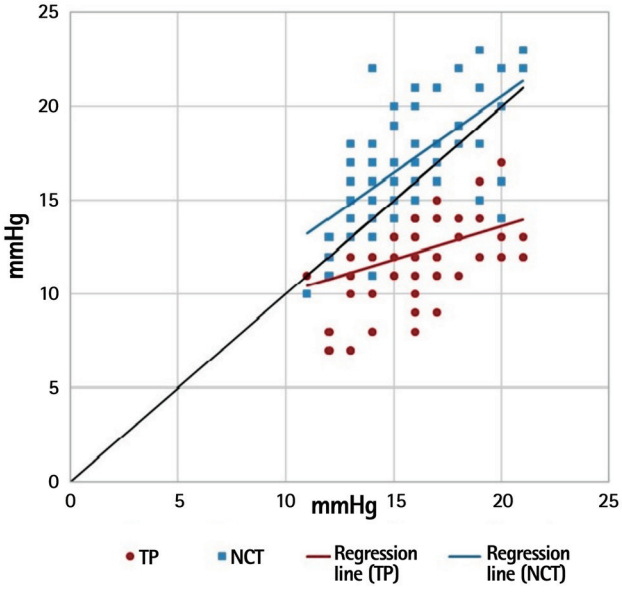

Figure 3. Correlation between the results of Goldmann applanation tonometry and measurements obtained using the Tono-Pen and non-contact tonometer. A moderately significant correlation was found between the measurements
TP: Tono-Pen, NCT: Non-contact tonometer

Discussion

Fewer comparative studies have been performed in pediatric patients than in adults. Although the TP may be easier to use with younger patients than the GAT and NCT, the results of our study show that measuring with the TP may yield IOP values which are artificially low. In this study we determined that NCT and GAT measurements show adequate reliability, while TP measurements showed low reliability. Furthermore, the difference between TP and GAT measurements grew as IOP values increased. This finding is consistent with previous studies demonstrating that the TP measures significantly lower than the GAT at IOP values over 20 mmHg.[7]

Other studies have shown that the NCT yields higher values than the GAT and that this difference increases as CCT increases.[8] In the present study, the discrepancies between GAT measurements and those made with TP and NCT were uncorrelated with CCT but were associated with IOP elevation. In their 2006 publication, Alagöz et al.[9] reported that the NCT gave significantly higher IOP values compared to the GAT, even in patients with normal IOP values. Akman et al.[10] obtained similar results using the NCT and GAT in subjects with normal IOP and recommended using the NCT as a screening test and confirming high values with the GAT. In a similar study from 2002, Güler et al.[11] found good agreement between the NCT and GAT and concluded that the NCT was a convenient, reproducible and reliable method.

Consistent with the results of the present study, Feng et al.[12] reported that the NCT yielded slightly higher values than the GAT in their 2015 study including 419 pediatric patients. They emphasized that the NCT may be a preferable method because it does not require local anesthetic.

In contrast, Buscemi et al.[13] conducted a study with 42 pediatric patients and argued that, compared to the GAT, the NCT may yield false negative results in pediatric patients under 9 years old and should not be used with patients under this age.

A previous study demonstrated that differences due to postural changes resulted in low reliability between measurements taken with the TP and pneumatic tonometry and those taken with the GAT.[14] As all measurements were taken with patients in a seated position, any differences arising due to postural changes are not an issue in the present study. However, Takenaka et al.[15] determined that the reliability of IOP measurements may be lower in children who move during assessment. Therefore, only cooperative subjects who were able to remain motionless during measurement were included in the present study. Despite this, the difference between GAT and NCT measurements significantly decreased with older age, while TP measurements were not affected. Furthermore, because TP measurement was done first, it is possible that the subjects may not have been able to sufficiently cooperate.

Many earlier studies have demonstrated the link between CCT and measured IOP values.[16,17] As none of the tonometers used in the present study allowed the evaluation of CCT or other parameters which may affect IOP measurement such as ocular rigidity or hysteresis, we used IOP values adjusted for CCT in our analysis. The formula we used in the present study was developed in 2004 by Shih et al.[6] based on a mathematical formula proposed by Orssengo and Pye[18] in their *in vivo* human cornea studies investigating the association between corneal elasticity and accurate IOP measurement.

Study Limitations

One of the limitations of our study was the order of the devices used for measurements. The use of two different contact tonometers made it impossible to prevent possible IOP changes due to corneal compression or aqueous massage. However, opposite to the expected outcome, measurement with the NCT after both contact tonometers yielded the highest IOP values, while the first measurement using the TP was lowest. It is therefore unlikely that the order we used impacted the results, but there is a slight possibility that it caused the underestimation of discrepancies which may have been more pronounced using a different measuring order.

Another limitation of our study was that the mean age of the subjects was 12.6±2.7 years. Larger studies which also include younger subsets of the pediatric population are needed.

Conclusion

Measurements obtained with both the TP and NCT were positively correlated with those from the GAT, the accepted gold standard IOP assessment method. It is expected that TP values will be lower and NCT values will be higher than GAT values, and these differences should be considered when following patients and making decisions regarding treatment and surgery. This study also demonstrated that measurements obtained with the TP are less reliable compared to those from the NCT, and that this discrepancy may be more pronounced at high IOP levels.

Ethics

Ethics Committee Approval: Available, Informed Consent: Available.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Muhsin Eraslan, Sena Sümmen, Concept: Muhsin Eraslan, Eren Çerman, Design: Muhsin Eraslan, Eren Çerman, Data Collection or Processing: Sena Sümmen, Analysis or Interpretation: Muhsin Eraslan, Eren Çerman, Literature Search: Muhsin Eraslan, Writing: Muhsin Eraslan.

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. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-713; discussion 829-730.
2. Kao SF, Lichter PR, Bergstrom TJ, Rowe S, Musch DC. Clinical comparison of the Oculab Tono-Pen to the Goldmann applanation tonometer. Ophthalmology. 1987;94:1541-1544.
3. Patel H, Gilmartin B, Cubbidge RP, Logan NS. In vivo measurement of regional variation in anterior scleral resistance to Schiotz indentation. Ophthalmic Physiol Opt. 2011;31:437-443.
4. Gupta S, Sinha G, Sharma R, Nayak B, Patil B, Kashyap B, Shameer A, Dada T. Agreement between diurnal variations of intraocular pressure by Tono-Pen and Goldmann applanation tonometer in patients on topical anti-glaucoma medication. Int Ophthalmol. 2016;36:9-15.
5. Shousha SM, Abo Steit MA, Hosny MH, Ewais WA, Shalaby AM. Comparison of different intraocular pressure measurement techniques in normal eyes, post surface and post lamellar refractive surgery. Clin Ophthalmol. 2013;7:71-79.
6. Shih CY, Graff Zivin JS, Trokel SL, Tsai JC. Clinical significance of central corneal thickness in the management of glaucoma. Arch Ophthalmol. 2004;122:1270-1275.
7. Horowitz GS, Byles J, Lee J, D'Este C. Comparison of the Tono-Pen and Goldmann tonometer for measuring intraocular pressure in patients with glaucoma. Clin Exp Ophthalmol. 2004;32:584-589.
8. Kim NR, Kim CY, Kim H, Seong GJ, Lee ES. Comparison of goldmann applanation tonometer, noncontact tonometer, and TonoPen XL for intraocular pressure measurement in different types of glaucomatous, ocular hypertensive, and normal eyes. Curr Eye Res. 2011;36:295-300.
9. Alagöz G, Serin D, Elçioğlu M, Doğan U. Non-Kontakt, Goldmann Aplanasyon ve Schiotz Tonometre Ölçümlerinin Karşılaştırılması. Fırat Tıp Dergisi. 2006;11:139-141.
10. Akman A, Yaylalı V, Ünal M, Sönmez M, Örge Y. Nonkontakt tonometre ve Goldmann aplanasyon tonometresi ile yapılan GİB ölçümlerinin karşılaştırılması. MN Oftalmoloji. 1999;6:343-345.
11. Güler C, Kayıkçıoğlu O, Toprak B, Erkin E. Comparison of Nidek NT-3000 non-contact tonometer with Goldmann applanation tonometry. Turk J Ophthalmol. 2002;32:75-79.
12. Feng CS, Jin KW, Yi K, Choi DG. Comparison of Intraocular Pressure Measurements Obtained by Rebound, Noncontact, and Goldmann Applanation Tonometry in Children. Am J Ophthalmol. 2015;160:937-943 e931.
13. Buscemi M, Capoferri C, Garavaglia A, Nassivera C, Nucci P. Noncontact tonometry in children. Optom Vis Sci. 1991;68:461-464.
14. Barkana Y. Postural change in intraocular pressure: a comparison of measurement with a Goldmann tonometer, Tonopen XL, pneumatonometer, and HA-2. J Glaucoma. 2014;23:e23-28.
15. Takenaka J, Mochizuki H, Kunihara E, Tanaka J, Kiuchi Y. Evaluation of rebound tonometer for measuring intraocular pressure at deviated angle and position. Curr Eye Res. 2011;36:422-428.
16. Shah S, Chatterjee A, Mathai M, Kelly SP, Kwartz J, Henson D, McLeod D. Relationship between corneal thickness and measured intraocular pressure in a general ophthalmology clinic. Ophthalmology. 1999;106:2154-2160.
17. Copt RP, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma. Arch Ophthalmol. 1999;117:14-16.
18. Orssengo GJ, Pye DC. Determination of the true intraocular pressure and modulus of elasticity of the human cornea in vivo. Bull Math Biol. 1999;61:551-572.

DOI: 10.4274/tjo.62444
Turk J Ophthalmol 2017;47:5-8

Original Article

Early Clinical Features of Pseudoexfoliation Syndrome in Anterior Segment and Gonioscopy Examination

Sirel Gür Güngör*, Atilla Bayer**, Ahmet Akman*, Leyla Asena*
*Başkent University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Dünyagöz Hospital, Ophthalmology Clinic, Ankara, Turkey

Abstract

Objectives: To determine the early signs of pseudoexfoliation (PEX) in fellow eyes of cases with unilateral PEX.

Materials and Methods: Fellow eyes of 34 cases with unilateral PEX were evaluated by slit-lamp and gonioscopy. Findings associated with PEX were recorded.

Results: Mean age was 67.8±8.1 years (range 55-86 years). Twenty-five patients (73.5%) had pigmentation in the inferior angle and 23 patients (67.6%) had Sampaolesi's line located on the inferior angle in fellow eyes. The other most common findings were loss of peripupillary ruff in 10 patients (29.4%) and pigment dispersion following pupil dilation in 14 patients (41.1%).

Conclusion: Pigmentation in the inferior angle and Sampaolesi's line on the inferior angle seem to be the most common early findings associated with PEX. Special attention should be paid to these findings in cases with ocular hypertension for proper management.

Keywords: Anterior segment, gonioscopy, pseudoexfoliation syndrome

Introduction

In pseudoexfoliation (PEX) syndrome, extracellular fibrillary material is deposited throughout the anterior segment, particularly over the anterior lens capsule in a characteristic double concentric ring pattern with a clear zone between the rings.[1,2] Clinically, ocular involvement in PEX syndrome is described as unilateral in half of the patients.[3,4] In an electron microscopic study, Parekh et al.[5] reported that 26 of 32 patients (81%) with clinically unilateral PEX had PEX material on either the lens capsule or conjunctival samples of the clinically unaffected eyes. Furthermore, several reports on the follow-up of patients with unilateral PEX documented that a proportion of the unilateral cases became bilateral.[6,7] This suggests that unilateral PEX is in fact a bilateral but asymmetric condition.

In this study we aimed to determine the early signs of PEX syndrome in fellow eyes of cases with unilateral PEX syndrome.

Materials and Methods

The study comprised 68 eyes of 34 patients aged 67.8±8.1 (range 55-86) years with unilateral PEX syndrome who were examined between January 2014 and March 2015. Written informed consent was obtained from all patients enrolled in this cross-sectional non-interventional study. The study was approved by the Local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. None of the patients had undergone ocular surgery or laser treatment. Patients with any ocular disease (other than glaucoma) which might interfere with gonioscopy and fundus examination results, such as corneal opacities, cataracts, or retinal lesions; the presence or history of ischaemic, compressive, or inflammatory optic neuropathies; refractive errors greater than ±6 diopter (D); or inflammation or trauma in any eye, were excluded. Unilateral exfoliation was defined clinically as the presence of biomicroscopically detectable exfoliation material on the anterior lens capsule or at the pupillary border in one eye after

Address for Correspondence: Sirel Gür Güngör MD, Başkent University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone: +90 312 212 68 68 E-mail: sirelgur@yahoo.com **Received:** 19.03.2016 **Accepted:** 11.06.2016

pupillary dilatation with 10% phenylephrine hydrochloride. Eyes were classified as clinically normal if there was no evidence of exfoliation material on the pupil, lens or angle.

All participants underwent a detailed ophthalmologic examination including slit-lamp examination, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy and +90 D fundus examination. Gonioscopy, employing the Goldmann tri-mirror goniolens under standard conditions, was performed to visualize the angle and the angle recess; trabecular pigmentation was noted and open angle and angle closure suspects were defined according to the International Society for Geographical and Epidemiological Ophthalmology classification.[8]

IOP measurements were performed between 08:00 AM and 10.00 AM. The highest IOP obtained from the medical history was accepted as "maximum IOP".

Optic disc assessments were performed biomicroscopically with a 90-D lens and the average of vertical cupping was recorded as the cup-to-disc ratio.

Statistical Analysis

Statistical analysis was performed using SPSS software version 10. Differences between eyes were analyzed using Student's t-test and Mann-Whitney U test for non-parametric variables, while the chi-square test was used for analysis of differences among proportions. Statistical significance was set at 0.05.

Results

The records of 68 eyes of 34 patients with unilateral PEX syndrome were evaluated. Mean patient age was 67.8±8.1 (range 55-86) years, and the male:female ratio was 20/14.

The mean IOP was 22.35±7.33 mmHg in eyes with PEX and 17.0±2.17 mmHg in normal eyes (p=0.001). The maximum IOP was 29.13±9.6 mmHg in eyes with PEX and 18.7±2.7 mmHg in normal eyes (p<0.001).

Topical anti-glaucomatous medication was being applied in 25 eyes with PEX and in 17 normal eyes (p=0.045). The disc cupping ratio was higher in eyes with PEX (0.58±0.25) than in normal eyes (0.17±0.07) (p=0.033).

Twenty-five eyes (73.5%) had pigmentation in the inferior angle and 23 eyes (67.6%) exhibited Sampaolesi's line located on the inferior angle. The other most common findings were loss of peripupillary ruff in 10 eyes (29.4%) and pigment dispersion following pupil dilation in 14 eyes (41.1%). The findings are shown in Tables 1, 2, 3 and 4.

Discussion

There has been great variability in the prevalence of PEX syndrome, from 0.5% up to 33%.[1,9] The prevalence of PEX syndrome in Turkey was reported as ranging between 11.2% and 17.7% in different studies.[10,11,12]

PEX syndrome is a systemic disease which leads to the development of glaucoma in up to 50% of cases.[13,14,15] Additionally, PEX syndrome is the most common identifiable cause of open-angle glaucoma, and accounts for an estimated 25% of the open-angle glaucoma worldwide.[16] The pathogenesis of exfoliation glaucoma represents an imbalance between aqueous humour secretion, outflow facility and optic nerve

Table 1. Comparison of anterior segment findings between eyes with pseudoexfoliation and normal fellow eyes

Findings	Eyes with PEX (n=34)	Normal eyes	p
Mean IOP (mmHg) Mean ± standard deviation (minimum - maximum)	22.35±7.33 (11-50)	17.0±2.17 (11-22)	0.001
Iris transillumination near the pupillary sphincter	23	4	0.001
Loss of peripupillary ruff	31	10	0.043
Peripupillary PEX	22	0	0.001
Pigment on the anterior surface of iris	9	1	0.001
Concentric transillumination defect on iris	0	0	
Pigment accumulation on the corneal endothelium	14	3	0.001
PEX flecks on the corneal endothelium	6	0	0.001

PEX: Pseudoexfoliation, IOP: Intraocular pressure

Table 2. Comparison of gonioscopic findings between eyes with pseudoexfoliation and normal eyes

Findings	Eyes with PEX (n=34)	Normal eyes	p
Superior angle Grade 0 1 2 3 4	 0 0 12 19 3	 0 0 10 20 4	0.691
Pigmentation of trabecular meshwork (inferior angle) Grade 0 1 2 3 4	 0 6 17 7 4	 9 21 3 1 0	0.055
Pigmentation of trabecular meshwork (superior angle) Grade 0 1 2 3 4	 1 18 11 1 3	 20 11 2 1 0	0.297
PEX on the angle	9	1	0.000
Sampaolesi's line (inferior angle)	33	23	0.323
Sampaolesi's line (superior angle)	6	0	0.000

PEX: Pseudoexfoliation

microcirculation.[17] Blockage of the trabecular meshwork by pigment and PEX material, and trabecular cell dysfunction eventually result in elevated IOP, which leads to PEX glaucoma.[16]

PEX syndrome is basically bilateral with asymmetric clinical manifestations,[18] related with the rate of production, aggregation, and accumulation of the abnormal extracellular material in each eye.[19] Immunohistochemical and electronmicroscopic studies in autopsy eyes obtained from donors with clinically unilateral PEX have also revealed that exfoliation is actually asymmetric rather than truly monocular.[18,20] PEX material has been demonstrated on the iris and ciliary epithelia and in the dilator muscle of the iris in fellow eyes of clinically unilateral donors,[19] and vasculopathy in iris vessels has been reported to precede the appearance of exfoliative material in the posterior and anterior chambers of the eye.[20] The vasculopathy and the consequent iris hypoperfusion have been documented in both glaucomatous and non-glaucomatous eyes with PEX and therefore, to some extent, are independent of IOP.[21]

Table 3. Comparison of findings after dilation between eyes with pseudoexfoliation and normal eyes

Findings	Eyes with PEX (n=34)	Normal eyes	p
Dispersion following pupil dilation	20	14	0.541
Homogeneous film on the surface of the anterior lens capsule	30	0	0.001
Poor mydriasis Grade 0 1 2 3	 10 14 2 0	 32 1 1 0	0.785
PEX on the surface of the anterior lens capsule	34	0	0.001
Bull's eye sign	31	0	0.001
PEX on the peripheral surface of the anterior lens capsule	32	0	0.001
PEX on the zonules	8	0	0.001
Phacodonesis	2	0	0.703
Tilted lens	1	0	0.643
Central corneal thickness	548.0±28.55 (471-592)	547.29±33.80 (461-600)	0.556
Maximum intraocular pressure	29.13±9.6 (16-60)	18.7±2.7 (14-26)	0.001
Cup-to-disc ratio	0.58±0.25 (0.4-1.00)	0.17±0.07 (0.1-0.5)	0.033

PEX: Pseudoexfoliation

Table 4. The comparison of eye colors and number of medications between eyes with pseudoexfoliation and normal eyes

	Eyes with PEX (n=34)	Normal eyes	p
Color of the eye Brown Hazel Green Blue	 20 7 5 2	 20 7 5 2	
Number of medications 0 1 2 ≥3	 9 5 11 9	 17 1 8 8	0.045

PEX: Pseudoexfoliation

In this study, we accepted that the PEX is a bilateral but asymmetric disease and investigated early clinical findings in the eye that seems to be "normal". This is the first study which investigated anterior segment and iridocorneal angle in this context in detail. In our study, the most common signs in fellow eyes were pigmentation in the inferior angle (73.5%) and Sampaolesi's line located on the inferior angle (67.6%). The other common findings were loss of peripupillary ruff (29.4%), and pigment dispersion following pupil dilation (41.1%).

Rao[22] conducted a study to compare clinical findings and retinal nerve fiber layer (RNFL) thickness in unilateral and bilateral PEX cases in order to identify predictors of early glaucomatous damage on optical coherence tomography. From a total of 32 unilateral PEX cases, 7 subjects demonstrated RNFL thinning in the clinically normal fellow eye; all of these eyes had evidence of pupillary ruff atrophy on slit-lamp examination in the absence of evident exfoliation material in the eye. Similar ruff atrophy with RNFL thinning was detected in 38 of 59 bilateral and in 16 of 32 unilateral cases. The authors suggested that iris sphincter abnormality, clinically detected as pupillary ruff atrophy, may reflect early glaucomatous damage. Loss of peripupillary ruff (29.4%) was one of the common findings in our study as well. We know already that eyes with PEX are under greater risk for ocular ischaemic conditions because of pathological vascular alterations associated with PEX.[7] Vasculopathy in iris vessels leads to iris hypoperfusion and precedes clinical visualization of the PEX material.[23]

Omura et al.[24] compared ocular parameters between PEX-positive and PEX-negative eyes in 49 subjects with unilateral PEX syndrome and reported that, compared to PEX-negative eyes, PEX-positive eyes had lower visual acuity, higher IOP, lower corneal endothelial cell density, thicker lenses, lower anterior chamber volume, higher flare values and required more antiglaucoma medications. The refractive errors, central corneal thickness and anterior chamber depth did not differ between the two groups. In that study, values such as corneal endothelial cell density, lens thickness, and anterior chamber volume were investigated. However, in our study we especially focused on studying the iridocorneal angle in more detail.

Conclusion

This study presents a thorough investigation of anterior segment and iridocorneal angle changes in patients with

unilateral PEX syndrome. Pigmentation and Sampaolesi's line at the inferior angle seem to be the earliest findings associated with PEX. Special attention should be paid to these findings in cases with ocular hypertension for proper management.

Ethics

Ethics Committee Approval: It was approved by the Ethics Committee of Başkent University Clinical Research (no: 15-20), Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Atilla Bayer, Ahmet Akman, Sirel Gür Güngör, Concept: Atilla Bayer, Ahmet Akman, Design: Atilla Bayer, Ahmet Akman, Data Collection or Processing: Atilla Bayer, Ahmet Akman, Sirel Gür Güngör, Analysis or Interpretation: Sirel Gür Güngör, Leyla Asena, Literature Search: Sirel Gür Güngör, Writing: Sirel Gür Güngör, Ahmet Akman, Leyla Asena.

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. Elhawy E, Kamthan G, Dong CQ, Danias C. Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. Hum Genomics. 2012;6:22-31.
2. Zheng X. New findings for an old disease: morphological studies on pseudoexfoliation syndrome-related keratopathy and binocular asymmetry. Cornea. 2013;32(Suppl 1):84-90.
3. Arnarsson A, Damji KF, Sverrisson T, Sasaki H, Jonasson F. Pseudoexfoliation in the Reykjavik Eye Study: prevalence and related ophthalmological variables. Acta Ophthalmol Scand. 2007;85:822-827.
4. Arnarsson A, Sasaki H, Jonasson F. Twelve-year Incidence of Exfoliation Syndrome in the Reykjavik Eye Study. Acta Ophthalmol. 2013;91:157-162.
5. Parekh P, Green WR, Stark WJ, Akpek EK. Electron microscopic investigation of the lens capsule and conjunctival tissues in individuals with clinically unilateral pseudoexfoliation syndrome. Ophthalmology. 2008;115:614-619.
6. Puska PM. Unilateral exfoliation syndrome: conversion to bilateral exfoliation and to glaucoma: a prospective 10-year follow-up study. J Glaucoma. 2002;11:517-524.
7. Tarkanen A, Kivelä T. Cumulative incidence of converting from clinically unilateral to bilateral exfoliation syndrome. J Glaucoma. 2004;13:181-184.
8. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86:238-242.
9. Schumacher S, Schlötzer-Schrehardt U, Martus P, Lang W, Naumann GO. Pseudoexfoliation syndrome and aneurysms of the abdominal aorta. Lancet. 2001;357:359-360.
10. İrkeç M. Senil psödoeksfoliyasyonun epidemiyolojik özellikleri üzerinde inceleme. Turk J Ophthalmol. 1979;9:263-268.
11. Yalaz M, Othman I, Nas K, Eroğlu A, Homurlu D, Cikintas Z, Ashouri A. The freguency of pseudoexfoliation syndrome in the eastern mediteranean area of Turkey. Acta Ophthalmol (Copenh). 1992;70:209-213.
12. Cumurcu T, Kilic R, Yologlu S. The frequency of pseudoexfoliation syndrome in the middle Black Sea region of Turkey. Eur J Ophthalmol. 2010;20:1007-1011.
13. Aström S, Lindén C. Incidence and prevalence of pseudoexfoliation and open-angle glaucoma in northern Sweden: I. Baseline report. Acta Ophthalmol Scand. 2007;85:828-831.
14. Jeng SM, Karger RA, Hodge DO, Burke JP, Johnson DH, Good MS. The risk of glaucoma in pseudoexfoliation syndrome. J Glaucoma. 2007;16:117-121.
15. Rao V, Doctor M, Rao G. Prevalence and Prognosis of Pseudoexfoliation Glaucoma in Western India. Asia Pac J Ophthalmol (Phila). 2015;2:121-127.
16. Ritch R, Schlötzer-Schrehardt U. Exfoliation syndrome. Surv Ophthalmol. 2001;45:265-315.
17. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. Am J Ophthalmol. 1997;124:685-687.
18. Hammer T, Schlötzer-Schrehardt U, Naumann GO. Unilateral or asymmetric pseudoexfoliation syndrome? An ultrastructural study. Arch Ophthalmol. 2001;119:1023-1031.
19. Gottanka J, Flügel-Koch C, Martus P, Johnson DH, Lütjen-Drecoll E. Correlation of pseudoexfoliative material and optic nerve damage in pseudoexfoliation syndrome. Invest Ophthalmol Vis Sci. 1997;38:2435-2446.
20. Kivela T, Hietanen J, Uusitalo M. Autopsy analysis of clinically unilateral exfoliation syndrome. Invest Ophthalmol Vis Sci. 1997;38:2008-2015.
21. Parodi MB, Bondel E, Saviano S, Ravalico G. Iris indocyanine green angiography in pseudoexfoliation syndrome and capsular glaucoma. Acta Ophthalmol Scand. 2000;78:437-442.
22. Rao A. Clinical and Optical Coherence Tomography Features in Unilateral versus Bilateral Pseudoexfoliation Syndrome. J Ophthalmic Vis Res. 2012;7:197-202.
23. Puska P, Harju M. Optic nerve head topography in nonglaucomatous, normotensive patients with unilateral exfoliation syndrome. Graefes Arch Clin Exp Ophthalmol. 2009;247:1111-1117.
24. Omura T, Tanito M, Doi R, Ishida R, Yano K, Matsushige K, Ohira A. Correlations among various ocular parameters in clinically unilateral pseudoexfoliation syndrome. Acta Ophthalmol. 2014;92:412-413.

DOI: 10.4274/tjo.28009
Turk J Ophthalmol 2017;47:9-17

Original Article

Diverse Clinical Signs of Ocular Involvement in Cat Scratch Disease

Merih Oray*, Sumru Önal**, Aylin Koç Akbay***, İlknur Tuğal Tutkun*
*İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
**Koç University Faculty of Medicine, Department of Ophthalmology; VKV American Hospital, Ophthalmology Clinic, İstanbul, Turkey
***Koç University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Objectives: To describe ocular manifestations, diagnosis, and treatment of cat scratch disease.

Materials and Methods: Clinical records of patients with ocular cat scratch disease were reviewed.

Results: Thirteen eyes of 10 patients (7 female, 3 male) with a mean age of 26.9±18.5 years were included. Nine patients had a history of cat contact and had systemic symptoms associated with cat scratch disease 2-90 days prior to the ocular symptoms. Ocular signs were: neuroretinitis in 4 eyes (associated with serous retinal detachment in the inferior quadrant in 1 eye), optic neuropathy in 2 eyes (1 papillitis and optic disc infiltration, 1 optic neuritis), retinal infiltrates in 6 eyes, retinochoroiditis in 1 eye, branch retinal arteriolar occlusion in 3 eyes, and endophthalmitis in 1 eye. Visual acuities at presentation were 1.0 in 7 eyes, 0.3 in 1 eye, ≤0.1 in 4 eyes, and light perception in 1 eye. *Bartonella henselae* immunoglobulin (Ig) M and/or IgG were positive in all patients. Systemic antibiotic therapy was administered in all patients. Systemic corticosteroid treatment (15-40 mg/day) was added to the therapy in 4 patients, following 5 days of intravenous pulse methylprednisolone in 2 patients. Treatment was ongoing for 1 patient and the mean treatment duration of the other 9 patients was 47±14.5 days. Visual acuities at final visit were 1.0 in 9 eyes, 0.8 in 1 eye, 0.4 in 1 eye, and no light perception in 1 eye.

Conclusion: Cat scratch disease may present with different ocular signs and should be considered in the differential diagnosis in patients with such presentations.

Keywords: Cat scratch disease, neuroretinitis, retinal infiltrate, optic neuropathy, endophthalmitis

Introduction

Cat scratch disease (CSD) is a systemic condition caused by the gram-negative zoonotic bacillus *Bartonella henselae*.[1] The disease is usually transmitted to humans via the scratch or bite of cats, its natural reservoir. Recently, the cat flea (*Ctenocephalides felis*) has also been implicated as an arthropod vector of the disease.[2,3] The most common clinical manifestation is lymphoid CSD. An individual infected as a result of cat scratch or bite develops erythematous papules or pustules at the site of primary cutaneous inoculation. Within 1-2 weeks, patients develop regional lymphadenopathy (LAP) as well as flu-like systemic symptoms such as fever and fatigue. This stage of the disease is usually self-limited, resolving within a few weeks. LAP is usually unilateral and may affect a single lymph node in 50% of cases, multiple lymph nodes in 20% and multiple lymph node regions in 30%. LAP may be painful and suppurative. Headache, anorexia, nausea, vomiting, and sore throat may also occur. Patients may develop nonspecific maculopapular rash and erythema nodosum.[4,5]

Rarely, CSD may follow a disseminated course. The eye is the most commonly affected organ in disseminated CSD. Besides ocular involvement, hepatosplenic disease (splenomegaly, splenic abscess, or granulomatous hepatitis), encephalitis, pneumonia, or osteomyelitis may be observed.[4,5] The clinical manifestations of ocular involvement include Parinaud oculoglandular syndrome, neuroretinitis, choroidal mass, retinal infiltrate, choroiditis, branch retinal vessel occlusion, serous retinal detachment,

Address for Correspondence: Merih Oray MD, İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 532 407 17 53 E-mail: emerih@yahoo.com **Received:** 27.01.2016 **Accepted:** 25.03.2016

intermediate uveitis, acute endophthalmitis, and anterior uveitis.[6,7]

This study was conducted with the aim of evaluating the various clinical findings associated with ocular involvement of CSD as well as management and follow-up of the disease.

Materials and Methods

The medical records of 6 patients treated and followed at the İstanbul University Faculty of Medicine, Department of Ophthalmology, Uveitis Clinic and 4 patients treated and followed at the Marmara University Faculty of Medicine, Department of Ophthalmology, Uveitis Clinic for CSD with ocular involvement between January 2007 and January 2016 were analyzed. The study was a retrospective observational case series and was conducted in accordance with the Declaration of Helsinki (2008).

The patients' files were evaluated in terms of demographic data, history of cat contact, medical and ocular history, visual acuity, intraocular pressure (IOP) and available anterior chamber flare measurements (Kowa Company Ltd., Electronics and Optics Division, Tokyo, Japan), anterior and posterior segment findings, laboratory findings, and treatment methods used.

The Standardization of Uveitis Nomenclature criteria were used in the evaluation of anterior chamber and vitreous cells.[8] We also evaluated color fundus photographs (Carl Zeiss Meditec, Hennigsdorf, Germany) taken at presentation and during follow-up, and any available fundus fluorescein angiography (Heidelberg Engineering, Heidelberg, Germany or Carl Zeiss Meditec, Hennigsdorf, Germany), optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany or OCT 3, Stratus OCT; Carl Zeiss Meditec), and 30-2 computerized perimeter (Humphrey Systems, Inc., Dublin, CA, USA) findings.

Results

Thirteen eyes of 10 patients (7 female, 3 male) with ocular CSD were included in the study. The mean age at presentation was 26.9±18.5 (6-58) years. There were 5 pediatric patients (≤16 years old). None of the patients were immunodeficient or had other systemic diseases such as diabetes. Prior to presentation, 2 patients (patients 3 and 7) had been previously misdiagnosed with noninfectious optic neuritis and treated with pulse methylprednisolone therapy without additional antibiotic therapy, while 1 patient (patient 9) had been misdiagnosed with autoimmune uveitis and treated with systemic corticosteroid monotherapy. All patients presented for ocular symptoms, and history of cat contact and systemic symptoms were only expressed upon detailed questioning. The patients' CSD-related systemic complaints and findings prior to presentation and ocular findings at time of presentation are presented in Table 1. Nine patients had history of cat contact and had experienced symptoms indicating disseminated disease (fever, abdominal pain, weight loss, malaise, shortness of breath, and/or flu-like

Table 1. Previous systemic complaints and ocular examination findings at time of presentation in patients with ocular involvement of cat scratch disease

Patient Age (years)/ Gender	Cat contact	Systemic complaint	Ocular involvement
1 29/Female	+ (pet)	Anorexia and weight loss for 3 months	Right retinal infiltrates
2 10/Female	*	-	Left optic neuritis
3 27/Male	+ (stray)	Shortness of breath, fatigue 2 days before ocular symptoms	Right retinal infiltrates, branch inferior temporal artery occlusion that developed during follow-up Left neuroretinitis
4 54/Female	+ (pet)	Flu-like symptoms for 15-20 days	Right retinal infiltrates, branch superior nasal artery occlusion Left retinal infiltrates
5 16/Male	+ (pet)	Fatigue, fever 2 weeks prior to ocular symptoms	Right retinal infiltrates Left retinal infiltrates and branch superior nasal artery occlusion
6 41/Female	+ (stray)	Flu-like symptoms 1 week prior to ocular symptoms	Left papillitis and optic disc infiltration
7 12/Female	+ (stray)	Fever and abdominal pain 1 week prior to ocular symptoms	Right neuroretinitis, posterior pole and inferior peripheral serous detachment
8 16/Female	+ (pet)	Flu-like symptoms for 2 weeks	Left neuroretinitis
9 6/Female	+ (stray)	Flu-like symptoms and swelling of the neck 1 month prior to ocular symptoms	Left endophthalmitis
10 58/Male	+ (pet)	Flu-like symptoms 1 month prior to ocular symptoms	Left neuroretinitis and posterior pole retinochoroiditis

*Despite inquiry, it was not clear whether or not the patient had come into contact with a cat

symptoms) starting 2-90 days earlier. For one child (patient 2), it was not clear after questioning whether or not there was a history of cat contact.

The patients' ophthalmologic examination findings at presentation are summarized in Table 2. These findings included neuroretinitis in 4 eyes (associated with inferior peripheral serous retinal detachment in 1 eye), optic neuropathy in 2 eyes (1 with papillitis and optic disc infiltration, 1 with optic neuritis), retinal infiltrate in 6 eyes, retinochoroiditis in 1 eye, branch retinal artery occlusion in 3 eyes, and endophthalmitis in 1 eye (Table 1). Fundus photographs of patients 4, 6, and 7 are shown in Figures 1, 2, and 3, respectively. Visual acuity at presentation was 1.0 in 7 eyes, 0.3 in 1 eye, ≤0.1 in 4 eyes, and light perception in 1 eye. Slit-lamp examination revealed anterior chamber reaction in 2 eyes (patients 7 and 9); patient 9 also presented with endophthalmitis and exhibited wide posterior synechia and vascularized inflammatory membrane posterior to the lens in addition to anterior chamber reaction. The mean IOP of 12 of the eyes was 12.9±1.8 mmHg and mean flare value in the 7 eyes measured was 4.4±0.9 photon/ms. The eye with endophthalmitis (patient 9) was so hypotonic that IOP could not be measured by applanation tonometer. One eye that presented with retinal infiltrate (patient 3) developed branch occlusion in the infiltrated artery on the 9th day of treatment.

All patients tested positive for *Bartonella henselae* immunoglobulin (Ig) M and/or IgG. The results of detailed laboratory, systemic, and ocular imaging are summarized in Table 3. Diagnostic vitreal aspiration was performed on the eye with endophthalmitis (patient 9), but no bacteria, fungi, or hyphae were visible on direct inspection. Bacterial and

Table 2. Ocular examination findings at presentation in patients with ocular involvement of cat scratch disease

Patient Age (years)/ Gender	Eye	Vision	RAPD	Slit-lamp	IOP (mmHg)	Flare (photon/ms)	Vitreous (cells)	Fundus
1 29/Female	Right	1.0	-	No cells	14	4.2	1+	PP retinal infiltrate, CME
2 10/Female	Left	CF 1 m	+	No cells	12	4.3	No cells	Papillary edema, increased vascular tortuosity
3 27/Male	Right	1.0	-	No cells	13	3.1	No cells	Inferior temporal retinal infiltrate*
	Left	0.1	+	No cells	14	3.9	No cells	Neuroretinitis, macular star
4 54/Female	Right	1.0	-	No cells	13	5.1	2+	PP temporal retinal infiltrate in and around the vascular arcades, SN BRAO, SN retinal whitening and edema
	Left	1.0	-	No cells	14	5.8	0.5+	PP temporal retinal infiltrate in and around the vascular arcades
5 16/Male	Right	1.0	-	No cells	14	-	0.5+	ST and IN retinal infiltrate
	Left	1.0	-	No cells	15	-	0.5+	SN BRAO, SN OD retinal infiltrate
6 41/Female	Left	CF 1 m	+	No cells	13	4.2	No cells	Papillitis and OD infiltration
7 12/Female	Right	CF 10 cm	+	1+	8	-	1+	Neuroretinitis, PP preretinal hemorrhage, PP and inferior peripheral serous retinal detachment
8 16/Female	Left	1.0	-	No cells	13	-	No cells	Neuroretinitis, macular star
9 6/Female	Left	LP	-	1+, wide PS, vascularized inflammatory membrane posterior to the lens	Digital hypotony	-	Opacities on orbital USG	Could not be visualized
10 58/Male	Left	0.3	-	No cells	12	-	1+	Submacular retinochoroiditis, macular star

IOP: Intraocular pressure, RAPD: Relative afferent pupillary defect, CF: Counting fingers, LP: Light perception, PP: Posterior pole, CME: Cystoid macular edema, BRAO: Branch retinal artery occlusion, SN: Superonasal, ST: Superotemporal, IN: Inferonasal, OD: Optic disc, PS: Posterior synechia, USG: Ultrasonography, *On the 9th day of treatment, inferotemporal BRAO developed in the infiltrate field

fungal cultures were negative. The vitreal fluid was determined acellular by cytopathologic analysis.

All patients received antibiotic (doxycycline, ciprofloxacin, clarithromycin, azithromycin, rifampicin, ceftriaxone) therapy. This therapy was augmented with intravenous pulse methylprednisolone therapy for 5 days in 2 patients and 15-40 mg/day oral corticosteroid therapy in 4 patients. Antibiotic therapies and systemic corticosteroid doses and durations administered to the patients are shown in Table 4. Treatment was ongoing for patient 6; the mean treatment duration for the other 9 patients was 47±14.5 (21-63) days. Table 5 shows the patients' ophthalmologic examination findings at final examination. Final visual acuity was 1.0 in 9 eyes, 0.8 in 1 eye, 0.4 in 1 eye, and no light perception in the eye that presented with endophthalmitis. Mean follow-up time was 106±79.7 (21-270) days.

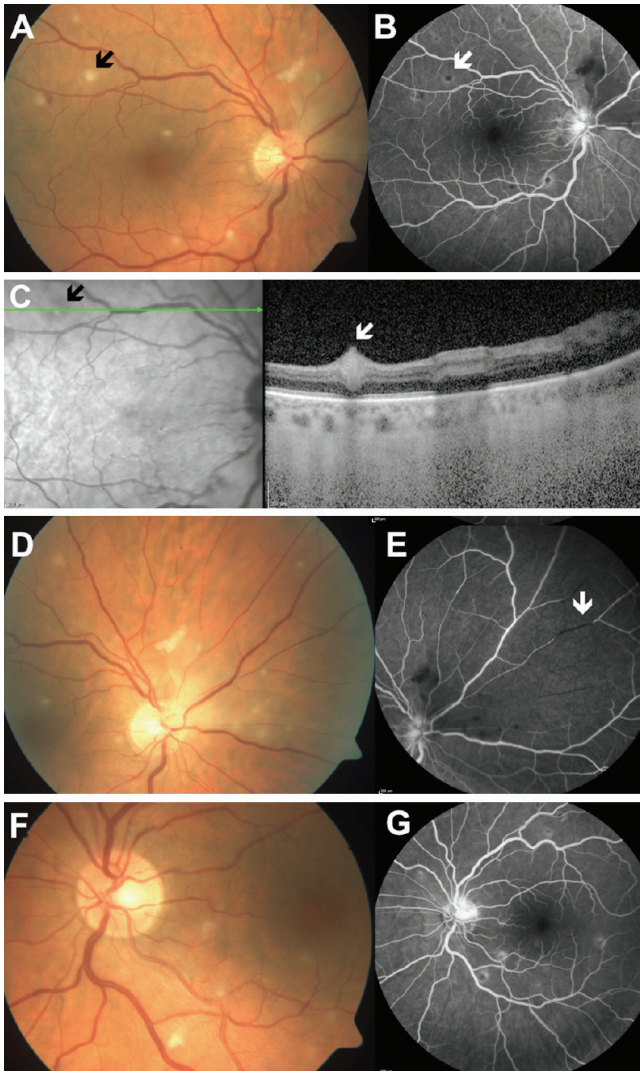

Figure 1. Imaging of patient 4 performed at time of presentation: right eye color fundus photographs (A and D), right eye fluorescein angiography (B and E), optical coherence tomography cross-section including retinal infiltrates in the superotemporal quadrant of the right eye (C), color photography of left eye (F), and fluorescein angiography image (G). Color fundus photography of the right eye shows multiple retinal infiltrates in the posterior pole and superonasal quadrant, and a superonasal area of retinal edema adjacent to the optic disc (A and D). Fluorescein angiography of the right eye shows partial staining of the optic disc, posterior pole retinal infiltrates with central hypofluorescence surrounded by hyperfluorescence, an area of retinal ischemia adjacent to the optic disc and arteriole filling defect (arrow) in the superonasal quadrant (B and E). Optical coherence tomography corresponding to the retinal infiltrates in the superotemporal quadrant of the right eye (indicated by arrows in A, B and C) shows focal hyperreflective retinal thickening (C). Color fundus photography of the left eye revealed multiple retinal infiltrates at the posterior pole (F). Fluorescein angiography of the left eye shows partial staining of the optic disc and posterior pole retinal infiltrates with central hypofluorescence surrounded by hyperfluorescence (G)

Discussion

CSD is a zoonotic disease which shows no discrimination based on gender or race. Though it may occur in patients of any age, the large majority of reported cases are in children and adolescents. According to the literature, adults represent an average of 20% of cases; however, 50% of the cases in our study were adults.[9]

Bartonella henselae often causes chronic bacteremia in kittens and nursing cats, and previous studies have reported feline infection rates of 10-40%.[1,2] Studies have also shown that 90-95% of CSD patients have a history of cat contact, although ocular CSD has also been documented in patients without a history of cat contact.[10] Nearly all of the patients in our series reported cat contact. However, patients only offered specific information regarding cat contact and systemic complaints when asked. None of the patients had been previously diagnosed with CSD, even those who had seen a doctor for the systemic symptoms they experienced prior to their ocular complaints. Therefore, raising awareness of the ocular findings of CSD is important in terms of diagnosis.

The most common and classic sign of ocular CSD is neuroretinitis characterized by sudden, painless vision loss, but this sign is not pathognomonic. Although *Bartonella henselae* is identified as the etiologic factor in two-thirds of neuroretinitis cases, it can also be caused by Behçet's disease, toxoplasma and other infectious diseases.[11,12] Neuroretinitis

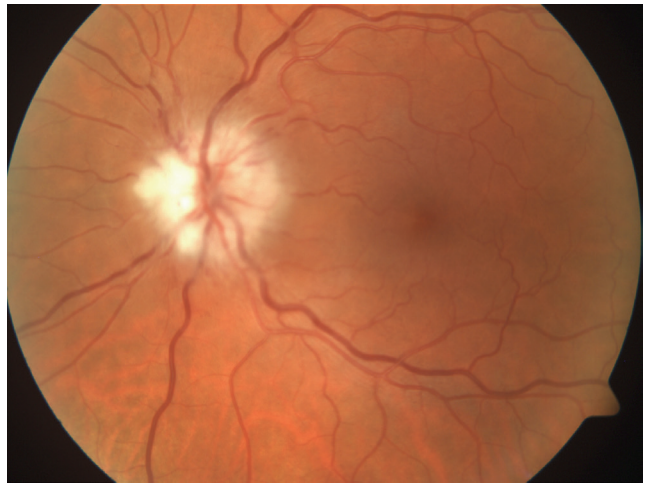

Figure 2. Left eye color fundus photograph of patient 6 taken at presentation shows papillitis and infiltrates in the nasal aspect of the optic disc

is usually unilateral, though bilateral cases have also been reported.[13] Visual acuity in the affected eye can vary between light perception and 1.0 at presentation and vision may rapidly deteriorate within a matter of days. Patients often exhibit relative afferent pupillary defect, dyschromatopsia, and central, cecocentral, or arcuate visual field defects. Macular star may appear a few days after vision loss begins and become more distinct over 2-3 weeks.[11,12,13] In our case series, we noted isolated unilateral neuroretinitis in 2 patients, neuroretinitis with serous retinal detachment in the inferior quadrant in 1 patient, and unilateral neuroretinitis with contralateral retinal infiltrate and subsequent inferotemporal branch arteriolar occlusion in 1 patient. Despite the presence of atypical findings accompanying neuroretinitis in these 2 patients, they had been diagnosed as optic neuritis and treated with pulse methylprednisolone at other medical centers. Isolated optic neuritis may occur rarely in CSD. In our case series, isolated optic neuritis was only observed in one child. Particularly in children and young adults, infectious agents like *Bartonella henselae* must be excluded before initiating pulse methylprednisolone therapy for neuroretinitis or optic neuritis.

CSD may also clinically manifest with retinal infiltrates resembling cotton-wool exudates, retinochoroiditis, retinal artery occlusion, or endophthalmitis, as we observed in our case series. Superficial infiltrates appearing as soft exudates lacking vitreous cells were observed on the retinal surface in 4 patients and on the optic disc in 1 patient in our series. Although the mechanism by which these infiltrates form is not fully understood, it is believed they arise secondary to ischemia resulting from retinal arteriole occlusion.[14] The superficial retinal infiltrates seen in ocular CSD must be differentiated from retinitis or retinal infiltrates seen in ocular manifestations of Behçet's uveitis, sarcoidosis, rickettsia and toxoplasma. Retinal infiltrates in CSD show central hypofluorescence and surrounding hyperfluorescence on FA. On OCT, they appear as focal hyperreflective thickening, particularly in the inner retinal layers. This OCT finding

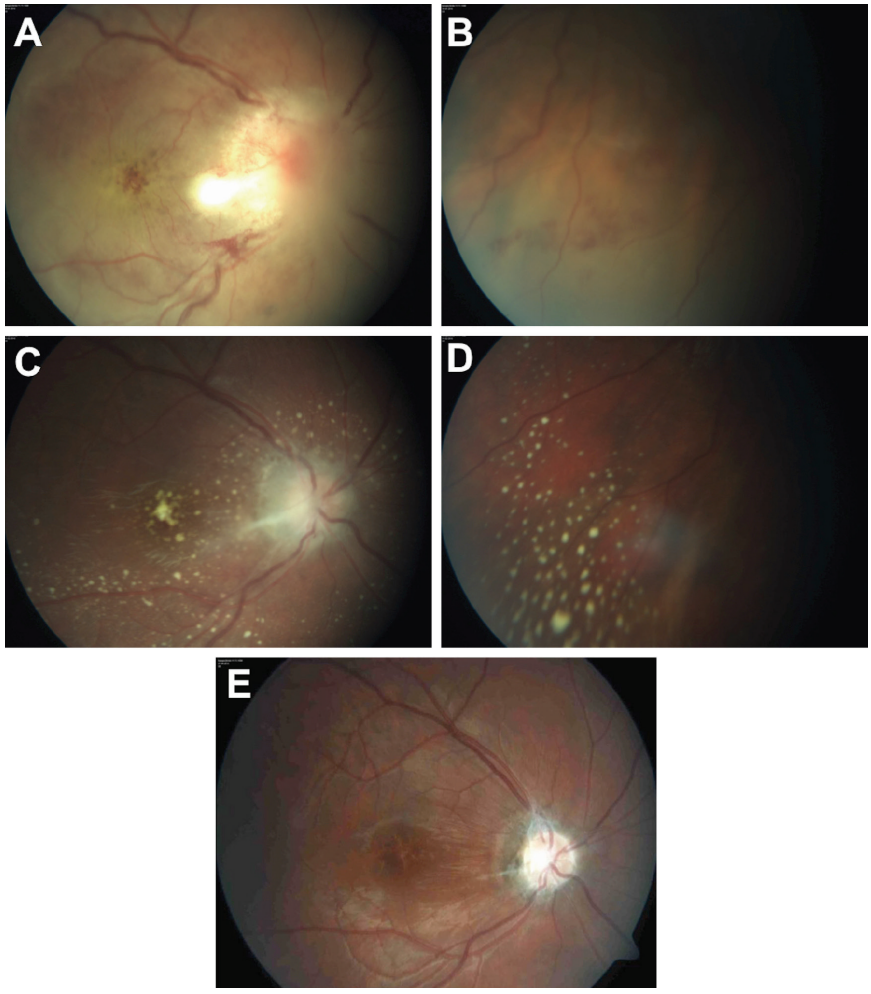

Figure 3. Right eye color fundus photographs from patient 7 taken at presentation (A and B), in the 4th week of treatment (C and D) and at final examination (E). Neuroretinitis, posterior pole hemorrhages, and posterior pole and inferior peripheral serous detachment are evident at presentation (A and B). Reduced optic disc edema, regression and slight pallor of the infiltrates, and multiple hard exudates in the posterior pole and inferior periphery are apparent after 4 weeks of treatment (C and D). At final examination, optic disc pallor and surrounding gliotic membrane as well as a large nerve fiber layer defect in the posterior pole are visible (E)

Table 3. Laboratory findings and imaging results at presentation in patients with ocular involvement of cat scratch disease

Patient Age (years)/ Gender	Negative laboratory results	Positive laboratory results	Ocular imaging	Other imaging
1 29/Female	CSD, PPD; Syphilis, Lyme disease, and Toxoplasma serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG (1:320), ESH: 20 mm/hr	Early hypo-, late hyperfluorescent lesion under the right ST vessel arcade OCT: Right CME and subretinal fluid	-
2 10/Female	TSD, CRP, ESR; Toxoplasma and Brusella serology, Quantiferon, Anti-NMO IgG, *Bartonella henselae* IgG	*Bartonella henselae* IgM	Visual field: Not reliable Retinal nerve fiber layer analysis: Thinning in the left superior quadrant	Cranial MRI: N Orbital MRI: Left optic nerve widening and enhancement Paranasal sinus CT: Sinusitis Chest X-ray: N
3 27/Male	CSD, Hepatitis and syphilis serology, ESR	*T. gondii* IgG, Anti-Hbs, Rubella IgG, Cytomegalovirus IgG, CRP, *Bartonella henselae* IgM (1:100) and IgG (1:320)	FA: Right IT infiltrates show central hypofluorescent surrounded by hyperfluorescent staining, delayed IT arteriolar filling and IT vein wall staining Heavy fluorescein leakage from the left OD, early hypo-, late hyperfluorescent juxtapapillary infiltrate Visual field: Bilateral generalized depression	Cranial MRI: N Orbital MRI: N
4 54/Female	CSD, PPD; Syphilis, ACE, Lysozyme, CRP	*Bartonella henselae* IgM (1:100) and IgG (1:320), ESR: 90 mm/hr,	FA: Focal staining of right/left optic disc, PP retinal infiltrates showing central hypofluorescence and surrounding hyperfluorescence located in and around the temporal vascular arcades Right SN arteriole filling delay Visual field: Right IT quadrantanopsia	Chest X-ray: N
5 16/Male	CSD, ESR, CRP	*Bartonella henselae* IgG	FA: Hyperfluorescence foci in the ST and IN of right eye; sheathing of the veins returning from the OD, SN branch retinal artery occlusion, vascular leakage in temporal periphery in left eye, Visual field: Left IT quadrantanopsia	-
6 41/Female	CSD, CRP, ESR; Toxoplasma, Syphilis, Hepatitis B and C serology, Quantiferon, anti-Aquaporin 4	*Bartonella henselae* IgM (1:100) and IgG (1:320), Homocysteine	FA: Left OD staining, early and late hyperfluorescent soft exudates in the nasal OD	Cranial MRI: N
7 12/Female	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology; ACE, Lysozyme, Peripheral spread	*Bartonella henselae* IgM (1:100) and IgG (1:320), ESR: 25 mm/hr, CRP	-	Chest CT: N
8 16/Female	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG	Visual field: Enlarged blind spot in the left eye	-
9 6/Female	CSD, peripheral spread, ACE, lysozome, PPD, cytomegalovirus serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG, ESR: 25 mm/hr, CRP	Orbital USG: Punctate opacities and choroidal thickening in the vitreous of the left eye	Chest CT: N Orbital MRI: Enhancement around the left ciliary body and along the choroid
10 58/Male	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology; ACE, Lysozyme, Peripheral spread	*Bartonella henselae* IgM and IgG, ESR: 68 mm/hr, CRP	OCT: Left central macular thickening and serous retinal detachment	Chest CT: N OCT: PP subretinal fluid

WBC: Whole blood count, PPD: Purified protein derivative, ESR: Erythrocyte sedimentation rate, FA: Fluorescein angiography, ST: Superotemporal, IT: Inferotemporal, OCT: Optical coherence tomography, CME: Cystoid macular edema, CT: Computed tomography, MRI: Magnetic resonance imaging, NMO: Neuromyelitis optica, IN: Inferonasal, SN: Superonasal, OD: Optic disc, PP: Posterior pole, ACE: Angiotensin converting enzyme, CRP: C-reactive protein, USG: Ultrasonography

resembles the retinal infiltrates seen in Behçet's and rickettsia. Typical OCT findings in toxoplasma retinochoroiditis are focal choroidal thickening under the lesion and concentrated cell infiltration in the posterior hyaloid overlying the lesion. The retinal infiltrates seen in active Behçet's uveitis are generally accompanied by diffuse vitritis, whereas vitreous cells are usually not present over CSD retinal infiltrates.

Superficial retinal infiltrates associated with CSD require close follow-up, as they can lead to branch artery thrombosis, as we observed in our cases. *Bartonella henselae* is an intracellular bacterium that infects erythrocytes and endothelial cells, and may cause vascular occlusion due to its affinity for vascular endothelium. Branch retinal artery occlusion due to CSD has been documented in the literature in various case reports and series.[15,16,17,18,19,20,21] Patients exhibit alterations in visual acuity in accordance with the location of the affected artery. Because our patient's peripheral arteries were involved, his central vision was unaffected, but there was permanent visual field loss in the area corresponding to the occlusion.

Endophthalmitis is a rare presentation of CSD, and only a few such cases have been previously reported. In these patients, Bartonella serology may yield negative results from serum but positive results from vitreous fluid.[22] In our case, serum was positive for *Bartonella henselae* IgM and IgG, thus eliminating the need to evaluate the vitreous fluid.

CSD may cause severe systemic involvement in immunosuppressed patients. It has been reported to lead to bacillary angiomatosis in patients who are HIV positive.[23] None of our patients were immunocompromised and none exhibited any signs of angiomatosis. On the other hand, we have never encountered ocular CSD in any of the HIV-positive patients followed in our clinic.

CSD is diagnosed based on clinical (systemic and/or ophthalmologic) symptoms and findings; serologic tests support the diagnosis. High *B. henselae* IgM titer is an indicator of acute infection and values typically return to normal within 3 months. *B. henselae* IgG rises over time and remains positive up to 2 years. Positive *B. henselae* IgM or high *B. henselae* IgG titer are sufficient for CSD diagnosis.[24] In the present study, all patients tested positive for *B. henselae* IgM and/or IgG. Five patients were positive for both IgM and IgG, 4 were positive for just IgG, and 1 was positive only for IgM.

CSD is self-limited in individuals with healthy immune systems, and treatment is controversial. Treatment with erythromycin, doxycycline, or azithromycin is recommended for patients without immune deficiency or other systemic diseases like diabetes. Rifampicin, trimethoprim-sulfametoxazol, quinolones, or intravenous aminoglycosides are also effective treatment alternatives.[25,26] Of the cases in our series, doxycycline was the most commonly used antibiotic and in most cases was administered in combination with quinolone, macrolide, and/or rifampicin. The duration of antibiotic treatment is disputed. HIV-positive patients are recommended to continue treatment for 2 to 4 months, whereas 10 days to 3 weeks has been reported as sufficient for patients with ocular involvement.[4] The use of systemic corticosteroids in treatment is also a subject of debate. In the present study, we were unable to assess the effect of systemic corticosteroids on prognosis because the cases in our series

Table 4. Treatment methods and durations in patients with ocular involvement of cat scratch disease

Patient Age (years)/Gender	Treatment and duration	Total treatment duration (days)
1 29/Female	Doxycycline 200 mg/day (55 days) + ciprofloxacin 1 g/day (from treatment day 3 to day 14), prednisolone* 15 mg/day (from treatment day 3 to day 21)	55
2 10/Female	Pulse methylprednisolone 750 mg/day (5 days) followed by prednisolone* 25 mg/day (30 days), intravenous ceftriaxone 2 g/day (5 days) and then clarithromycin 500 mg/day (25 days)	30
3 27/Male	Doxycycline 200 mg/day (42 days) + ciprofloxacin 1 g/day (42 days), prednisolone* 40 mg/day (35 days)	42
4 54/Female	Doxycycline 200 mg/day (60 days) + ciprofloxacin 1 g/day (14 days), prednisolone 40 mg/day (60 days)	60
5 16/Male	Doxycycline 200 mg/day (50 days) + ciprofloxacin 1 g/day (50 days), prednisolone 20 mg/day (30 days)	50
6 41/Female	Pulse methylprednisolone 1 g/day (5 days) followed by prednisolone* 40 mg/day, doxycycline 200 mg/day + azithromycin 500 mg/day + rifampicin 600 mg/day (starting on the 11th day of treatment)	Treatment ongoing
7 12/Female	Intravenous clarithromycin 500 mg/day (7 days) followed by doxycycline 100 mg/day (56 days) + rifampicin 300 mg/day (56 days)	63
8 16/Female	Azithromycin 500 mg/day (21 days)**	21
9 6/Female	Doxycycline 100 mg/day (60 days)	60
10 58/Male	Doxycycline 200 mg/day (42 days)	42

*Initial dose is indicated, dosage was gradually reduced each week, **Treatment was discontinued early

Table 5. Ocular examination findings at final follow-up in patients with ocular involvement of cat scratch disease

Patient Age (years)/ Gender	Eye	Vision	RAPD	Slit-lamp	IOP (mmHg)	Flare (photon/ms)	Vitreous (cells)	Fundus
1 29/Female	Right	1.0	-	No cells	13	3.6	No cells	Isolated hard exudates in the macula
2 10/Female	Left	1.0	-	No cells	12	4.6	No cells	Peripapillary atrophy
3 27/Male	Right	1.0	-	No cells	13	3.2	No cells	IT arteriolar sheathing
	Left	0.8	-	No cells	14	3.4	No cells	Peripapillary atrophy, temporal OD whitening
4 54/Female	Right	1.0	-	No cells	13	3.8	No cells	SN arteriolar narrowing
	Left	1.0	-	No cells	13	6.1	No cells	Normal
5 16/Male	Right	1.0	-	No cells	12	-	No cells	Normal
	Left	1.0	-	No cells	11	-	0.5+	Collaterals adjacent to the area of SN branch artery occlusion
6* 41/Female	Left							
7 12/Female	Right	0.4	-	No cells	10	-	No cells	Gliosis over OD, RPE changes in the macula
8 16/Female	Left	1.0	-	No cells	12	-	No cells	Normal
9 6/Female	Left	NLP	-	Regression of the PS and vascularized inflammatory membrane posterior to the lens	Digital hypotony	-	Could not be visualized	Could not be visualized
10 58/Male	Left	1.0	-	No cells	13	-	No cells	Normal

RAPD: Relative afferent pupillary defect, IOP: Intraocular pressure, IT: Inferotemporal, OD: Optic disc, SN: Superonasal, RPE: Retina pigment epithelium, NLP: No light perception, PS: Posterior synechia, *Patient's treatment was ongoing

represented the treatment approaches of two different clinics, the number of patients was low, and the study was retrospective. The prognosis was very good in all patients except the case with endophthalmitis.

Conclusion

CSD is not limited to neuroretinitis or optic neuritis, but can also manifest with superficial retinal infiltrates, retinal artery occlusion, or endophthalmitis. Asking patients about their history of cat contact and performing *Bartonella henselae* serologic analysis are important in the differential diagnosis of these clinical manifestations.

Ethics

Ethics Committee Approval: The research followed the tenets of the Declaration of Helsinki, Informed Consent: An informed consent was obtained before all diagnostic and therapeutic procedures.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Merih Oray, Sumru Önal, İlknur Tuğal Tutkun, Concept: Merih Oray, Aylin Koç Akbay, Sumru Önal, İlknur Tuğal Tutkun, Design: Merih Oray, Sumru Önal, İlknur Tuğal Tutkun, Data Collection or Processing: Merih Oray, Aylin Koç Akbay, Analysis or Interpretation: Merih Oray, Aylin Koç Akbay, Sumru Önal, İlknur Tuğal Tutkun, Literature Search: Merih Oray, Writing: Merih Oray.

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. Kordick DL, Wilson KH, Sexton DJ, Hadfield TL, Berkhoff HA, Breitschwerdt EB. Prolonged Bartonella bacteremia in cats associated with cat-scratch disease patients. J Clin Microbiol. 1995;33:3245-3251.
2. Koehler JE, Glaser CA, Tappero JW. Rochalimaea henselae infection: a new zoonosis with the domestic cat as reservoir. JAMA. 1994;16;271:531-535.
3. Chomel BB, Kasten RW, Floyd-Hawkins K, Chi B, Yamamoto K, Roberts-Wilson J, Gurfield AN, Abbott RC, Pedersen NC, Koehler JE. Experimental transmission of Bartonella henselae by the cat flea. J Clin Microbiol. 1996;34:1952-1956.
4. Spach DH, Koehler JE. Bartonella-associated infections. Infect Dis Clin North Am. 1998;12:137-155.
5. Midani S, Ayoub EM, Anderson B: Cat-scratch disease. Adv Pediatr. 1996;43:397-422.
6. Ormerod LD, Dailey JP. Ocular manifestations of cat-scratch disease. Curr Opin Ophthalmol. 1999;10:209-216.
7. Saatci AO, Oner FH, Kargi A, Kavukcu S. Unilateral neuroretinitis and peripapillary serous detachment in Cat- scratch disease. Korean J Ophthalmol. 2002:16:43-46.
8. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.
9. Koehler JE, Sanchez MA, Garrido CS, Whitfield MJ, Chen FM, Berger TG, Rodriguez-Barradas MC, LeBoit PE, Tappero JW. Molecular epidemiology of Bartonella infections in patients with bacillary angiomatosis-peliosis. N Engl J Med. 1997;337:1876-1883.
10. Zangwill KM, Hamilton DH, Perkins BA, Regnery RL, Plikaytis BD, Hadler JL, Cartter ML, Wenger JD. Cat-scratch disease in Connecticut: epidemiology, risk factors, and evaluation of a new diagnostic test. N Engl J Med. 1993;329:8-13.
11. Dreyer RF, Hopen G, Gass JDM, Smith JL. Leber's idiopathic stellate neuroretinitis. Arch Ophthalmol. 1984;102:1140-1145.
12. Weiss AH, Beck RW. Neuroretinitis in childhood. J Pediatr Ophthalmol Strabismus. 1989;26:198-203.
13. Reed JB, Scales KD, Wong MT, Lattuada CP, Dolan MJ, Schwab IR. Bartonella henselae neuroretinitis in cat scratch disease: diagnosis, management, and sequelae. Ophthalmology. 1998:105:459-466.
14. Ormerod LD, Skolnick KA, Menosky MM, Pavan PR, Pon DM. Retinal and choroidal manifestations of cat-scratch disease. Ophthalmology. 1998;105:1024-1031.
15. Eiger-Moscovich M, Amer R, Oray M, Tabbara KF, Tugal-Tutkun I, Kramer M. Retinal artery occlusion due to Bartonella Henselae infection: a case series. Acta Ophthalmol. 2016;94:e367-370.
16. Cohen SM, Davis JL, Gass DM. Branch retinal arterial occlusions in multifocal retinitis with optic nerve edema. Arch Ophthalmol. 1995;113:1271-1276.
17. Batsos G, Kabanarou SA, Fotiou P, Rouvas A, Xirou T. Retinal arterial occlusive disease in a young patient with cat scratch disease. Case Rep Ophthalmol. 2013;4:87-92.
18. Gray A, Michels K, Lauer A, Samples J. Bartonella henselae infection associated with neuroretinitis, central retinal artery and vein occlusion, neovascular glaucoma, and severe vision loss. Am J Ophthalmol. 2004;137:187-189.
19. Gray AV, Reed JB, Wendel RT, Morse LS. Bartonella henselae infection associated with peripapillary angioma, branch retinal artery occlusion, and severe vision loss. Am J Ophthalmol. 1999;127:223-224.
20. Solley WA, Martin DF, Newman NJ, King R, Callanan DG, Zacchei T, Wallace RT, Parks DJ, Bridges W, Sternberg P Jr. Cat scratch disease: posterior segment manifestations. Ophthalmology. 1999;106:1546-1553.
21. Pinna A, Puglia E, Dore S. Unusual retinal manifestations of cat scratch disease. Int Ophthalmol. 2011;31:125-128.
22. Goldstein DA, Mouritsen L, Friedlander S, Tessler HH, Edward DP. Acute endogenous endophtalmitis due to Bartonella henselae. Clin Infect Dis. 2001;33:718-721.
23. Warren K, Goldstein E, Hung VS, Koehler JE, Richardson W. Use of retinal biopsy to diagnose Bartonella (formerly Rochalimaea) henselae retinitis in an HIV-infected patient. Arch Ophthalmol. 1998;116:937-940.
24. Gulati A, Yalamanchili S, Golnik KC, Lee AG. Cat scratch neuroretinitis: the role of acute and convalescent titers for diagnosis. J Neuroophthalmol. 2012;32:243-245.
25. Jerris RC, Regnery RL. Will the real agent of cat-scratch disease please stand up? Annu Rev Microbiol. 1996;50:707-725.
26. Schwartzman W. Bartonella (Rochalimaea) infections: beyond cat scratch. Annu Rev Med. 1996;47:355-364.

DOI: 10.4274/tjo.81598
Turk J Ophthalmol 2017;47:18-23

Original Article

Demographic Characteristics and Clinical Outcome of Work-related Open Globe Injuries in the Most Industrialised Region of Turkey

Sertaç Argun Kıvanç*, Berna Akova Budak*, Emina Skrijelj*, Mediha Tok Çevik**
*Uludağ University Faculty of Medicine, Department of Ophthalmology, Bursa, Turkey
**Düziçi Sate Hospital, Ophthalmology Clinic, Osmaniye, Turkey

Abstract

Objectives: To evaluate demographic characteristics and clinical outcomes of work-related open globe injuries in the most industrialized region of Turkey.

Materials and Methods: The demographic and medical records of patients with work-related open globe injuries who presented to the ophthalmology or emergency departments with an official occupational accident report were retrospectively reviewed. Visual acuity categories were defined according to the World Health Organization. The injury types and zones of the open globes were classified according to Birmingham Eye Trauma Terminology System.

Results: Among 479 patients with work-related eye injuries in 5 years, there were 102 eyes of 101 patients with open globe injuries (21%). The mean age of the patients was 34.5±8.9 years with a mean follow-up of 12.5±12.6 months. The injuries peaked in June in the hour between 12:00 and 13:00. Eighty-six percent presented to emergency services within 12 hours after the injury. Twenty-two percent of the patients had been wearing protective eyewear at the time of injury. The open globe injuries were penetrating in 51%, intraocular foreign body in 40%, rupture in 7% and perforation in 2% of the eyes. The most frequent finding was traumatic cataract. Final visual acuity of 33.3% of patients was below 3/60. Seventy-eight percent of patients that had visual acuity worse than 6/18 at presentation had visual acuity of 6/18 or better at final visit. Sixty-three percent of eyes which had injuries involving all 3 zones resulted in phthisis bulbi, enucleation or evisceration.

Conclusion: Work-related open globe injuries may have severe consequences such as visual impairment and blindness among the young male working population in industrialized areas. Nearly half of the occupational open globe injuries resulted in visual impairment and blindness.

Keywords: Blindness, work-related eye injury, open globe injury, visual impairment, work accident

Introduction

Work-related ocular trauma is an important cause of visual impairment and blindness globally, with a significant socioeconomic impact.[1,2,3,4] In Turkey, it has been reported that among the work-related injuries admitted to tertiary emergency centers, 3.9-5% were ocular trauma.[5,6] Open globe injuries were found to be most serious type of ocular trauma with regard to visual outcome.[7,8] Work-related open globe injuries constitute a considerable proportion of all open globe injuries (28.4-40.3%) in different reports from Turkey.[9,10,11,12] To our knowledge, the outcome of work-related open globe injuries in Turkey has not been reported before. In this study, our aim was to evaluate demographic characteristics and clinical outcome of work-related open globe injuries in the most industrialized region of Turkey.

Materials and Methods

The medical records of patients with ocular injuries who presented to the Ophthalmology or Emergency departments of Uludağ University between January 2010 and December 2015 with official occupational accident reports were retrospectively reviewed. The patients with work-related open globe injuries were included. Age, sex, information about the injury season and time, the injured eye, the use of protective eyewear, the objects

Address for Correspondence: Berna Akova Budak MD, Uludağ University Faculty of Medicine, Department of Ophthalmology, Bursa, Turkey
Phone: +90 224 295 24 47 E-mail: bernaakova@hotmail.com **Received:** 01.02.2016 **Accepted:** 02.05.2016

that caused the trauma, initial and follow-up examinations, zone of injury, primary and secondary surgical procedures and outcomes were recorded. Patients were contacted by phone to complete missing information regarding their workplace and use of protective eyewear. We obtained complete information for 85 of 101 patients; information about 16 patients was not available. The initial and final visual acuities (VA) of the patients were divided into visual impairment categories as defined by the World Health Organization (WHO). WHO criteria are accepted worldwide, so we used these criteria for standardization. Blindness is defined as a presenting VA worse than 3/60 or a corresponding visual field loss of less than 10° in the better eye. Visual impairment is defined as a presenting VA of worse than 6/18 and equal to or better than 3/60.[13] The injury types and zones of the open globes were classified according to the Birmingham Eye Trauma Terminology System.[14]

The SPSS 22 statistical programme (IBM Corp., USA) was used for statistical analysis. Pearson correlation test was used to assess the correlation between initial VA, number of surgeries and final VA. Pearson chi-squared test was used to compare initial and final visual impairment/blindness status. Fisher's exact test was used to assess the relation between the use of protective eyewear and the presence of protective eyewear in the workplace. Paired samples t-test was used to compare initial and final VA.

Results

Among 479 patients with work-related eye injuries seen at Uludağ University in 5 years, there were 102 eyes of 101 patients with open globe injuries (21%). The mean age of the patients was 34.5±8.9 years with a mean follow-up of 12.5±12.6 months. The majority of the injuries occurred in men (99%). About 40% of the injuries took place in June (13.7%), December (12.7%) and March (11.8%) (Figure 1). Right eyes were injured in 39 patients (38.3%), and left eyes were injured in 61 patients (60.4%). Bilateral open globe injury was observed in one patient. Distribution of time of injury over 24 hours (expressed as one hour intervals) is shown in Figure 2. The mean time elapsed from injury to presentation to emergency services was 7.4±13.3 hours. Eighty-six percent presented to emergency services within 12 hours of the injury, 6% presented 12-24 hours after the injury, and 6% presented 24-48 hours after the injury. One patient presented 4 days after the injury and one presented 12 days after the injury. Both had endophthalmitis at initial examination. The objects that caused the injury and the occupations of the patients are given in Table 1 and Table 2.

Nineteen patients (22%) had been wearing protective eyewear at the time of injury, 91.7% (17 patients) of them stated that their workplace provided protective eyewear. Sixty-six patients (78%) had not been wearing protective eyewear at the time of injury, and 39.5% of them (26 patients) stated that their workplace had protective eyewear. The ratio of patients who wore protective eyewear was significantly higher in workplaces that provided protective eyewear (p=0.002), and a significantly higher proportion of large-scale companies provided protective eyewear when compared with small-scale companies (p<0.001). Most of the patients who had been wearing protective eyewear at the time of injury were working in large companies (p=0.019).

Of 101 patients, 9 (9%) had another work-related injury, before or after the work-related open globe injury; these were hand injury in 5 patients, fall in 1 patient, and ocular trauma and corneal foreign body in 3 patients.

The open globe injuries were classified according to Birmingham Eye Trauma Terminology System[14] as penetrating in 52 (51%), intraocular foreign body in 41 (40%) and rupture in 7 (7%) and perforation in 2 (2%) eyes. There were 52 zone I (50.9%), 10 zone II (9.9%) and 2 zone III (1.9%) injuries. Fifteen eyes (14.7%) had injuries involving zones I and II, 16 eyes (15.7%) had injuries involving all 3 zones and 7 eyes (6.9%) had injury involving zones II and III. Traumatic cataract and/or crystalline lens dislocation were observed in 73

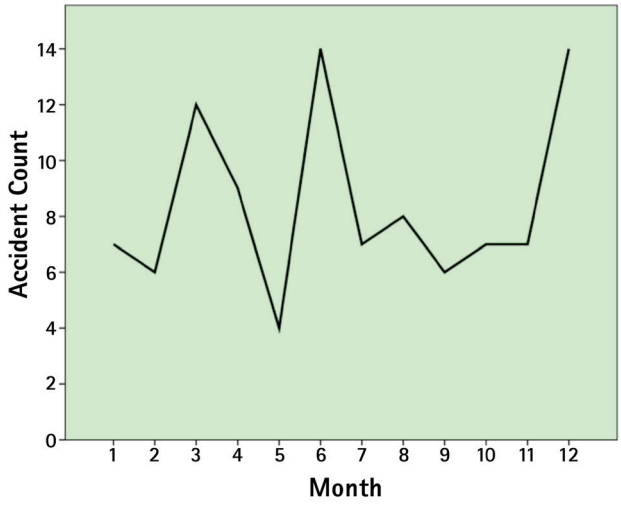

Figure 1. Distribution of work-related open globe injuries by month of occurrence

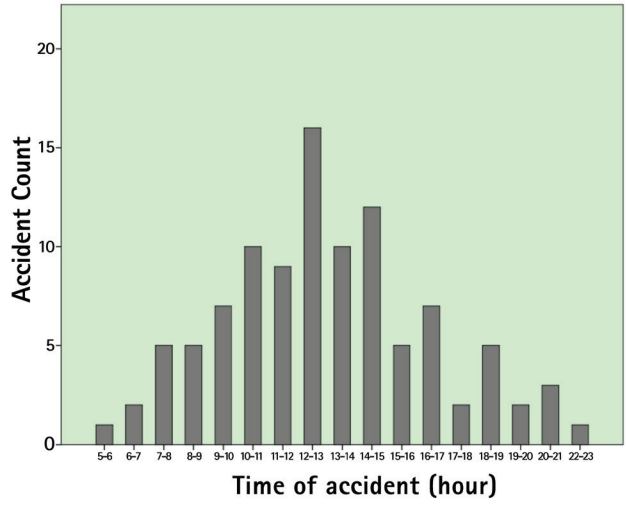

Figure 2. Distribution of work-related open globe injuries by time of occurrence

eyes (71.5%), and other findings were iris injury in 63 eyes (61.8%), hyphema in 47 eyes (46.1%), vitreous hemorrhage and/or posterior segment injury in 40 eyes (39.2%). In 16 (15.7%) cases, there were additional injuries: limb injury in 2, eyelid laceration in 10, multiple lacerations involving the eyebrow and face in 3, and orbital wall and zygomatic fracture in 1 patient. Presenting VA acuity was light perception in 26 (25.7%) and no light perception in 10 (9.9%) patients. The mean logMAR VA of the others was 1.7±1.3. The mean final logMAR VA was 0.6±0.8. Final VA was no light perception in 16 patients (15.8%) and light perception in 7 patients (6.9%). The final VAs were significantly improved compared to initial VA ($p<0.001$) and there was a significant positive correlation between initial and final VA ($r=0,385$, $p=0,002$). The initial and final VAs of the patients and categories of visual impairment according to WHO criteria[13] are shown in Table 3. Forty-six percent of patients who were blind at presentation were blind at final visit. Seventy-eight percent of patients that had vision worse than 6/18 at presentation had VA of 6/18 or better at final visit. Three patients who had 6/18 or better VA initially became visually impaired or blind during follow-up ($p<0.001$). Out of 102 eyes, 83 underwent primary repair. Lens aspiration was performed in 4 eyes and lens aspiration with removal of intralenticular foreign body was performed simultaneously with primary repair in one patient. Nine patients underwent primary repair and removal of foreign bodies in the anterior chamber. Out of 19 eyes that did not require primary repair, 3 eyes without IOFB were treated with bandage contact lens for corneal laceration, 13 eyes underwent pars plana vitrectomy and IOFB removal, 2 underwent phacoemulsification for removal of intralenticular foreign body, and 1 underwent anterior chamber washout for removal of foreign body in the anterior chamber. Primary repair was performed within 12 hours of admission in 60 patients and within 24 hours in 16 patients. Six patients were referred to our department after primary repair elsewhere. The primary surgery was performed after 48 hours in 2 patients. The others who did not require primary repair underwent surgery for IOFB removal after an average of 4.6±3.5 days. Of 43 eyes with IOFB, 29 were in the vitreous or lodged in the retina, 10 were in the anterior chamber, and 2 were intralenticular. Two foreign bodies were actually outside the globe, 1 in the orbit and the other in the ethmoid sinus. Forty of the IOFBs were metallic and 3 were stone. The mean number of surgeries was 1.8±1.0. There was a positive correlation between the number of surgeries performed and logMAR VA ($r=0.252$, $p=0.025$). Primary and additional surgeries performed after primary repair are shown in Table 4.

At final visit, 46 eyes were pseudophakic, 26 were phakic, 10 had traumatic cataract, 15 eyes were aphakic, and 4 eyes had undergone evisceration and 1 eye had undergone enucleation. Twelve of the 34 eyes that had VA under 3/60 resulted in phthisis bulbi, enucleation or evisceration. Ten of these 12 eyes had injuries encompassing all zones, and 2 eyes had injuries in zones II and III. The final clinical outcomes of patients with respect to visual impairment and blindness are shown in Table 5.

Table 1. Causative objects of the work-related open globe injuries

	Number	Ratio (%)
Metallic foreign body	32	31.3
Unknown foreign body	21	20.6
Nail	12	11.8
Wire	9	8.8
Wood	6	5.9
Stone	3	2.9
Glass	3	2.9
Wrench	2	2.0
Screwdriver	2	2.0
Scissors	1	1.0
Finger	1	1.0
Plastic	1	1.0
Iron plate	1	1.0
Ceramic	1	1.0
High pressure oil	1	1.0
Accumulator explosion	1	1.0
Knife	1	1.0
Air hose	1	1.0
Screw	1	1.0
Coil spring	1	1.0
Pressure gauge explosion	1	1.0
Total	102	100.0

Table 2. Industrial sectors of work-related open globe injuries occurred

Industrial sector	Number	Ratio (%)
Metalworking industry	39	38.2
Construction industry	22	21.6
Automotive industry	11	10.8
Furniture industry	11	10.8
Textile industry	4	3.9
Machinery industry	3	2.9
Municipal employees	3	2.9
Glass and ceramic industry	3	3.0
Office worker	2	2.0
Mining industry	2	2.0
Conduit industry	1	1.0
Total	101	100.0

Discussion

Both in Turkey and worldwide, eye injuries, especially open globe injuries (either work-related or not), predominantly affect men.[15,16,17,18,19,20] Accordingly, 99% of the patients in the

Table 3. The initial and final visual acuities of the patients and categories of visual impairment according to World Health Organization criteria[13]

	Final visual acuity											
	<3/60			6/18-3/60			≥6/18			Total		
Initial visual acuity	Count	Row n %	Column n %	Count	Row n %	Column n %	Count	Row n %	Column n %	Count	Row n %	Column n %
<3/60	32	**46.4**	94.1	10	14.5	76.9	27	39.1	49.1	69	100.0	67.6
6/18-3/60	1	11.1	2.9	1	11.1	7.7	7	**77.8**	12.7	9	100.0	8.8
≥6/18	1	4.2	2.9	2	8.3	15.4	21	87.5	38.2	24	100.0	23.5
Total	34	33.3	100.0	13	12.7	100.0	55	53.9	100.0	102	100.0	100.0

Table 4. Primary and additional surgeries performed after primary repair

Operations*	Primary repair	Eyelid repair	Traumatic ctaract surgery	IOL implantation	Pars plana vitrectomy	IOFB extraction	Silicon oil removal	Evisceration	Enucleation	Anterior chamber washout	Penetrating keratoplasty
1st	83	10	14	7	13	26	-	-	-	-	-
2nd	-	1	33	28	23	15	1	3	-	1	-
3rd	-	-	4	10	10	-	2	1	1	-	-
4th	-	-	-	-	2	-	5	-	-	-	1
5th	-	-	1	1	-	-	2	-	-	-	-

*Some of the operations in each row were performed simultaneously with other operations, IOL: Intraocular lens, IOFB: Intraocular foreign body

Table 5. The final clinical outcomes of patients according to World Health Organization visual acuity categories

	Globe	Lens				Cornea		Retina						
VA	Phthisis, evisceration, enucleation	Aphakic	Phakic	Traumatic cataract	Pseudophakic	Corneal scar	Band keratopathy, corneal decompensation	Macular scar	Retinal traction	Retinal detachment	Macular hole	Retinal scar except macula	Macular fold	Retinal vein occlusion
<3/60	12	13	2	5	9	3	2	3	-	2	1	1	-	2
3/60-6/18	-	-	3	-	10	5	-	-	-	-	-	1	-	-
>6/18	-	2	21	5	27	1	-	-	2	-	-	2	1	-
Total	12	15	26	10	46	9	2	3	2	2	1	4	1	2

VA: Visual acuity

present study were men. This may be related to the working sectors of the patients. The metalwork and construction sectors, which employ mostly men, were predominant in this study. In this study, the mean age of the subjects was 34.5±8.9 years. A study involving work-related eye injuries from western Turkey reported that the mean age was 28.1±6.5 years, but the majority of the injuries occured in individuals 25-34 years old.[21] In another study from China, the mean age was reported to be 39.2±11.16 years.[1] A similar result was reported from northern Thailand.[4] However, these studies evaluated all occupational eye trauma involving both closed and open globe injuries. Kanoff et al.[22] reported a mean age of 35.8 years in 146 patients with open globe injuries sustained at work, similar to this study.

The injuries in this study peaked in June. This was in accordance with a study evaluating open globe injuries from northwest Turkey, in which 33.7% of the injuries occurred in the workplace. They noted peaks in July and June.[17] In southern Turkey, most of the penetrating eye injuries also took place in summer.[23] Other studies have also reported that the majority of both work-related and non-work-related eye trauma occurred during summer months.[1,24] In a large series of work-related eye injuries, the injuries peaked after lunch between 13:00 and 14:00.[21] In contrast, another study reported that most work-related injuries occurred from 16:00 to 18:00.[1] In the present study, the injuries peaked between 12:00 and 13:00. The second peak was between 14:00 and 15:00. A previous study reported that most of the work-related open globe injuries occurred at 10:00 to 11:00 and 15:00 to 16:00,[22] which was corroborated by another study.[25] It seems that the injuries usually occur around noon and afternoon. These variations may be related with working shifts or timing of lunch or the hazard of tasks performed in these time intervals. Various studies have documented metallic objects as the most common reported cause of injury in occupational eye injuries, with nails constituting the higher percentages.[1,22,26] In the present study, miscellaneous metallic foreign bodies were the most common cause of injury, followed by iron particles and nails. These may be attributed to the industrial sectors in which the patients worked. Metalwork was the most common sector (38.2%) in this study. Most of the patients (86%) in the present study presented to emergency services within 12 hours after the injury, similar to another report of work-related open globe injury.[22] The time between injury and presentation may be critical to achieve favorable outcome of primary repair.[27,28]

In this study, 78% of the patients did not wear protective eyewear. This is consistent with the findings of other studies.[20,29] A study identifying risk factors for occupational eye injuries observed a 50% reduction in the incidence rate of eye injury among workers wearing protective eyewear compared to those who did not.[30] Therefore, it may be useful to study what factors have an impact on use of protective eyewear both in Turkey and worldwide.

The clinical outcomes of the occupational traumas seen in the present study varied. Evisceration was performed in 4 eyes and enucleation in 1 eye. Similar rates of enucleation have been reported after work-related open globe injuries.[22,26] In our study, two-thirds of the eyes that had injuries involving all 3 zones and one-third of the eyes that had injuries involving zones II and III resulted in phthisis bulbi, evisceration and enucleation. These findings suggest that large injuries and posterior segment involvement were related with poor visual outcomes.

In another study including 43 patients with occupational open globe injuries, the final VA was below 6/60 in 67% of the patients.[29] In a study of nail-gun-induced open globe injuries, 86% were work-related, and 40.6% of the patients had a final VA below 20/200.[31] Bauza et al.[26] reported a final VA below 20/200 in 37.2% and Kanoff et al.[22] reported that 25.9% of their patients had a VA below 20/200. In the present study, 33.3% of the patients had a final VA below 3/60. The relatively higher percentage of blindness in this study may be due to the fact that our department is the only tertiary center that receives complicated cases from a large industrialized region. Work-related open globe injuries may have severe consequences such as visual impairment and blindness among the young male worker population in industrialized areas. Nearly half of occupational open globe injuries result in visual impairment and blindness.

Conclusion

Workers suffering work-related injuries may need several surgeries, and are unable to work during the treatment and rehabilitation period. Most of them lose their job or retire. Those who continue to work are usually monocular, which may increase their exposure to another occupational injury. These situations may cause financial, social and psychological burden on the workers, their families, employers and society. To avoid these burdens, simple protective measures such as use of protective eyewear or regular checking of working hours should be taken, especially in small-scale industrial sectors. Education of both workers and employers about protective measures and occupational injuries may raise their awareness.

Ethics

Ethics Committee Approval: Retrospective study, Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sertaç Argun Kıvanç, Berna Akova Budak, Concept: Sertaç Argun Kıvanç, Berna Akova Budak, Design: Sertaç Argun Kıvanç, Berna Akova Budak, Data Collection or Processing: Emina Skrijelj, Mediha Tok Çevik, Analysis or Interpretation: Sertaç Argun Kıvanç, Berna Akova Budak, Emina Skrijelj, Mediha Tok Çevik, Literature Search: Emina Skrijelj, Mediha Tok Çevik, Writing: Berna Akova Budak, Sertaç Argun Kıvanç.

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. Cai M, Zhang J. Epidemiological Characteristics of Work-Related Ocular Trauma in Southwest Region of China. Int J Environ Res Public Health. 2015;12:9864-9875.

2. Xiang H, Stallones L, Chen G, Smith GA. Work-related eye injuries treated in hospital emergency departments in the US. Am J Ind Med. 2005;48:57-62.
3. Mansouri MR, Hosseini M, Mohebi M, Alipour F, Mehrdad R. Work-related eye injury: the main cause of ocular trauma in Iran. Eur J Ophthalmol. 2010;20:770-775.
4. Chaikitmongkol V, Leeungurasatien T, Sengupta S. Work-Related Eye Injuries: Important Occupational Health Problem in Northern Thailand. Asia Pac J Ophthalmol (Phila). 2015;4:155-160.
5. Karakurt Ü, Satar S, Açıkalın A, Bilen A, Gülen M, Baz Ü. Analysis of Occupational Accidents Admitted to the Emergency Medicine Department. JAEM. 2013;12:19-23.
6. Ozkan S, Kiliç S, Durukan P, Akdur O, Vardar A, Geyik S, Ikizceli I. Occupational injuries admitted to the Emergency Department. Ulus Travma Acil Cerrahi Derg. 2010;16:241-247.
7. Liggett PE, Pince KJ, Barlow W, Ragen M, Ryan SJ. Ocular trauma in an urban population. Review of 1132 cases. Ophthalmology. 1990;97:581-584.
8. Pimolrat W, Choovuthayakorn J, Watanachai N, Patikulsila D, Kunavisarut P, Chaikitmongkol V, Ittipunkul N. Predictive factors of open globe injury in patients requiring vitrectomy. Injury. 2014;45:212-216.
9. Çankaya AB, Taşdemir G, Taşdemir S, Zilelioğlu O. Long Term Results Of Our Penetrating Eye Injury Cases And Factors Influencing Final Visual Outcome. Turk J Ophthalmol. 2009;39:220-226.
10. Ortak H, Erbil HH. Perforan göz yaralanmalarının epidemiyolojik değerlendirilmesi. Tıp Araştırmaları Dergisi. 2010;8:150-155.
11. Özkurt Y, Oral Y, Kocamış Ö, Çömez A, Karacan Ö, Erbaydar T, Doğan ÖK. Açık göz yaralanmalarının yaş, meslek ve epidemiyolojik özelliklerinin değerlendirilmesi. Turk J Ophthalmol. 2004;34:424-428.
12. Uçgun Nİ, Şerefli Ş, Evren Ö. Açık göz yaralanmalarının yaş,meslek ve epidemiyolojik özelliklerinin değerlendirilmesi. Mn Oftalmoloji. 2008;15:177-179.
13. Word Health Organization. Universal eye health : a global action plan 2014-2019. WHO Press; Spain; 2013: p.7.
14. Kuhn F, Morris R, Witherspoon CD, Heimann K, Jeffers JB, Treister G. A standardized classification of ocular trauma. Ophthalmology. 1996;103:240-243.
15. Alpay A, Ozcan O, Uğurbaş SC, Uğurbaş SH. Eye injuries at a tertiary health center in the west Black Sea region, Turkey. Ulus Travma Acil Cerrahi Derg. 2012;18:118-124.
16. Pelitli Gürlü V, Esgin H, Benian O, Erda S. The factors affecting visual outcome in open globe injuries. Ulus Travma Acil Cerrahi Derg. 2007;13:294-299.
17. Altıntaş L, Altıntaş O, Yüksel N, Pirhan D, Ozkan B, Cağlar Y. Pattern of open eye injuries in northwest Turkey: a retrospective study. Ulus Travma Acil Cerrahi Derg. 2011;17:334-339.
18. Kaptan AŞ, Kandemir B, Dib NE, Sayman IB, Selvi C, Doğan ÖK. Epidemiology of Open-Globe Injuries. Turk J Ophthalmol. 2010;40:84-88.
19. Akova Budak B, Kıvanç SA, Başkaya K, Baykara M, Yücel AA. İş kazaları sonucu gelişen kapalı glob yaralanmalarının değerlendirilmesi. J Clin Anal Med. 2015;6:375-378.
20. Thompson GJ, Mollan SP. Occupational eye injuries: a continuing problem. Occup Med. 2009;59:123-125.
21. Serinken M, Turkcuer I, Cetin EN, Yilmaz A, Elicabuk H, Karcioglu O. Causes and characteristics of work-related eye injuries in western Turkey. Indian J Ophthalmol. 2013;61:497-501.
22. Kanoff JM, Turalba AV, Andreoli MT, Andreoli CM. Characteristics and outcomes of work-related open globe injuries. Am J Ophthalmol. 2010;150:265-269.
23. Cakmak SS, Unlu MK, Olmez G, Caca I, Sakalar YB, Acemoglu H. Penetrating eye injuries from southeastern Anatolia region of Turkey. Public Health. 2004;118:570-575.
24. Mansouri M, Faghihi H, Hajizadeh F, Rasoulinejad SA, Rajabi MT, Tabatabaey A, Shoaee S, Faghihi S, Khabazkhoob M. Epidemiology of open-globe injuries in Iran: analysis of 2,340 cases in 5 years. Retina. 2009;29:1141-1149.
25. Chen SY, Fong PC, Lin SF, Chang CH, Chan CC. A case-crossover study on transient risk factors of work-related eye injuries. Occup Environ Med. 2009;66:517-522.
26. Bauza AM, Emami P, Son JH, Langer P, Zarbin M, Bhagat N. Work-related open-globe injuries: demographics and clinical characteristics. Eur J Ophthalmol. 2013;23:242-248.
27. Zhang Y, Zhang MN, Jiang CH, Yao Y, Zhang K. Endophthalmitis following open globe injury. Br J Ophthalmol. 2010;94:111-114.
28. Ahmed Y, Schimel AM, Pathengay A, Colyer MH, Flynn HW Jr. Endophthalmitis following open-globe injuries. Eye (Lond). 2012;26:212-217.
29. Vasu U, Vasnaik A, Battu RR, Kurian M, George S. Occupational open globe injuries. Indian J Ophthalmol. 2001;49:43-47.
30. Blackburn J, Levitan EB, MacLennan PA, Owsley C, McGwin G Jr. A case-crossover study of risk factors for occupational eye injuries. J Occup Environ Med. 2012;54:42-47.
31. Kolomeyer AM, Shah A, Bauza AM, Langer PD, Zarbin MA, Bhagat N. Nail gun-induced open-globe injuries: a 10-year retrospective review. Retina. 2014;34:254-261.

DOI: 10.4274/tjo.73659
Turk J Ophthalmol 2017;47:24-27

Original Article

Anterior Segment Findings in Women with Polycystic Ovary Syndrome

Seda Karaca Adıyeke*, İbrahim Karaca***, Suna Yıldırım**, Mehmet Adıyeke****, İbrahim Uyar**, Gamze Türe*

*Tepecik Training and Research Hospital, Ophthalmology Clinic, İzmir, Turkey
**Tepecik Training and Research Hospital, Gynecology and Obstetrics Clinic, İzmir, Turkey
***Aliağa State Hospital, Gynecology and Obstetrics Clinic, İzmir, Turkey
****Bergama State Hospital, Gynecology and Obstetrics Clinic, İzmir, Turkey

Abstract

Objectives: This study aimed to investigate the anterior segment in women with polycystic ovary syndrome (PCOS) and to compare them with those of healthy reproductive-age female volunteers.

Materials and Methods: The study included 50 right eyes of 50 women with PCOS (group 1) and 50 right eyes of 50 healthy women (group 2). Intraocular pressure, Schirmer's test, tear film break-up time and central corneal thickness were evaluated in all subjects. Correlations between serum hormone (estradiol and testosterone) levels and observed findings were also investigated.

Results: Mean central corneal thickness values were significantly higher in the PCOS group (p=0.001). The mean intraocular pressures values were similar between the two groups (p=0.560). Schirmer's test results and tear film break-up time values were significantly lower in the PCOS group (p=0.001 and p=0.001 respectively). Serum estradiol levels were moderately positively correlated with mean central corneal thickness (r=0.552), weakly positively correlated with intraocular pressure (r=0.351) and weakly negatively correlated with tear film break-up time (r=-0.393). Serum free testosterone levels were weakly correlated with intraocular pressure (r=0.342) and central corneal thickness (r=0.303), and showed weak negative correlations with Schirmer's test results (r=-0.562) and tear film break-up time (r=-0.502).

Conclusion: PCOS leads to physiological and structural changes in the eye. Dry eye symptoms were more severe and central corneal thickness measurements were greater in patients with PCOS. Those are correlated serum testosterone and estradiol levels.

Keywords: Polycystic ovary syndrome, dry eye, corneal thickness

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age. The prevalence is generally about 17%, though the rate varies with different diagnostic criteria.[1] Chronic anovulation seems to be the main physiopathologic factor.[1] It is characterized by elevated circulating levels of the most biologically active androgens secreted primarily by the ovaries, such as androstenedione and testosterone.

In recent years it has been discovered that female sex steroids have both systemic and ocular effects. Estrogen, progesterone and androgen receptors have been found in the cornea, lens, iris, ciliary body, retina, lacrimal glands, meibomian glands and conjunctiva.[2] This is best illustrated by the fact that dry eye is more prevalent among women, especially following menopause, increases during pregnancy and lactation, and resolves with hormone replacement therapy.[3] In the present study, we aimed to compare central corneal thickness (CCT), intraocular pressure (IOP), tear film break-up time (TBUT) and Schirmer test values between PCOS patients and healthy individuals. We evaluated the correlation between these findings and testosterone and estradiol levels and body mass index.

Address for Correspondence: Seda Karaca Adıyeke MD, Tepecik Training and Research Hospital, Ophthalmology Clinic, İzmir, Turkey
Phone: +90 532 610 26 21 E-mail: skaracaadiyeke@hotmail.com **Received:** 17.12.2015 **Accepted:** 15.05.2016

Materials and Methods

The study was approved by the Turkish Ministry of Health Public Hospitals Administration, General Secretary of the Association of Public Hospitals in the Northern İzmir Province, Tepecik Training and Research Hospital Local Ethics Committee. Informed consent was obtained from all study subjects. The study included 50 women who presented to the Tepecik Training and Research Hospital and were diagnosed with PCOS between September 2014 and November 2014, and 50 female volunteers with no endocrine-related complaints or disorders who presented to our clinic during the same period. The study was conducted in accordance with the principles stated in the Declaration of Helsinki. As per the Rotterdam 2003 criteria, PCOS diagnosis was based on the presence of at least 2 of the following: oligomenorrhea (more than 45 days between menstrual periods or fewer than 8 menstrual periods per year), hyperandrogenism, clinical hirsutism (acne, hirsutism, androgenic alopecia, acanthosis nigricans) or laboratory findings indicating elevated androgen levels (elevated serum total or free testosterone levels), and the appearance of polycystic ovary on ultrasonography (2-9 mm in diameter, 12 or more follicles and/or increased ovary volume [>10 mL]).[4] Thyroid functions, luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, and prolactin, dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, and total testosterone levels were assessed for all patients. Samples were taken from all patients at the same time of day. Patients with thyroid disease, hyperprolactinemia, Cushing's syndrome, or congenital adrenal hyperplasia, and patients who used drugs such as hormonal drugs, ovulation-inducing agents, glucocorticosteroids, or antiandrogens within the previous 6 months were not included in the study. Patients with optic neuropathy, retinal disease which may affect visual field or the retinal nerve fiber layer, or history of ocular surgery, severe ocular trauma, intracranial lesion, head trauma, massive blood loss, or contact lens use were not included in the study. A detailed medical history was obtained from the study participants and demographic data such as their age, personal history and family history were recorded. All subjects underwent a standard ophthalmologic examination. IOP was measured using a Goldmann applanation tonometer and CCT was measured using a non-contact specular biomicroscope. The average of 3 consecutive measurements varying less than 10 µm was recorded as the CCT value.

All patients underwent TBUT and Schirmer tests. The Schirmer test was performed under topical anesthesia. Wetting less than 6 mm in 5 minutes was considered abnormal. The tear film was examined at the slit-lamp under cobalt-blue filter using a wide beam. TBUT was evaluated as the interval between last blink and the first appearance of a dry spot in any area of the ocular surface. A TBUT of less than 10 s was considered abnormal.

Venous blood samples were collected from participants in the early follicular phase between the 3rd and 5th days of a spontaneous or gestagen-induced menstrual cycle. Venous blood was collected from the forearm between 8:00 and 10:00 a.m. following a 12-hour fast. LH, FSH, estradiol, and total testosterone measurements were done in the biochemistry laboratory of the Tepecik Training ve Research Hospital. Correlation analysis was performed between the serum estradiol and testosterone levels of PCOS patients and their Schirmer test scores, TBUT, mean CCT and IOP values. Data were statistically analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) software package. Pearson correlation analysis was used to assess relationships between variables. The normality of variable distributions was assessed. Continuous variables were presented as median, minimum and maximum values. Normally distributed independent variables not suitable for a t-test were compared using the Mann-Whitney U test. Intergroup differences with p values less than 0.05 were accepted as statistically significant.

Results

The study included a total of 100 right eyes from 50 patients in the PCOS group and 50 patients in the control group. The mean age was 27±4.18 years (range, 19-30 years) in the PCOS group and 26.4±3.78 years (range, 18-30 years) in the control group. There was no significant difference in age between the two groups (p=0.34).

Mean CCT was 550.60±32.38 µm in the PCOS group and 518.40±24.77 µm in the control group, which was a significant difference (p=0.001). Mean IOP values in the PCOS and control groups were 16.16±2.68 mmHg and 15.62±3.41 mmHg, respectively (p=0.56). The PCOS group had a significantly lower mean Schirmer test value compared to the control group (10.80±3.14 mm vs 16.74±2.61 mm; p=0.001). TBUT was 11.10±3.28 s in the PCOS group and 14.64±2.81 s in the control group. The PCOS group had a significantly shorter TBUT than the control group (p=0.001). In correlation analysis between estradiol and testosterone levels of PCOS patients and the ocular variables, estradiol showed a weak positive correlation with IOP (r=0.351) and a weak negative correlation with TBUT (r=-0.393). A moderate correlation was detected between serum estradiol level and CCT (r=0.552) (Figures 1-4). Weak correlations emerged between serum testosterone level and IOP (r=0.342) and CCT (r=0.303) (Figure 3). There was a moderate negative correlation between testosterone level and Schirmer test distance (r=-0.562) and TBUT (r=-0.494) (Figure 4).

Discussion

PCOS is the most common endocrinopathy in reproductive-age women, and is also referred to as ovarian hyperandrogenemia.[4] The hyperestrogenemic effect cannot be balanced by progesterone and induces changes in the target organs. Ogueta et al.[5] described estrogen-induced proteins (e.g. cathepsin D, alpha-2-macroglobulin, and aromatase cytochrome P45) which play an important role in vital cellular functions like differentiation, proliferation and maturation. Most of these proteins are found in ocular tissues such as the ciliary body and the retinal pigment epithelium.[5] As in the cardiovascular system and endometrium,

elevated sex steroid levels in PCOS also affect ocular structures and physiology.[6] Steroid hormones play an important role in cellular processes like proliferation, differentiation and growth.[5] Magness et al.[7] found that estradiol is a potent vasodilator, while Sarrel[8] reported that progesterone has the opposite effect. Yucel et al.[9] proposed that low estrogen and high progesterone levels may have a vasoconstrictive effect that can reduce ocular perfusion.

Therefore, in the present study we compared tear function, IOP, and CCT in PCOS patients and healthy women. We analyzed the correlations between ocular findings and levels of free testosterone and estradiol.

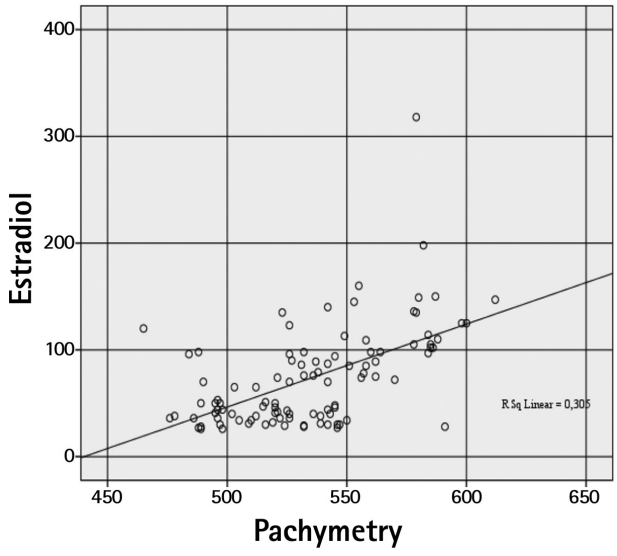

Figure 1. Correlation between serum estradiol level (pg/mL) and central corneal thickness (µm)

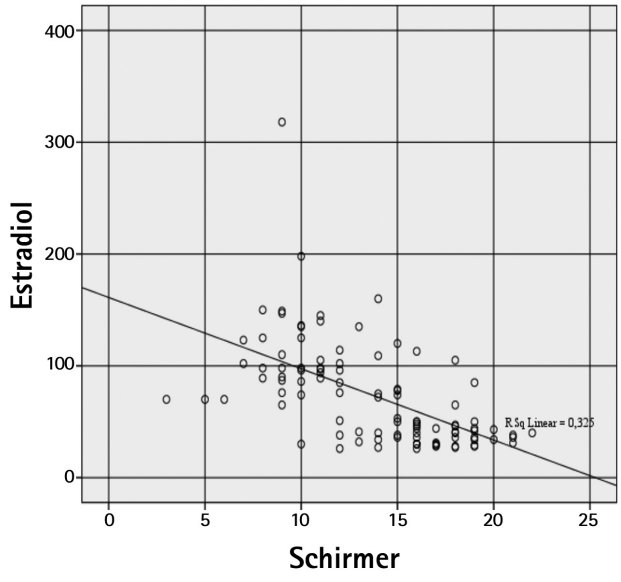

Figure 2. Correlation between serum estradiol level (pg/mL) and Schirmer test distance (mm)

Previous studies have reported that hormonal effects may cause aqueous layer deficiency and evaporative dry eye disease.[10,11,12,13,14] Meibomian glands are a target organ of androgen hormones, which have been shown to regulate gene expression and lipid synthesis in these tissues.[10,11,12] Androgen deficiency may lead to meibomian gland dysfunction and evaporative dry eye syndrome. Estrogen is an antagonist of meibomian gland function and may promote the development of evaporative dry eye.[13,14] Na et al.[15] documented substantial increases in dry eye syndrome and IOP in postmenopausal women using exogenic estrogen. IOP elevation was thought to be associated with the steroid effect of estrogen replacement therapy. Consistent with previous studies, the PCOS group in the current study showed significantly lower Schirmer test and

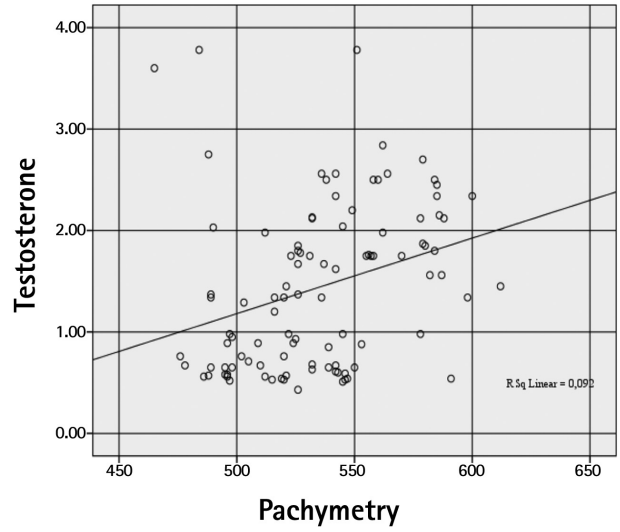

Figure 3. Correlation between serum testosterone level (pg/mL) and central corneal thickness (µm)

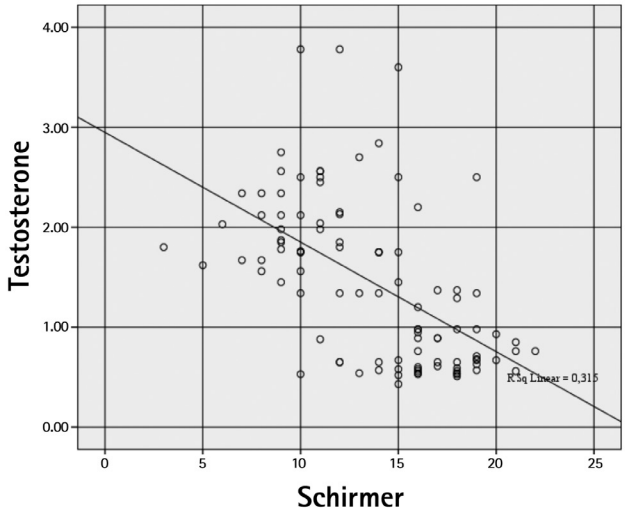

Figure 4. Correlation between serum testosterone level (pg/mL) and Schirmer test distance (mm)

TBUT values compared to the control group. Elevated serum estradiol and testosterone levels are correlated with dry eye findings. The strongest correlation was the negative correlation between estradiol levels and Schirmer test distance. Akar et al.[16] reported that the neuroretinal rim showed significant thinning during the luteal phase, though no significant differences emerged in IOP, keratometry or refractive error when compared with the menstrual phases. A study by Demir et al.[17] revealed comparable IOP and CCT values between PCOS patients and healthy subjects. In the current study, no significant difference in IOP values was detected between the PCOS and control groups. A weak correlation was observed between IOP and both free testosterone and estradiol levels. In a study by Kebapcılar et al.,[18] PCOS patients exhibited significantly greater CCT bilaterally. The authors reported that CCT in both eyes was positively correlated with total testosterone levels, body mass index, insulin and insulin-like growth factor-1 (IGF-1). They attributed the significantly greater CCT values seen in PCOS patients to IGF-1 inhibition of the corneal endothelial pump and increased endothelial permeability.

Kiely et al.[19] found that corneal thickness increased in association with rising estrogen levels during the menstrual cycle. In the current study, CCT was also significantly higher in the PCOS group than in the control group. Pachymetry values were weakly correlated with testosterone levels and moderately correlated with estradiol levels.

Study Limitations

Limitation of this study are the variable repeatability and reliability of the Schirmer and TBUT tests, a relatively short follow-up period and a study design that was not prospective. Due to the large patient number and hormonal changes, a longer follow-up period is required.

Conclusion

Our PCOS patients had significantly greater CCT and higher rates of tear film dysfunction compared to the control group. In light of these data, for PCOS patients it is advisable to plan corneal surgical procedures after hormone regulation has been achieved with medical therapy.

Ethics

Ethics Committee Approval: The study was approved by the Turkish Ministry of Health Public Hospitals Administration, General Secretary of the Association of Public Hospitals in the Northern İzmir Province, Tepecik Training and Research Hospital Local Ethics Committee, Informed Consent: Informed consent was obtained from all study subjects.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Seda Karaca Adıyeke, İbrahim Karaca, Concept: Seda Karaca Adıyeke, Design: Seda Karaca Adıyeke, İbrahim Karaca, Data Collection or Processing: Seda Karaca Adıyeke, Suna Yıldırım, İbrahim Uyar, Analysis or Interpretation: Seda Karaca Adıyeke, İbrahim Karaca, Mehmet Adıyeke, Gamze Türe, Literature Search: Seda Karaca Adıyeke, İbrahim Karaca, Writing: Seda Karaca Adıyeke.

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. Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab. 1999;84:1897-1899.
2. Gupta PD, Johar K Sr, Nagpal K, Vasavada AR. Sex hormone reseptors in the human eye. Surv Ophthalmol. 2005;50:274-284.
3. Sullivan DA. Tearful relationships? Sex, hormones, the lacrimal gland, and aqueous-deficient dry eye. Ocul Surf. 2004;2:92-123.
4. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25:544-551.
5. Ogueta SB, Schwartz SD, Yamashita CK, Farber DB. Estrogen receptor in the human eye: influence of gender and age on gene expression. Invest Ophthalmol Vis Sci. 1999;40:1906-1911.
6. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the androgen excess and polycystic ovary syndrome (AE-PCOS) society. J Clin Endocrinol Metab. 2010;95:2038-2049.
7. Magness RR, Rosenfeld CR. Local and systemic estradiol-17 beta. Effects on uterine and systemic vasodilation. Am J Physiol. 1989;256:E536-42.
8. Sarrel PM. Ovarian hormones and the circulation. Maturitas. 1990;12:287-298.
9. Yucel I, Akar ME, Dora B, Akar Y, Taskin O, Ozer HO. Effect of the menstrual cycle on Standard achromatic and blue-on-yellow visual field analysis of women with migraine. Can J Ophthalmol. 2005;40:51-57.
10. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand. 2000;78:146-153.
11. Rocha EM, Wickham LA, Silveira LA, Krenzer KL, Yu FS, Toda I, Sullivan BD, Sullivan DA. Identification of androgen receptor protein and 5 alpha reductase mRNA in humanocular tissues. Br J Ophthalmol. 2000;84:76-84.
12. Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, Toda I, Doane MG, Evans JE, Wickham LA. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci. 2000;41:3732-3742.
13. Krenzer KL, Dana MR, Ullman MD, Cermak JM, Tolls DB, Evans JE, Sullivan DA. Effect of androgen deficiency on the human meibomian gland and ocular surface. J Clin Endocrinol Metab. 2000;85:4874-4882.
14. Cermak JM, Krenzer KL, Sullivan RM, Dana MR, Sullivan DA. Is complete androgen insensitivity syndrome associated with alterations in the meibomian gland and ocular surface? Cornea. 2003;22:516-521.
15. Na KS, Jee DH, Han K, Park YG, Kim MS, Kim EC. The ocular benefits of estrogen replacement therapy: a population-based study in postmenopausal Korean women. PLoS One. 2014;9:e106473.
16. Akar ME, Yucel I, Erdem U, Taskin O, Ozel A, Akar Y. Effect of the menstrual cycle on the optic nerve head in diabetes: analysis by confocal scanning laser ophthalmoscopy. Can J Ophthalmol. 2005;40:175-182.
17. Demir M, Guven D, Koc A, Ozdemir S, Can E. Retinal nerve fiber layer thickness in women with polycystic ovary syndrome. J Ophthalmol. 2013;2013:752186.
18. Kebapcılar AG, Tatar MG, Ipekci SH, Gonulalan G, Korkmaz H, Baldane S, Celik C. Cornea in PCOS patients as a possible target of IGF-1 action and insülin resistance. Arch Gynecol Obstet. 2014;290:1255-1263.
19. Kiely PM, Carney LG, Smith G. Menstrual cycle variations of corneal topography and thickness. Am J Optom Physiol Opt. 1983;60:822-829.

DOI: 10.4274/tjo.54289
Turk J Ophthalmol 2017;47:28-33

Original Article

Retina and Optic Disc Characteristics in Amblyopic and Non-amblyopic Eyes of Patients with Myopic or Hyperopic Anisometropia

Arzu Taşkıran Çömez, Elif Şanal Ulu, Yeliz Ekim
Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Ophthalmology, Çanakkale, Turkey

Abstract

Objectives: To compare retinal and optic disc characteristics between amblyopic and non-amblyopic eyes in patients with myopic and hyperopic anisometropia measured with optical coherence tomography (OCT).

Materials and Methods: Patients with myopic (25 patients: 17 female, 8 male; median age 27 years, range 16-40 years) and hyperopic (31 patients: 19 female, 12 male; median age 20 years, range 13-41 years) anisometropic amblyopia were included. Eye examination included determination of best-corrected visual acuity (BCVA) with a Snellen chart, measurement of manifest and cycloplegic refraction after pupillary dilation, alternate cover testing, globe movement evaluation, A-scan biometry for axial length, biomicroscopy, fundus examination, and OCT scanning. Main outcome measures were spherical equivalence, BCVA, axial length, retinal nerve fiber layer (RNFL) thickness, macular thickness, macular volume, and optic disc area.

Results: In both myopic and hyperopic patients, the absolute value of the mean spherical equivalence was significantly greater in the amblyopic than non-amblyopic eyes, and the mean BCVA was significantly less in the amblyopic than the non-amblyopic eyes. In both myopic and hyperopic patients, there were no significant differences in mean RNFL thickness, macular thickness, macular volume, axial length, or optic disc area between amblyopic and non-amblyopic eyes.

Conclusion: The amblyopic process may have no significant effect on the RNFL, macula, or optic disc. Further studies with more patients, including postmortem studies, may clarify the retinal, histopathologic, and anatomic differences between amblyopic and non-amblyopic eyes.

Keywords: Anisometropia, amblyopia, macula, retinal nerve fiber layer, optical coherence tomography

Introduction

Amblyopia is a condition that includes a decrease in the best-corrected visual acuity (BCVA) without a known organic etiology.[1] This condition develops most frequently in children aged ≤6 to 8 years and may affect one or both eyes.[1] It is caused by the abnormal development of the visual cortex arising from several factors, including strabismus, blurred vision from refractive error, or visual deprivation.[2] Although the visual cortex is the primary area responsible for amblyopia, changes in the retina and in the lateral geniculate body may also exist.[3,4,5,6,7]

Amblyopia is primarily a cortical disorder, caused by unequal competitive input from the two eyes into the primary visual cortex. Anisometropia may produce amblyopia via a loss of foveal resolution in the less-focused eye due to localized mechanisms of foveal inhibition with loss of stereo acuity and binocular function.[8] Anisometropia is one of the leading causes of amblyopia, which is the only identifiable amblyogenic factor in 37% of cases.[9] In a case-control sibling study, patients with anisometropia of at least 1 diopter (D) were shown to have a slight increase in the amblyopia or strabismus risk.[10,11] Studies of normal human subjects have demonstrated that induced anisometropia greater than 1 D causes abnormalities in resolution and induces a suppression scotoma.[12] In animal models of amblyopia caused by visual deprivation during the neonatal period, histologic changes have been noted in the lateral geniculate body and cortex.[3,4] Similar observations have been reported in humans.[5,6]

Optical coherence tomography (OCT) is a non-invasive, non-contact device that measures retinal nerve fiber layer (RNFL) thickness, macular thickness, macular volume, and optic disc

Address for Correspondence: Arzu Taşkıran Çömez MD, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Ophthalmology, Çanakkale, Turkey
Phone: +90 286 263 59 50-1045 E-mail: arzucomez@yahoo.com **Received:** 14.12.2015 **Accepted:** 22.04.2016

area.[13,14,15,16] The RNFL thickness measured by OCT is similar to RNFL thickness measured histologically.[15]

The purpose of this study was to investigate differences in peripapillary RNFL thickness, macular thickness, macular volume, and optic disc area between the amblyopic and non-amblyopic eyes of patients with myopic or hyperopic anisometropia using OCT.

Materials and Methods

Patients with myopic (25 patients: 17 female, 8 male) or hyperopic (31 patients: 19 female, 12 male) anisometropic amblyopia were included in the study. All patients had no previous intraocular surgery, glaucoma, nystagmus, neurologic disease, or retinal disease. Exclusion criteria included strabismic and deprivation amblyopia. For all patients, amblyopia treatment had not been previously prescribed or implemented. Anisometropia was defined as an interocular difference in spherical equivalent refraction (spherical value + ½ cylinder value) ≥1 D and interocular difference in BCVA ≥2 lines of Snellen acuity.[17] The study was approved by the Institutional Ethics Committee of Çanakkale Onsekiz Mart University. Written informed consent was obtained from each adult patient or from a parent or legal guardian of participants aged <18 years. The study was performed according to the guidelines of the Declaration of Helsinki for research involving human subjects. All patients had detailed eye examination that included BCVA determination with a Snellen chart (distance, 6 m); measurement of manifest and cycloplegic refraction after pupillary dilation (1% cyclopentolate hydrochloride and 1% tropicamide); alternate cover testing; extraocular movement testing; fundus examination; A-scan biometry for axial length; slit-lamp biomicroscopy; and OCT scanning (Opko/OTI Inc., Miami, FL, USA). Peripapillary RNFL thickness was measured using the fast RNFL thickness (3.4) scan protocol. The patients were asked to look at an internal fixation target and a circular scan with a diameter of 3.4 mm was centered around the optic disc. The location of the scan was observed to ensure the proper positioning in relation to the optic nerve head. The average of three consecutive OCT images of the RNFL was obtained.

Macular thickness was measured as the distance between the internal limiting membrane and retinal pigment epithelium using the fast macular thickness map protocol.[18] Optic nerve head images were acquired with optic nerve topography scan mode.[19]

Data analysis was performed with statistical software (NCSS-2004, NCSS Inc., Kaysville, UT, USA). All quantitative variables were reported as mean ± standard deviation and range (minimum to maximum), and qualitative variables were expressed as a number (%). After assessing normality, mean values for the amblyopic and non-amblyopic eyes of both myopic and hyperopic groups were compared with t test or Mann-Whitney U test. Categorical variables between groups were compared with chi-square test. The association between amblyopia and retinal function was estimated by multivariate logistic regression analysis with hierarchical models and Pearson product moment correlation or Spearman rank correlation. All statistical analyses used 2-sided hypothesis tests. Statistical significance was defined as $p \leq 0.05$.

Results

Age was similar between patients with myopia (median, 27 years; range, 16 to 40 years) and those with hyperopia (median, 20 years; range, 13 to 41 years). In all patients, examination of the anterior segment, fundus, and intraocular pressure was normal. In both myopic and hyperopic patients, the absolute value of the mean spherical equivalence was significantly greater in the amblyopic than non-amblyopic eyes ($p \leq 0.004$), and the mean BCVA was significantly less in the amblyopic than the non-amblyopic eyes ($p \leq 0.001$, Table 1). In myopic patients, the cylindrical error was significantly greater in the amblyopic eyes ($p \leq 0.001$), whereas in hyperopic patients, the spherical error was significantly greater in the amblyopic eyes ($p \leq 0.002$, Table 1). In both myopic and hyperopic patients, there were no significant differences in mean RNFL thickness, macular thickness, macular volume, axial length, or optic disc area between amblyopic and non-amblyopic eyes (Table 1).

In the non-amblyopic eye of patients with myopia, patient age was negatively correlated with RNFL thickness, macular thickness, and macular volume, and BCVA was negatively correlated with axial length ($p \leq 0.05$, Table 2). In both amblyopic and non-amblyopic eyes of patients with myopia, significant correlations were noted between spherical equivalence and BCVA; spherical equivalence and axial length; macular thickness and macular volume; macular thickness and axial length; and macular volume and axial length ($p \leq 0.05$, Table 2).

In the amblyopic eyes of patients with hyperopia, spherical equivalence was negatively correlated with axial length, and optic disc area was positively correlated with axial length ($p \leq 0.05$, Table 2). In both amblyopic and non-amblyopic eyes of patients with hyperopia, significant correlations were noted between spherical equivalence and BCVA; and macular thickness and macular volume ($p \leq 0.007$, Table 2). No other significant correlations were noted between ocular parameters in patients with myopia or hyperopia.

Discussion

In the present study, there were no significant differences in peripapillary RNFL thickness, macular thickness, macular volume, axial length, or optic disc area between the amblyopic and non-amblyopic eyes of patients with myopia or hyperopia (Table 1). Numerous previous studies have evaluated the involvement of visual pathways, including parameters such as RNFL thickness and macular thickness in amblyopia in animals and humans; however, there are significant methodological differences such as measuring devices used, population age, subgroups of amblyopia, and refractive status. Lack of standard methodological approach makes comparison difficult and especially contributes to diverse and conflicting results.[7,16,17,20,21,22,23,24,25,26,27,28,29]

In a study by Walker et al.,[24] RNFL measurements by OCT in 30 patients older than 18 years of age with amblyopia were performed. They did not find a difference in peripapillary RNFL or macular thickness between the amblyopic eye and fellow eye. Repka et al.[25] performed peripapillary RNFL thickness of amblyopic and fellow eyes in 37 patients 7 to 12 years of age. They did not indicate that peripapillary RNFL thickness is thinner in eyes with moderate amblyopia compared with their fellow eyes. In a study by Kee et al.,[26] OCT was performed on 26 children with unilateral amblyopia that was due to anisometropia or strabismus. OCT was also performed on 42 normal children. There were no differences in the fovea and the RNFL thickness found between normal children and children with amblyopia. There are two more studies that evaluated RNFL in amblyopic eyes. Neither of them found any differences between normal and amblyopic eyes.[27,28] On the other hand, there are three studies conducted using OCT that suggest RNFL thickness may be greater in eyes with refractive amblyopia.[1,30,31] In one of these studies, Yen et al.[30] evaluated 38 patients with unilateral amblyopia. Among them, 20 patients had amblyopia with strabismus and 18 had refractive amblyopia without strabismus. RNFL was measured by OCT with scan pattern nerve head 2.0R (Carl Zeiss Meditec, Dublin, CA, USA). Average RNFL thickness was multiplied with their corresponding scan circumferences to estimate the integral values of the total RNFL area RNFL thickness (estimated integrals). In all 38 patients with unilateral amblyopia, the differences between the amblyopic eyes and the normal fellow eyes in RNFL thickness and in RNFL thickness (estimated integrals) were statistically significant. Another study included children younger (mean age, 7.7 years; range, 5 to 12 years) than the present patients, which may limit comparisons with the present data.[1] Taken together, different age groups, different OCT devices, and different inclusion criteria (including strabismic patients, etc.) make healthy comparisons between the studies mentioned above and the present study almost impossible.[30,31] In the current study, there was no significant difference in mean macular thickness between the amblyopic and non-amblyopic eyes in patients with myopia or hyperopia (Table 1). Previous studies reported conflicting results of macular thickness measurements from OCT in eyes with strabismic and anisometropic amblyopia.[1,20,21,24,26,30] In a study by Kee et al.,[26] there were no differences in the fovea thickness found between normal children and children with amblyopia. Other previous studies including patients with amblyopia and normal controls showed that macular thickness, foveal volume, and foveal thickness were similar in both eyes of the amblyopic group and were also similar to those eyes of the normal control groups.[26,32]

Kantarci et al.[33] compared choroidal thickness and central macular and peripapillary RNFL thickness in adults with anisometropic amblyopia and also failed to find a difference in RNFL and central macular thicknesses, in agreement with our findings.

The present study showed no significant difference in macular thickness between amblyopic and non-amblyopic eyes in patients with myopia or hyperopia (Table 1). In contrast, a previous study in young myopic anisometropic amblyopic patients (mean age, 9.6 years; range, 5 to 18 years) showed thicker fovea and thinner inner and outer macular thickness in amblyopic eyes compared to normal eyes.[34] Another study using OCT showed that central macular thickness was significantly increased in patients with anisometropic amblyopia, but mean RNFL thickness

Table 1. Ocular characteristics of amblyopic and non-amblyopic eyes in patients with myopia and hyperopia

	Myopia			Hyperopia		
	Amblyopic	**Non-amblyopic**	**p≤†**	**Amblyopic**	**Non-amblyopic**	**p≤†**
Number of eyes	25	25		31	31	
Spherical equivalence (D)	-5.78±4.71 (-16.50 to -0.75)	-2.89±3.82 (-13.50 to 0.50)	0.004	3.09±2.01 (0.63 to 8.25)	1.65±1.87 (0.00 to 6.88)	0.001
BCVA	0.45±2.81 (0.1 to 0.8)	0.82±2.17 (0.7 to 1.0)	0.001	0.41±0.20 (0.1 to 0.8)	0.83±0.19 (0.4 to 1.00)	0.001
RNFL thickness (µm)	99.1±12.66 (81.25 to 123.75)	95.37±12.43 (74.00 to 127.00)	NS	103.65±12.55 (85.25 to 128.50)	101.01±14.70 (74.75 to 138.50)	NS
Macular thickness (µm)	297.68±82.01 (233 to 449)	287.84±54.78 (223 to 424)	NS	291.61±51.86 (172 to 422)	282.06±36.97 (214 to 414)	NS
Macular volume (mm^3)	7.60±3.05 (1.63 to 15.49)	7.45±2.48 (1.81 to 11.86)	NS	7.72±2.03 (2.09 to 11.85)	7.69±1.48 (1.98 to 11.68)	NS
Axial length (mm)	24.29±2.21 (23.69 to 28.48)	23.59±2.18 (21.34 to 26.96)	NS	21.62±1.10 (18.83 to 23.50)	22.07±1.07 (19.25 to 23.42)	NS
Optic disc area (mm^2)	3.08±0.79 (2.01 to 5.26)	2.93±0.62 (2.12 to 4.05)	NS	2.70±0.68 (1.11 to 4.38)	2.91±0.70 (1.12 to 3.98)	NS

*n=25 patients with myopia and 31 patients with hyperopia, data reported as mean ± standard deviation (range, minimum to maximum), BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, †NS: Not significant (p>0.05)

was similar between amblyopic (95.4 µm) and non-amblyopic eyes (94.0 µm).[35] We excluded anisoastigmatism patients and included only spherical anisometropia patients. We did not find a significant correlation between axial length, macular thickness/volume or spherical equivalence. Anisometropic amblyopic eyes have statistically and clinically significant differences in refractive error. This refractive error can be attributed to corneal curvature changes, lens changes, anterior chamber depth and vitreous depth changes. In subjects with anisometropic amblyopia, interocular differences in spherical refractive error might be attributed to axial length with no differences in corneal curvature, whereas anisoastigmatism can also be observed, which results from asymmetric corneal curvature without a significant change in axial length.

Table 2. Correlations between ocular parameters in patients with myopia or hyperopia

	Myopia amblyopic	Myopia non-amblyopic	Hyperopia amblyopic	Hyperopia non-amblyopic
Age				
Spherical equivalence	NS	NS	NS	NS
BCVA	NS	NS	NS	NS
RNFL thickness	NS	-0.477‡ (0.02)	NS	NS
Macular thickness	NS	-0.418‡ (0.04)	NS	NS
Macular volume	NS	-0.389‡ (0.05)	NS	NS
Axial length	NS	NS	NS	NS
Optic disc area	NS	NS	NS	NS
Spherical equivalence				
BCVA	0.674‡ (0.0001)	-0.733‡ (0.0001)	-0.432‡ (0.0001)	-0.475‡ (0.007)
RNFL thickness	NS	NS	NS	NS
Macular thickness	NS	NS	NS	NS
Macular volume	NS	NS	NS	NS
Axial length	0.748‡ (0.0001)	0.731‡ (0.0001)	-0.439† (0.02)	NS
Optic disc area	NS	NS	NS	NS
BCVA				
RNFL thickness	NS	NS	NS	NS
Macular thickness	NS	NS	NS	NS
Macular volume	NS	NS	NS	NS
Axial length	NS	-0.463† (0.02)	NS	NS
Optic disc area	NS	NS	NS	NS
RNFL thickness				
Macular thickness	NS	NS	NS	NS
Macular volume	NS	NS	NS	NS
Axial length	NS	NS	NS	NS
Optic disc area	NS	NS	NS	NS
Macular thickness				
Macular volume	0.727‡ (0.0001)	0.803‡ (0.0001)	0.781‡ (0.0001)	0.892‡ (0.0001)
Axial length	-0.239‡ (0.04)	-0.194† (0.05)	NS	NS
Optic disc area	NS	NS	NS	NS
Macular volume				
Axial length	-0.514‡ (0.009)	-0.532‡ (0.006)	NS	NS
Optic disc area	NS	NS	NS	NS
Axial length				
Optic disc area	NS	NS	0.350‡ (0.05)	NS

n=25 patients with myopia and 31 patients with hyperopia, correlation between variable 1 and variable 2 reported as correlation coefficient (p≤), NS: Not significant (p>0.05), BCVA: Best-corrected visual acuity, RNFL: Retinal nerve fiber layer, †: Pearson product moment correlation coefficient, ‡: Spearman rank correlation coefficient

In our study, there was no difference in spherical error between the study groups. However, cylindrical error was significantly different between groups. This finding means that the difference in mean spherical equivalent between groups is mainly caused by astigmatism. In other words, many of our subjects have anisoastigmatism, which does not have a significant effect on axial length. From this point of view, although amblyopic eyes have a longer axial length, this difference failed to reach statistical significance. We believe that including more subjects without significant anisoastigmatism may lead to statistically significant difference in axial length.

Optic disc area is directly associated with the number of nerve fibers in the optic nerve.[36] The present study failed to find a significant difference between amblyopic and fellow eyes, as mean optic disc area was similar between amblyopic and non-amblyopic eyes of patients with both myopia and hyperopia (Table 1). Eyes with long diameters may have a large retinal surface and large optic disc.[37] Conversely, small hyperopic eyes may have smaller optic discs. A deficiency of nerve fibers may be responsible for decreased visual acuity in amblyopic eyes.[38,39,40]

Other studies have shown that eyes with amblyopia may have smaller optic disc area than non-amblyopic eyes and healthy control eyes, and subclinical optic disc anomalies may be associated with amblyopia.[30,41] However, the association between amblyopia and disc anomalies is controversial; the previously reported small disc area associated with amblyopia may have been caused by a correlation with hyperopia and anisometropia, and not necessarily because of a direct causal association between small disc area and amblyopia.[42] The results of the previous studies are conflicting due to the differences in study design, OCT devices, and the subjects' race, age, and amblyopia types. The majority of the studies included pediatric patients, whereas our study examined patients over 13 years of age, for whom amblyopia can no longer be treated. We believe that examining patients over 13 years old and comparing the retina characteristics in both myopic and hyperopic anisometropic patients makes an important contribution to the literature.

Study Limitations

There are several limitations to our study. The small number of patients limits the power of the study, but the number of participants in this study is similar to other studies. The lack of a control group of normal children is another limitation, but we were able to use the non-amblyopic eye in each patient as a control.

Conclusion

The present study showed no significant difference in mean RNFL thickness, macular thickness, macular volume, or optic disc area between amblyopic and non-amblyopic eyes in myopic and hyperopic anisometropic patients. This suggests that the amblyopic process may have no significant effect on the RNFL, macula, or optic disc in patients.

Acknowledgments

The authors thank Associate Professor Coşkun Bakar, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Family Medicine and Associate Professor Semra Akgöz, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Biostatistics, for their valuable contributions to the statistical analysis of the study.

Ethics

Ethics Committee Approval: Çanakkale Onsekiz Mart University Ethics Committee, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Arzu Taşkıran Çömez, Concept: Arzu Taşkıran Çömez, Design: Arzu Taşkıran Çömez, Data Collection or Processing: Arzu Taşkıran Çömez, Elif Şanal Ulu, Yeliz Ekim, Analysis or Interpretation: Arzu Taşkıran Çömez, Elif Şanal Ulu, Literature Search: Arzu Taşkıran Çömez, Elif Şanal Ulu, Yeliz Ekim, Writing: Arzu Taşkıran Çömez.

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. 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.
2. Von Noorden GK. Classification of amblyopia. Am J Ophthalmol.1967;63:238-244.
3. Rasch E, Swift H, Riesen AH, Chow KL. Altered structure and composition of retinal cells in dark reared mammals. Exp Cell Res. 1961;25:348-363.
4. Von Noorden GK, Crawford ML, Middleditch PR. Effect of lid suture on retinal ganglion cells in Macaca Mulatta. Brain Res.1977;122:437-444.
5. vonNoorden GK, Crawford ML. The lateral geniculate nucleus in human strabismic amblyopia. Invest Ophthalmol Vis Sci. 1992;33:2729-2732.
6. Kiorpes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. J Neurosci.1998;18:6411-6424.
7. Chow KL. Failure to demonstrate changes in the visual system of monkeys kept in darkness or in colored lights. J Comp Neurol. 1955;102:597-606.
8. Donaghue SP. The relationship between anisometropia, patient age and the development of amblyopia. Trans Am Ophthalmol Soc. 2005;103:313-336.
9. Pediatric Eye Disease Investigator Group. The clinical profile of moderate amblyopia in children younger than 7 years. Arch Ophthalmol. 2002;120:281-287.
10. Ingram RM, Walker C. Refraction as a means of predicting squint or amblyopia in preschool siblings of children known to have these defects. Br J Ophthalmol. 1979;63:238-242.
11. Latvala ML, Paloheimo M, Karma A. Screening of amblyopic children and long-term follow-up. Acta Ophthalmol Scand.1996;74:488-492.
12. Legras R, Hornain V, Monot, Chateau N. Effect of induced anisometropia on binocular through-focus contrast sensitivity. Optom Vis Sci. 2001;78:503-509.
13. Hee MR, Puliafito CA. Wong C, Duker JS, Reichel E, Rutledge B, Schuman JS, Swanson EA, Fujimoto JG. Quantitative assessment of macular edema with optical coherence tomography. Arch Ophthalmol.1995;113:1019-1029.
14. Puliafito CA, Hee MR, Lin CP, Reichel E, Schuman JS, Duker JS, Izatt JA, Swanson EA, Fujimoto JG. Imaging of macular diseases with optical coherence tomography. Ophthalmology.1995;102:217-229.

15. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, et al. Optical coherence tomography. Science.1991;254:1178-1181.
16. Hee MR, Izatt JA, Swanson EA, Huang D, Schuman JS, Lin CP, Puliafito CA, Fujimoto JG. Optic coherence tomography of the human retina. Arch Ophthalmol. 1995;113:325-332.
17. Giordano L, Friedman DS, Repka MX, Katz J, Ibironke J, Hawes P, Tielsch JM. Prevalence of refractive error among preschool children in an urban population: the Baltimore Pediatric Eye Disease Study. Ophthalmology. 2009;116:739-746.
18. Wolf-Schnurrbusch UEK, Ceklic L, Brinkmann CK, Iliev ME, Frey M, Rothenbuehler SP, Enzmann V, Wolf S. Macular Thickness Measurements in Healthy Eyes Using Six Different Optical Coherence Tomography Instruments. Invest Ophthalmol Vis Sci. 2009;50:3432-3437.
19. Mansoori T, Kslluri V, Balakrishna N. Optic disc topography in normal Indian eyes using spectral domain optical coherence tomography. Indian J Ophthalmol. 2011;59:23-27.
20. Headon MP, Powell TS. Cellular changes in the lateral geniculate nucleus of infant monkeys after suture of eyelids. J Anat. 1973;116:135-145.
21. von Noorden GK. Histological studies of the visual system in monkeys with experimental amblyopia. Invest Ophthalmol. 1973;12:727-738.
22. von Noorden GK, Middleditch PR. Histology of the monkey lateral geniculate nucleus after unilateral lid closure and experimental strabismus: further observations. Invest Ophthalmol.1975;14:674-683.
23. Wendell-Smith CP. Effect of light deprivation on the postnatal development of the optic nerve. Nature.1964;204:707.
24. Walker RA, Rubab S, Voll AR, Erraguntla V, Murphy PH. Macular and peripapillary retinal nerve fibre layer thickness in adults with amblyopia. Can J Ophthalmol. 2011;46:425-427.
25. Repka MX, Kraker RT, Tamkins SM, Suh DW, Sala NA, Beck RW; Pediatric Eye Disease Investigator Group. Retinal nerve fiber layer thickness in amblyopic eyes. Am J Ophthalmol. 2009;148:143-147.
26. Kee SY, Lee SY, Lee YC. Thicknesses of the fovea and retinal nerve fiber layer in amblyopic and normal eyes in children. Korean J Ophthalmol. 2006;20:177-181.
27. Baddini-Caramelli C, Hatanaka M, Polati M, Umino AT, Susanna R Jr. Thickness of the retinal nerve fiber layer in amblyopic and normal eyes: a scanning laser polarimetry study. J AAPOS. 2001;5:82-84.
28. Bozkurt B, Irkeç M, Orhan M, Karaağaoğlu E. Thickness of the retinal nerve fiber layer in patients with anisometropic and strabismic amblyopia. Strabismus. 2003.11:1-7.
29. Huynh SC, Samarawickrama C, Wang XY, Rochtchina E, Wong TY, Gole GA, Rose KA, Mitchell P. Macular and nerve fiber layer thickness in amblyopia: the Sydney Childhood Eye Study. Ophthalmology. 2009;116:1604-1609.
30. Yen MY, Cheng CY, Wang AG. Retinal nerve fiber layer thickness in unilateral amblyopia. Invest Ophthalmol Vis Sci. 2004;45:2224-2230.
31. Quoc EB, Delepine B, Tran TH. Thickness of retinal nerve fiber layer and macular volume in childrens and adults with strabismic and anisometropic amblyopia. J Fr Ophtalmol. 2009;32:488-495.
32. Dickmann A, Petroni S, Salerni A, Dell'Omo R, Balestrazzi E. Unilateral amblyopia: an optical coherence tomography study. J AAPOS. 2009;13:148-150.
33. Kantarci FA, Tatar MG, Uslu H, Colak HN, Yıldırım A, Goker H, Karaca EE, Gurler B. Choroidal and peripapillary retinal nerve fiber layer thickness in adults with anisometropic amblyopia. Eur J Ophthalmol. 2015;25:437-442.
34. Pang Y, Goodfellow GW, Allison C, Block S, Frantz KA. A prospective study of macular thickness in amblyopic children with unilateral high myopia. Invest Ophthalmol Vis Sci. 2011;52:2444-2449.
35. Al-Haddad CE, Mollayess GM, Cherfan CG, Jaafar DF, Bashshur ZF. Retinal nerve fibre layer and macular thickness in amblyopia as measured by spectral-domain optical coherence tomography. Br J Ophthalmol. 2011;95:1696-1699.
36. Quigley HA, Coleman AL, Dorman-Pease ME. Larger optic nerve heads have more nerve fibers in normal monkey eyes. Arch Ophthalmol. 1991;109:1441-1443.
37. Papastathopoulos KI, Jonas JB, Panda-Jonas S. Large optic discs in large eyes, small optic discsin small eyes. Exp Eye Res. 1995;60:459-461.
38. Hess RF, Field DJ. Is the spatial deficit in strabismic amblyopia due to loss of cells or an uncalibrated disarray of cells? Vision Res. 1994;34:3397-3406.
39. Leguire LE, Rogers GL, Bremer DL. Amblyopia:the normal eye is not normal. J Pediatr Ophthalmol Strabismus.1990;27:32-38.
40. Lempert P. Optic nerve hypoplasia and small eyes in presumed amblyopia. J AAPOS. 2000;4:258-266.
41. Lempert P. Retinal area and optic disc rim area in amblyopic, fellow, and normal hyperopic eyes: a hypothesis for decreased acuity in amblyopia. Ophthalmology. 2008;115:2259-2261.
42. Archer SM. Amblyopia? J AAPOS. 2000;4:257.

DOI: 10.4274/tjo.75032
Turk J Ophthalmol 2017;47:34-41

Review

Comparison of Efficacy and Side Effects of Multispot Lasers and Conventional Lasers for Diabetic Retinopathy Treatment

Hande Çeliker, Azer Erdağı Bulut, Özlem Şahin
Marmara University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract

Panretinal photocoagulation (PRP) is a standard treatment for proliferative diabetic retinopathy. Conventional laser (CL) therapy is performed in one or more sessions in single spot mode. Visual disabilities have been reported after treatment with CL, including central vision loss due to macular edema and peripheral visual field loss resulting from extensive inner retinal scarring. Multispot laser (MSL) photocoagulation has recently been introduced to clinical practice. Studies comparing PRP conducted with MSL and CL have reported that MSLs resulted in less retinal tissue damage and pain, and greater patient comfort compared to CL. The aim of this review was to compare the efficacy and side effects of MSLs and CLs for diabetic retinopathy treatment.

Keywords: Conventional lasers, diabetic retinopathy treatment, multispot lasers, side effects

Introduction

Panretinal laser photocoagulation (PRP) has been the gold standard for the management of proliferative diabetic retinopathy (PDR) since its efficacy was demonstrated in the Diabetic Retinopathy Study (DRS).[1] PDR is performed with conventional laser (CL) over multiple sessions under local or topical anesthesia. The procedure is painful and time-consuming, which is tiring for both patients and physicians. As it requires multiple visits to an outpatient clinic, it also creates an additional load on retina clinics. Automated laser systems were developed in order to speed the photocoagulation process.[2,3] However, the lack of constant physician control was also a disadvantage of these devices. A more recent innovation is the semiautomated multispot laser (MSL). These instruments allow multiple laser shots with a single pedal push, use frequency-doubled 532 nm Nd:YAG laser and are fully controlled by the physician.[4,5] The aim of this review is to present an evaluation of the implementation, efficacy and side effects of the most recent generation of lasers currently in use.

Multispot Lasers

There are four MSLs in clinical use (Table 1).

Pattern Scanning Laser

The pattern scanning laser (PASCAL) is a semiautomated scanning laser application system that uses a frequency-doubled Nd:YAG laser to delivery multiple laser shots simultaneously to the retina, and was introduced to the market in 2006 (PASCAL® Laser, Optimedica Corp., Santa Clara, CA, USA) (Figure 1). The system can apply the laser as a single shot or as a 5x5 array, circle, arch, or line.[4] As the pulse duration is much shorter (10-20 ms) compared to CL (100-200 ms) and multiple laser spots can be applied simultaneously, the procedure is faster and more comfortable for patients.[6,7] The term semiautomated means that the physician has control at every stage of the procedure. Like older systems, the laser can be started and stopped using a foot pedal. As previously stated, other than its ability to deliver multiple or single laser shots, it is comparable to other CLs with similar features.[4] There are many studies demonstrating the safety and efficacy of the PASCAL system.[8,9,10,11,12,13]

Valon

Like the PASCAL, the Valon MSL is also a semiautomated scanning laser system using a frequency-doubled Nd:YAG (532 nm) laser. The system is integrated into a Haag-Steit

Address for Correspondence: Özlem Şahin MD, Marmara University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 374 253 46 56-3290 E-mail: ozlem.sahin@marmara.edu.tr **Received:** 01.01.2016 **Accepted:** 22.04.2016

biomicroscope and is controlled via a touch screen and a joystick. Figure 2 shows a photograph of the device and its features are presented in Table 1. Various patterns, sizes, intensities and intervals can be selected on the screen and treatment settings can be adjusted as desired with the joystick.

As with the PASCAL, the spot number within a pattern can be adjusted from 1 to 36 depending on the pattern type and spot size. Valon's most important feature, not shared by the PASCAL, is that the settings chosen with the joystick are displayed over the retinal image. This feature eliminates the need for physicians to look away from the microscope while making adjustments, thus saving time spent to focus back on the retina. Spot sizes of 50, 100, 200 or 300 µm can be selected from the microscope.

Figure 1. The PASCAL 532 nm instrument and panel showing available treatment patterns

Pulse duration can be adjusted to 10, 20 or 30 ms for multispot and up to 1,000 ms for single spots. The power can be increased up to 1,500 mW.[5]

Visulas 532s *VITE*

The Visulas 532s *VITE* is a 532 nm solid-state laser system. Similar to the PASCAL and Valon systems, the Visulas 532s *VITE* can delivery laser as single spots or in preprogrammed multispot patterns. Linear or radial patterns are available. Selectable patterns are shown in Figure 3.

In a randomized, prospective study of 101 patients undergoing peripheral laser photocoagulation for various reasons, Röckl and Blum[14] applied conventional single spot laser therapy in 35 patients (group A) and MSL therapy using the Visulas 532s *VITE* in 66 patients (group B). Spot size was consistent between the two groups (300 µm), while pulse duration was 100-150 ms for group A versus 20 ms for group B. Laser power was adjusted to produce moderate burns and the treatment time was recorded. After the procedure, patients were asked to rate their pain from 0 (painless) to 10 (maximum pain). Treatment time was shorter in group B than in group A. In group A, 46% of the patients

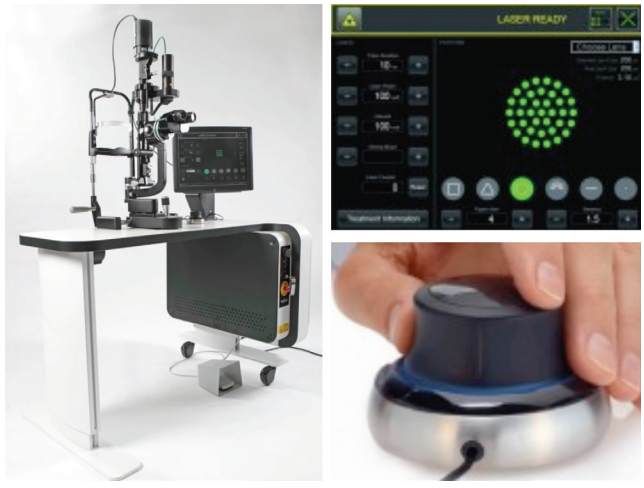

Figure 2. Valon laser instrument, screen and joystick

Table 1. General features of multispot lasers

Features	PASCAL	Valon	Visulas 532 *VITE*	Navilas
Laser wavelength	532 nm	532 nm	532 nm	532 or 577 nm
Laser type	Nd:YAG laser	Nd:YVO laser	Nd:YAG laser	Nd:YVO laser
Laser patterns	Single spot, arc, square, semicircle, triple ring, line	Single spot, square, triangle, circle, triple arc, line	Single spot, square, circle, triple arc, line	No preset patterns, desired pattern can be selected from the screen
Power (maximum)	2000 mW	1500 mW	1500 mW	2000 mW
Power control	Touch screen, joystick	Touch screen, smart joystick	Touch screen, joystick	Touch screen, wireless mouse and keyboard, joystick
Pulse duration	10-1000 ms	10-650 ms	10-2500 ms	10-4000 ms
Wavelength	635 nm	635 nm	620-650 nm	635 nm
Spot size	60-400 µm	50-400 µm	50-400 µm	50-750 µm

reported pain at an average level of 4.4 (range, 2-8); in group B, only 1.3% of patients reported pain at a level of 3 or 4. The device's features are summarized in Table 1.

Navilas

The Navilas laser photocoagulation system (OD-OS GmbH, Teltow, Germany), is a retinal navigation system and laser photocoagulation device including digital fundus imaging (live color fundus photography, red-free and infrared imaging and fluorescein angiography [FA]) (Figure 4). The instrument comprises an imaging camera, photocoagulation device (Merilas 532 nm) and a system that sends the laser beam from the ophthalmoscope to the target via moving mirrors. Its laser is a diode pumped solid-state laser (532 nm). The use of a fundus camera to aim the laser is a distinct feature from CLs and MSLs. This allows a larger glare-free field of view compared to a slit lamp. Because the displayed image is in the same format as that of an ordinary fundus camera, it is easier to implement a treatment plan based on the actual appearance. Treatment points, planned according to fundus photography or FA, are reflected on the live retinal image during treatment. This system was developed to allow the accurate localization of treatment to delicate lesions like microaneurysms and increase treatment efficacy. The device's features are summarized in Table 1.

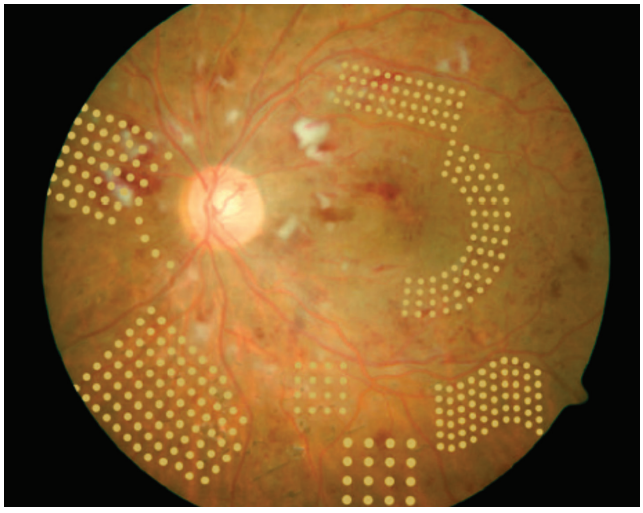

Figure 3. Multi-spot laser patterns available with the Visulas 532 *VITE*

Figure 4. The Navilas system with integrated fundus camera

Another difference between this system and other slit-lamp laser devices is the touch screen used for visualization, planning and treatment (Figure 5). The retinal surgeon determines the laser application site using the screen and applies the laser in multispot or single spot mode. The surgeon manually actuates the laser after verifying the target lock.[15]

The laser spot qualities of the Navilas and PASCAL systems were compared in a study of PRP including 73 eyes of 51 high-risk PDR patients.[16] Eyes underwent PRP with PASCAL or Navilas at pulse durations of 30 ms (16 and 21 eyes, respectively) or 100 ms (16 and 20 eyes, respectively). Laser spot size (major and minor diameters and area) and ellipticity (ratio of the major to minor diameter) were measured from fundus photographs taken from all quadrants 5 minutes after the procedure. Pain perception on a visual analog scale (from 0-10) was also compared. Burn size variation was 22% with 30-ms Navilas laser, 24% with 100-ms Navilas laser, 21% with 30-ms PASCAL pattern laser and 35% with PASCAL 100-ms single-spot laser. Nearing the equator, the Navilas showed less variation compared to the PASCAL (15% vs 25%). Toward the periphery, burn areas were more elliptical with the PASCAL, while Navilas spots were more uniform. Patients treated with 100-ms pulse durations reported less pain with the Navilas system than the PASCAL. Patients also reported less pain with the Navilas at 30 ms pulse duration, but the difference was not statistically significant. Previous studies using the Navilas have focused on the treatment of diabetic

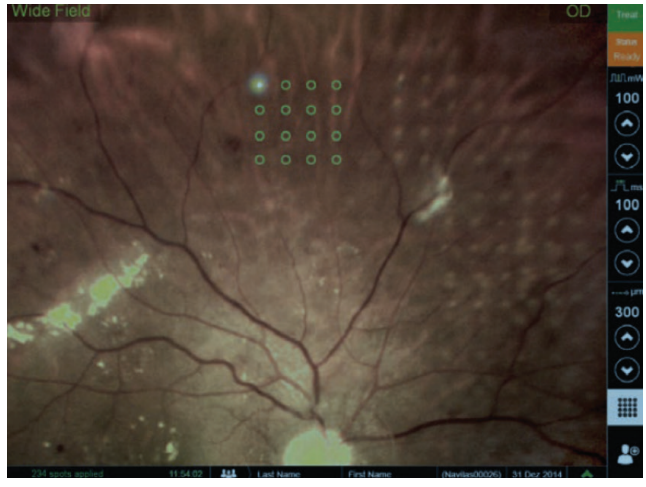

Figure 5. The Navilas screen

macular edema (DME). In a study published in 2011, 86 eyes of 61 patients with DR and DME were treated with Navilas; as a control group, 4 eyes of 4 patients were treated with standard manual laser.[17] Pretreatment FA images marked with the treatment plan were overlaid on posttreatment color fundus photographs in order to measure efficacy. Analysis of 400 randomly selected focal spots showed that Navilas hit 92% of microaneurysm targets, while analysis of 100 focal spots from the control group showed an accuracy rate of 72%. In summary, the Navilas has been demonstrated reliable and more effective than standard techniques in laser photocoagulation.

Treatment Efficacy of Multispot Lasers

Guidelines regarding how and to what extent PRP therapy should be implemented and when it should be repeated were set forth in the Early Treatment Diabetic Retinopathy Study (ETDRS).[18] Laser application is performed at pulse durations of 100-200 ms, spot size of 500 µm, and power ranging between 100 and 750 mW to produce gray-white burns. For PDR, a total of about 1,500 burns spaced one spot width apart are applied in an area from 1 optic disc (OD) width nasal to the OD and 2 disc widths temporal to the macula, extending to one spot width of the inferior and superior vascular arcades and the equator in the periphery.[18] The procedure may be performed in one session under local (peribulbar) anesthesia, or in 2 or 3 sessions at 1-2 week intervals under topical anesthesia. Single-session (SS) therapy is reported to be less preferable due to a higher rate of side effects (associated with both PRP and local anesthesia).[19]

With the introduction of MSLs, SS therapy has become a viable option once more. Treatment time with MSLs is approximately one-fifth that required with CLs, resulting in less pain, less inflammation and thus a lower incidence of complications like macular edema.

Although no multicenter studies have been conducted to date, there are single-center studies from medical facilities using these systems. These studies have reported comparable efficacy and reliability between MSLs and CLs. Nagpal et al.[8] performed PRP on 30 eyes using the PASCAL system and 30 eyes using a 532 nm CL. Both treatments were performed in two sessions. Patients underwent follow-up examination at 1, 3, and 6 months after treatment. Based on clinical findings and fundus imaging, both treatments were determined effective.

In a study by Muraly et al.[9] comparing PASCAL and 532 nm CL, one eye of each patient was treated with SS-PRP using the PASCAL system (mean 2,795 spots), while the other eye was treated with multisession PRP (MS-PRP) using a CL over 2 or 3 sessions (mean 1,414 spots). SS-PRP was 90% effective and MS-PRP was 64% effective at 1 month; both were 98% effective at 6 months.

Muqit et al.[11] studied 40 eyes of 24 patients with PDR. Half of the eyes were treated with 1,500 single spots at 100 ms duration using PASCAL over the course of 3 sessions at 2-week intervals; the other eyes were treated with 1,500 spots in a SS of 20-ms multispot laser. Twelve weeks after treatment, SS-PRP was 74% effective and MS-PRP was 53% effective, although the difference was not statistically significant.

Muqit et al.[20] later retrospectively evaluated 36 eyes of 22 patients included in the abovementioned study. The patients, which had all undergone PRP with 1,500 100-ms or 20-ms PASCAL laser spots, were divided into 3 groups (mild, moderate, severe) based on their baseline PDR severity. Eyes that did not show PDR regression in later follow-up visits were treated with an additional SS of PASCAL PRP (top-up) therapy. They evaluated treatment efficacy after 18 months in patients for whom FA imaging was obtained using wide-field Optos® angiography. A total of 10 eyes (28%) exhibited complete PDR regression after one session of PRP. Top-up therapy resulted in PDR regression in 75% (n=6) of mild PDR cases, 67% (n=14) of moderate cases, and 43% (n=3) of severe cases. Mild PDR required an average of 2,187 burns, moderate cases required an average of 3,998 burns, and severe cases required an average of 6,924 burns to achieve complete PDR regression.

Effect of Multispot Laser on Visual Field

Diabetic patients may experience visual field defects due to severe nonPDR (NPDR) or PDR.[21] The DRS and ETDRS both reported that visual field defects may worsen following laser therapy.[22,23] In the ETDRS, visual field analysis was done at baseline and at 4 and 48 hours after treatment using Goldmann I-4e and I-2e test objects. I-4e was used to assess total score, I-2e was used to evaluate paracentral scotoma in the central 20 degrees. At 4 months, patients who had undergone full treatment had significantly more visual field loss compared to patients whose treatment was delayed ($p<0.001$). This loss was more moderate in cases with mild treatment. In a study comparing the effects of full PRP and mild PRP, both treatment methods caused comparable reductions in central visual field sensitivity. However, full therapy caused a markedly greater reduction in sensitivity in the peripheral visual field compared to mild therapy[24]. Muqit et al.[25] evaluated the effect of argon laser PRP on the retinal nerve fiber layer (RNFL) and visual field in a study including 10 eyes. Visual field analysis of the central 10 degrees and 24 degrees using 24-2 SITA-fast at 10 weeks and 6 months post-treatment revealed improved mean deviation (MD) in a majority (8/10) of eyes.

In another study by Muqit et al.,[11] 40 eyes of 24 patients with PDR were treated with 1,500 laser pulses, delivered to half of the eyes as 100-ms PASCAL spots in 3 sessions at 2-week intervals, and to the other half of the eyes as 20-ms PASCAL in a SS. Visual field analysis done 4 weeks after treatment showed significant improvement in MD compared to baseline in the 20-ms treatment group. They reported no significant change in the other group.

In a later study by Muqit et al.,[10] areas with ischemia and retinal capillary nonperfusion on wide-field angiography were treated with 1,500 PASCAL laser burns with 20 ms pulse

duration and 200 µm spot size through a Mainster 165 PRP lens. SITA-standard visual field analysis at 12 and 24 weeks post-laser showed a 1.25 dB improvement in MD.

Nagpal et al.[8] compared CL and PASCAL in 60 patients who underwent PRP. They conducted visual field analysis at 1 month post-treatment and found that the eyes treated with PASCAL had higher retinal sensitivity, but the difference was not statistically significant.

None of the studies using Visulas 532s *VITE*®, Valon®, and Navilas® have evaluated the effect of PRP on visual field.

Effect of Multispot Lasers on Retina Nerve Fiber Layer Thickness and Central Macular Thickness

Laser photocoagulation primarily affects the retinal pigment epithelium (RPE) and outer retinal layers. Examination of laser burns after 1 week reveals that laser therapy also causes edema in the inner retinal layers. Longer pulse durations have been reported to cause more pronounced edema compared to shorter durations.[13] OCT studies have demonstrated that short pulse duration (20 ms) creates conical burns in the outer retinal layers, thus sparing the inner retinal layers.[26] It has also been reported that high-power laser can cause full-thickness destruction of the retina, including the ganglion cell layer.[13] Over time, ganglion cell damage can lead to reduced RNFLT and peripapillary RNFL thinning.

Blankenship[27] reported thickening of the temporal RNFL following experimental laser photocoagulation in rabbits.

Muqit et al.[25] applied 2,000 argon laser pulses at 100 ms duration, 300 µm spot size, and 136 mW power in multiple sessions (MS) to 10 eyes. They assessed RNFLT before and at 10 weeks and 6 months after laser therapy using time-domain (TD) OCT. They observed an 8 µm increase in RNFLT at 10 weeks ($p<0.05$) and a 4 µm decrease at 6 months ($p<0.05$) compared to baseline.

Eren et al.[28] investigated the effect of PRP on CMT and RNFL by applying PRP to 52 eyes of 30 patients who were newly diagnosed with PDR and had undergone no previous treatment, then evaluating patients at 3 and 6 months post-laser. They noted marked RNFL thickening at 3 months, followed by a pronounced thinning compared to baseline at 6 months.

In a retrospective study of the effect of MSL on RNFLT, Park and Jee[29] evaluated 33 eyes treated with PASCAL, 34 eyes treated with CL and 38 eyes that were not treated. Peripapillary RNFLT showed no significant changes at 6 months or 1 year in the PASCAL group but was markedly lower at both 6 months and 1 year in the CL group.

The effect of PRP on RNFLT was not evaluated in any of the Visulas 532s *VITE*®, Valon® or Navilas® studies.

In another study from our clinic which has not been published yet, mean RNFLT was 2.27 µm and 4.39 µm greater than baseline at 1 and 3 months, respectively, after 20-ms Valon laser therapy ($p>0.05$). Treatment with 100-ms CL resulted in a 3.74 µm increase in RNFLT at 1 month ($p=0.03$) and a 2.32 µm increase at 3 months ($p=0.19$).

Transient or persistent macular edema may occur after PRP. The DRS reported macular edema at 6 weeks post-treatment in 21% of eyes treated with argon laser and 46% of those treated with xenon arch.[30]

In a recent multicenter study by the Diabetic Retinopathy Clinical Research group, 155 eyes with NPDR or PDR were treated with 1,260-1,274 argon laser shots of 50-200 ms duration and 200-500 µm spot size. The physicians decided whether to apply the treatment in a SS or in 4 MS held at 4-week intervals. On day 3 after the SS or the first MS, CMT was increased by 9 µm in the SS group and 5 µm in the MS group. At 4 weeks, the increase was 13 µm in the SS group and 5 µm in the MS group, whereas the increase was equivalent (14 and 15 µm) in both groups at 17 weeks.[31]

In the previously discussed study by Muqit et al.[11] including 40 eyes of 24 patients with PDR, CMT was also evaluated and the MS group showed 22 µm and 20 µm increases in CMT at 4 and 12 weeks, respectively ($p<0.001$). They reported no significant increase in CMT in the SS group.

In their previously mentioned study, Nagpal et al.[8] noted no increase in macular thickness at 3 or 6 months in either study group. In a study by Muraly et al.[9] comparing PASCAL and 532 nm CL, the authors reported that none of their patients developed macular edema.

In a study evaluating the effect of MSL on CMT, Watanachai et al.[32] applied SS-PRP to 40 eyes newly diagnosed PDR with no prior treatment and central foveal thickness (CFT) <300 µm. They observed significant increases in CMT after 4 and 12 weeks (24 µm, $p=0.001$ and 17.4 µm, $p=0.002$, respectively). Two eyes developed macular edema at 12 weeks.

Oh et al.[33] evaluated development rates and risk factors of macular edema after SS-PRP in 129 eyes with pre-treatment CFT <300 µm. Macular edema was noted in 11 eyes at 1 month after treatment; the edema had resolved in 5 of those eyes at 3 months. The formation of edema has been associated with the presence of subretinal fluid and retinal cystoid space on OCT.

CMT was not evaluated in any of the PRP studies using Visulas 532s *VITE* or Navilas.

Pain Studies with Multispot Lasers

Laser photocoagulation is painful for some patients. This pain may result in some patients not completing their treatment. Various methods for pain prevention have been recommended in the literature (such as oral or topical nonsteroid anti-inflammatory drugs [NSAID] and peribulbar anesthesia).[34,35] Possible causes of pain include thermal diffusion into the choroid, stimulation of the ciliary nerves in suprachoroidal space, thermal diffusion to the RNFL or direct thermal damage to the posterior ciliary nerves.

Al-Hussainy et al.[36] conducted a prospective study in 20 patients indicated for PRP for various reasons. In a SS, they applied 500 CL shots with 0.1 s duration, 300 µm spot size to the superior or inferior region, and 500 CL shots with

0.02 ms duration, 300 µm spot size to the rest of the retina. Although greater power was required to induce moderate burns with 0.02 s pulse durations, pain assessment indicated that shorter durations caused less pain (1.41 for 0.02 s, 5.11 for 0.1 s).

Muqit et al.[7] randomly applied 20-ms or 100-ms PASCAL PRP under topical oxybuprocaine to 40 treatment-naive eyes of 24 patients. A researcher blinded to the treatments used a pain questionnaire at 1 hour (numerical pain score [NPS]) and a headache questionnaire at 1 month (numerical headache score [NHS]). Mean NPS was 2.4 (mild) for the 20-ms group and 4.9 (moderate) for the 100-ms group; mean NHS was 1.5 for the 20-ms group and 3.2 for the 100-ms group. Both of the differences were significant.

In the previously mentioned study by Muraly et al.[9] comparing PASCAL and a CL, patients were asked to rate their pain as mild, moderate, or severe after treatment. Patients reporting mild, moderate, and severe pain in the PASCAL group were 40, 10, and 11, while in the CL group these numbers were 11, 25, and 14, respectively.

Nagpal et al.[8] performed PRP using PASCAL in one eye and a 532 nm CL in the fellow eye in 60 patients with bilateral symmetric PDR or severe NPDR. Following treatment, patients scored their pain using a visual analog scale (VAS). The average score was 4.6 in the CL group, compared to 0.33 in the PASCAL group.

Seymenoğlu et al.[37] performed PRP in 70 PDR patients, half using PASCAL and half using a CL. Pain was scored 5 minutes after the procedure using the VAS. Mean pain score was 1.54±1.22 in the PASCAL group and 5.54±3.28 in the CL group, which was a statistically significant difference.

Pain assessment by VAS was also done in a study comparing the Navilas and PASCAL. Patients treated with 100-ms pulse durations reported less pain with the Navilas system than the PASCAL (1.0±0.91 vs 2.4±1.99). Patients also reported less pain with the Navilas at 30-ms pulse duration (0.9±1.14 vs 1.6±1.41), but the difference was not statistically significant.

In a randomized, prospective study by Röckl and Blum,[14] 46% of the patients who underwent 100-ms single-spot peripheral laser photocoagulation with the Visulas 532s *VITE* reported pain at an average level of 4.4 (range, 2-8), while only 1.3% of those treated with 20-ms MSL reported pain at a level of 3 or 4.

Küçümen[38] used the VAS to evaluate pain in 107 patients who underwent PASCAL photocoagulation for various reasons. Reported pain score distribution was 0 in 46%, 1 in 20.8%, 2 in 8.2%, 3 in 12.5%, and 4 in 12.5% of patients.

In a study from our clinic pending publication, 42 treatment-naive eyes of 21 patients underwent PRP. Each patient received 20 ms, 300 µm spot size Valon laser therapy in a SS or 100 ms, 300 µm spot size in 3 sessions. After each session, patients scored their pain using the VAS. Pain was in the mild range with both treatment methods (2.4 for 20 ms, 3.0 for 100 ms).

Choroidal Detachment in Single-session Multispot Laser Therapy

In their comparison of SS and MS argon laser PRP, Doft and Blankenship[19] noted a significantly higher incidence of side effects such as exudative retinal detachment, choroidal detachment and elevated IOP in the SS group compared to the MS group. The PASCAL® laser has been used since 2006 and the Valon® laser and Visulas 532s *VITE*® since 2009 for SS-PRP. The aforementioned side effects have been reported in the literature as isolated cases. Of a series of 883 patients who underwent PASCAL SS-PRP within a period of 2 years, Natesh et al.[39] observed symptomatic choroidal detachment in a single patient. Velez-Montoya et al.[40] reported 2 cases of choroidal detachment and 1 case of exudative retinal detachment from among 1,301 patients who underwent PASCAL PRP in a span of 7 months. Sheth et al.[41] noted choroidal detachment in 2 of 666 patients who underwent PASCAL PRP within a period of 2 years.

In another study from our clinic which will be published in the near future, we observed exudative retinal detachment in 1 eye from a series of 20 patients who underwent PRP using the Valon laser. The retinal detachment resolved within 15 days with topical NSAID and the patient experienced no reduction in visual acuity compared to baseline.

Conclusion

PRP has been the gold standard in PDR treatment since it was proven effective in the DRS.[1] PRP may be completed over MS conducted at intervals of 1-2 weeks. Completion in a SS is less common due to the need for more local anesthesia to manage the higher pain levels and the higher incidence of side effects such as macular edema, angle closure, and exudative retinal detachment. However, completion in MS requires a physician to spend more time per patient, requires the patient to make multiple trips to the hospital, and increases the economic burden of treatment. It also means that treatment remains incomplete in more patients due to poor patient compliance. SS CL therapy is not preferred by many physicians due to the higher incidence of side effects, the need for peribulbar anesthesia in most patients and possible complications related to anesthesia. However, dividing treatment into MS may delay the onset of treatment effect, particularly in high-risk PDR eyes. Complications of PDR may occur during the treatment period or before treatment takes effect. Because the complications that frequently arose due to CL MS-PRP are not a problem with new generation lasers, 20-ms SS-PRP with these lasers may be a favorable alternative to both SS and MS CL therapy. However, these patients must be followed and monitored in case further treatment is required.

The consensus among previous studies is that SS therapy with short duration MSL results in shorter treatment time and less pain compared to single spot therapy. However, as is evident from the above studies, it has not yet been determined whether

the ETDRS-recommended number of burns is still applicable or whether more burns are required when applying 20-ms laser treatment with PASCAL® and similar systems like Valon®, Visulas *VITE*® and Navilas®. Patients who have undergone SS therapy with short duration MSL should also be monitored for treatment effect, and physicians should not hesitate to provide additional therapy when necessary.

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Özlem Şahin, Design: Özlem Şahin, Data Collection or Processing: Hande Çeliker, Azer Erdağı Bulut, Analysis or Interpretation: Hande Çeliker, Literature Search: Hande Çeliker, Azer Erdağı Bulut, Writing: Hande Çeliker, Azer Erdağı Bulut.

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. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. Ophthalmology. 1978;85:82-106.
2. Markow MS, Yang Y, Welch AJ, Rylander HG, Weinberg WS. An automated laser system for eye surgery. IEEE Eng Med Biol Mag. 1989;8:24-29.
3. Wright CH, Ferguson RD, Barrett SF, Rylander HG, Welch AJ, Oberg ED. Hybrid retinal photocoagulation system using analog tracking. Biomed Sci Instrum. 1997;33:366-371.
4. Blumenkranz MS, Yellachich D, Andersen DE, Wiltberger MW, Mordaunt D, Marcellino GR, Palanker D. Semiautomated patterned scanning laser for retinal photocoagulation. Retina. 2006;26:370-376.
5. http://www.valon.fi/valon-lasers/valon-sta/
6. Sanghvi C, McLauchlan R, Delgado C, Young L, Charles SJ, Marcellino G, Stanga PE. Initial experience with the Pascal photocoagulator: a pilot study of 75 procedures. Br J Ophthalmol. 2008;92:1061-1064.
7. Muqit MM, Marcellino GR, Gray JC, McLauchlan R, Henson DB, Young LB, Patton N, Charles SJ, Turner GS, Stanga PE. Pain responses of Pascal 20 ms multi-spot and 100 ms single-spot panretinal photocoagulation: Manchester Pascal Study, MAPASS report 2. Br J Ophthalmol. 2010;94:1493-1498.
8. Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser (PASCAL). Retina. 2010;30:452-458.
9. Muraly P, Limbad P, Srinivasan K, Ramasamy K. Single session of pascal versus multiple sessions of conventional laser for panretinal photocoagulation in proliferative diabetic retinopathy. A Comparitive Study. Retina. 2011;31:1359-1365.
10. Muqit MM, Marcellino GR, Henson DB, Young LB, Patton N, Charles SJ, Turner GS, Stanga PE.Optos-guided pattern scan laser (Pascal)-targeted retinal photocoagulation in proliferative diabetic retinopathy. Acta Ophthalmol. 2013;91:251-258.
11. Muqit MM, Marcellino GR, Henson DB, Young LB, Patton N, Charles SJ, Turner GS, Stanga PE.Single-Session vs Multiple-Session Pattern Scanning Laser Panretinal Photocoagulation in Proliferative Diabetic Retinopathy: The Manchester Pascal Study. Arch Ophthalmol. 2010;128:525-533.
12. Muqit MM, Marcellino GR, Henson DB, Fenerty CH, Stanga PE. Randomized clinical trial to evaluate the effects of pascal Panretinal photocoagulation on macular nerve fiber layer. Manchester Pascal Study Report 3. Retina. 2011;31:1699-1707.
13. Jain A, Blumenkranz MS, Paulus Y, Wiltberger MW, Andersen DE, Huie P, Palanker D.Effect of pulse duration on size and character of the lesion in retinal photocoagulation. Arch Ophthalmol. 2008;126:78-85.
14. Röckl A, Blum M. Panretinal laser photocoagulation with reduced pulse duration--first experience with linear multispot cascades Klin Monbl Augenheilkd. 2012;229:52-55.
15. Kernt M, Cheuteu R, Vounotrypidis E, Haritoglou C, Kampik A, Ulbig MW, Neubauer AS. Focal and panretinal photocoagulation with a navigated laser (NAVILAS). Acta Ophthalmol. 2011;89:e662-4.
16. Chhablani J, Mathai A, Rani P, Gupta V, Arevalo JF, Kozak I. Comparison of conventional pattern and novel navigated panretinal photocoagulation in proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 2014;55:3432-3438.
17. Kozak I, Oster SF, Cortes MA, Dowell D, Hartmann K, Kim JS, Freeman WR. Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. Ophthalmology. 2011;118:1119-1124.
18. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy. Early Treatment Diabetic Retinopathy Study report no. 3. The Early Treatment Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin. 1987;27:254-264.
19. Doft BH, Blankenship GW. Single versus multiple treatment sessions of argon laser panretinal photocoagulation for proliferative diabetic retinopathy. Ophthalmology. 1982;89:772-779.
20. Muqit MMK, Marcellino GR, Henson DB, Young LB, Turner GS, and Stanga PE. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study Report 4. Eye (Lond). 2011;25:1447-1456.
21. Chee CK, Flanagan DW. Visual field loss with capillary non-perfusion in preproliferative and early proliferative diabetic retinopathy. Br J Ophthalmol. 1993;77:726-730.
22. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. Am J Ophthalmol. 1976;81:383-396.
23. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(Suppl 5):766-785.
24. Pahor D. Visual field loss after argon laser panretinal photocoagulation in diabetic retinopathy: full versus mild scatter coagulation. Int Ophthalmol. 1998;22:313-319.
25. Muqit MM, Wakely L, Stanga PE, Henson DB, Ghanchi FD. Effects of conventional argon panretinal laser photocoagulation on retinal nerve fibre layer and driving visual fields in diabetic retinopathy. Eye (Lond). 2010;24:1136-1142.
26. Muqit MM, Gray JC, Marcellino GR, Henson DB, Young LB, Charles SJ, Turner GS, Stanga PE. Fundus autofluorescence and Fourier-domain optical coherence tomography imaging of 10 and 20 millisecond Pascal retinal photocoagulation treatment. Br J Ophthalmol. 2009;93:518-525.
27. Blankenship GW. Red krypton and blue-green argon panretinal laser photocoagulation for proliferative diabetic retinopathy: a laboratory and clinical comparison. Trans Am Ophthalmol Soc. 1986;84:967-1003.
28. Eren S, Ozturk T, Yaman A, Oner H, A OS. Retinal Nerve Fiber Layer Alterations After Photocoagulation: A Prospective Spectral-Domain OCT Study. Open Ophthalmol J. 2014;8:82-86.
29. Park YR, Jee D. Changes in peripapillary retinal nerve fiber layer thickness after pattern scanning laser photocoagulation in patients with diabetic retinopathy. Korean J Ophthalmol. 2014;28:220-225.
30. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. The Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin. 1987;27:239-253.
31. Brucker AJ, Qin H, Antoszyk AN, Beck RW, Bressler NM, Browning DJ, Elman MJ, Glassman AR, Gross JG, Kollman C, Wells JA. Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. Arch Ophthalmol. 2009;127:132-140.

32. Watanachai N, Choovuthayakorn J, Patikulsila D, Ittipunkul N. Changes in Central Macular Thickness following Single Session Multispot Panretinal Photocoagulation. J Ophthalmol. 2015;2015:529529.
33. Oh JH, Kim SW, Kwon SS, Oh J, Huh K. The change of macular thickness following single-session pattern scan laser panretinal photocoagulation for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2015;253:57-63.
34. Wu WC, Hsu KH, Chen TL, Hwang YS, Lin KK, Li LM, Shih CP, Lai CC. Interventions for relieving pain associated with panretinal photocoagulation: a prospective randomized trial. Eye (Lond). 2006;20:712-719.
35. Zakrzewski PA, O'Donnell HL, Lam WC. Oral versus topical diclofenac for pain prevention during panretinal photocoagulation. Ophthalmology. 2009;116:1168-1174.
36. Al-Hussainy S, Dodson PM, Gibson JM. Pain response and follow-up of patients undergoing panretinal laser photocoagulation with reduced exposure times. Eye (Lond). 2008;22:96-99.
37. Seymenoğlu G, Kayıkçıoğlu Ö, Başer E, İlker SS. Comparison of Pain Response of Patients Undergoing Panretinal Photocoagulation for Proliferative Diabetic Retinopathy: 532 nm Standard Laser vs. Multispot Pattern Scan Laser. Turk J Ophthalmol. 2013;43:221-224.
38. Küçümen RB. Çeşitli Retina Patolojilerinde Patern Lazer Fotokoagülasyon Sonuçlarımız. Ret-Vit. 2011;19:166-170.
39. Natesh S, Ranganath A, Harsha K, Yadav NK, Bhujang BS. Choroidal detachment after PASCAL photocoagulation. Can J Ophthalmol. 2011;46:91.
40. Velez-Montoya R, Guerrero-Naranjo JL, Gonzalez-Mijares CC, Fromow-Guerra J, Marcellino GR, Quiroz-Mercado H, Morales-Cantón V. Pattern scan laser photocoagulation: safety and complications, experience after 1301 consecutive cases. Br J Ophthalmol. 2010;94:720-724.
41. Sheth S, Lanzetta P, Veritti D, Zucchiatti I, Savorgnani C, Bandello F. Experience with the Pascal® photocoagulator: An analysis of over 1200 laser procedures with regard to parameter refinement. Indian J Ophthalmol. 2011;59:87-91.

DOI: 10.4274/tjo.26780
Turk J Ophthalmol 2017;47:42-46

Case Report

Rituximab Treatment in a Patient with Active Graves' Orbitopathy and Psoriasis

Tülay Şimşek*, Nilgün Yıldırım*, Belgin Efe**, Nur Kebapçı**
*Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
**Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology, Eskişehir, Turkey

Abstract
Management of Graves' orbitopathy remains an important therapeutic challenge. Current therapeutic modalities are unsatisfactory in about one third of patients. Rituximab is a monoclonal antibody against CD20 antigen that is expressed in mature and immature B cells. Early experience with rituximab suggests that it is a promising alternative therapy for Graves' orbitopathy. Here we report a case of a 49-year-old woman with Graves' orbitopathy and psoriasis. The patient received 2 infusions of 1 g rituximab 2 weeks apart. Although there was improvement in inflammatory signs of the disease, proptosis did not change after the treatment.
Keywords: Graves' orbitopathy, rituximab, psoriasis

Introduction

Graves' disease (GD) is an autoimmune disease that affects multiple systems including the thyroid, orbits and skin.[1] Graves' orbitopathy (GO) is the most common (in 25-50% of GD patients) and serious clinical manifestation of extrathyroidal GD.[2] It has been shown that hyperthyroidism in GD results from the stimulation of thyroid stimulating hormone (TSH) receptors located on thyrocytes by immunoglobulin G, which is continuously produced by B cells. Although the pathogenesis of GO has not been fully elucidated, it is believed to be related to immunologic cross-activity between thyroid and orbital tissue antigens.[3] Orbital fibroblasts are the primary cellular target of this autoimmunity. Autoantibodies produced in GD activate orbital fibroblasts, which stimulates the release of T cell cytokines and the subsequent synthesis of extracellular matrix components. TSH receptor (TSHR) autoantibodies as well as insulin-like growth factor 1 receptor (IGF-1R) autoantibodies are also present in GD, and they stimulate the production of T cell chemoattractants. B lymphocytes are reportedly responsible for the production of TSHR and IGF-1R antibodies. IGF-1R has been found on the surface of both T and B lymphocytes.[4] Considering these data, it is understandable that there are many mechanisms responsible for GO pathogenesis and thus the search for the most appropriate treatments for this disease is still ongoing.

Immunomodulatory therapy has recently emerged as a treatment option for patients with mild to moderate active GO. Rituximab is a monoclonal antibody against the transmembrane protein CD20 found in both mature and immature B cells. CD20 antigen enables B cell activation and differentiation.[5] There are several studies regarding the use of intravenous (IV) rituximab therapy in GO patients.[6,7,8] These studies report a rapid reduction in GO activity score following rituximab infusion, no relapse for over 18 months and no serious drug-related side effects.[6,7] With this report, we aimed to determine the efficacy and safety of IV rituximab therapy in a patient with GO and psoriasis and to evaluate therapeutic approaches in such cases.

Case Report

A 49-year-old female patient presented with hyperemia, pain, proptosis, and blurred vision in both eyes. The patient had a 2-year history of hyperthyroidism and 35-year history of psoriasis. It was learned that she had radioactive iodine therapy 1.5 years earlier and her ocular symptoms had started about

Address for Correspondence: Tülay Şimşek MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Ophthalmology, Eskişehir, Turkey
Phone: +90 222 229 10 01 E-mail: tulaysimsek@hotmail.com **Received:** 14.02.2015 **Accepted:** 30.03.2015

1 year after this treatment. The patient also reported having stomach discomfort and a smoking habit. She was diagnosed with active GO. Rituximab was chosen for treatment because she was already taking adalimumab for psoriasis and was contraindicated for steroid use. Full ophthalmologic examination, visual field and visual evoked potential (VEP) tests were done prior to treatment and at 2 weeks, 1 and 2 months, and 1 year after treatment. GO was assessed using Hertel measurement, Hess screen, orbital ultrasonography and magnetic resonance imaging (MRI). The patient's clinical activity score (CAS) was determined, and thyroid function tests, antithyroid antibody levels, and B lymphocytes were evaluated. Chest radiograph, routine biochemistry, liver function tests, hepatitis screening (prophylaxis based on results), and immunoglobulin levels were measured to screen for potential side effects of rituximab. The patient's pretreatment visual acuity was 0.8 in the right eye and 0.9 in the left eye. There was bilateral eyelid edema which was more pronounced on the right, and eyelid retraction was evident. The palpebral aperture was 16 mm on the right and 13 mm on the left. The conjunctivae were hyperemic, and chemosis and caruncular edema were apparent in the right eye. Eye movement in the right eye was limited in upgaze. There was pronounced proptosis bilaterally: 26 mm on the right and 23 mm on the left with a base measure of 105 mm. Orbital MRI revealed bilateral thickening of the medial rectus (MR; 6.25 mm right, 4.8 mm left) and inferior rectus (IR; 8.1 mm right, 7.2 mm left) muscles. Hess screen test revealed underaction of the left IR muscle. The patient reported spontaneous pain in the right eye and her CAS was 7/7 in the right and and 5/7 in the left eye. Intraocular pressure in the right and left eye was 23 mmHg and 22 mmHg in primary gaze position and 27 and 24 mmHg in upgaze, respectively. Visual field and VEP tests were normal. Antithyroid antibody levels were elevated (antithyroglobulin antibody: 717.2 IU/mL, TSHR antibody: 20.98 U/L); thyroid hormones and B lymphocytes were within normal range. Systemic screening prior to rituximab therapy revealed no pathologies. The patient received 2 infusions of 1000 mg IV rituximab administered 2 weeks apart. To prevent allergic reaction, 1 g paracetamol and 10 mg chlorpheniramine were administered prior to infusion. After the second dose of rituximab was administered, improvements were observed in the soft tissue findings of eyelid edema, hyperemia, conjunctival edema, hyperemia, and caruncular edema. CAS score was 5/7 for the right and 4/7 for the left eye. Orbital MRI revealed significant reduction in MR (5.6 mm right, 4.6 mm left) and IR (5.6 mm right, 5.5 mm left) muscle thickness, but there was no change in the degree of proptosis. Antithyroid antibody levels decreased to baseline levels (antithyroglobulin antibody: 606.5 IU/mL, TSHR antibody: 13.56 U/L). There was also improvement in the patient's signs of psoriasis. The patient has been followed for 4 months and no treatment-related side effects have been observed. Figures 1, 2 and 3 show pre- and posttreatment images of the patient's eyes, orbital MRI, and psoriatic lesions.

Discussion

GO is an autoimmune disease resulting from cross-reactivity between antigens of the thyroid and orbital tissues. Stimulation of orbital TSHRs induces the release of glycosaminoglycans from fibroblasts, which in turn alters the osmotic balance, leading to fluid retention and an increase in orbital volume.[9,10]

Although GO is usually mild and resolves spontaneously, it may be severe enough to threaten sight in 3-5% of cases.[9] The course of the disease has two distinct stages, an active phase followed by an inactive phase. Signs and symptoms in the active phase include proptosis, lid hyperemia, periorbital edema, conjunctival hyperemia (particularly near the extraocular muscles), chemosis, caruncular edema, diplopia, corneal ulceration, and rarely vision loss due to optic nerve compression.[3] These findings are associated with inflammation, glycosaminoglycan accumulation, and increased adipose tissue. As the bony orbit cannot expand, an increase in orbital volume disrupts venous drainage, leading to edema and chemosis in the orbital region.[3,9] The active phase is marked by the effect of cytokines (interleukin-6, interleukin-1, and gamma interferon) released from T helper (Th) type 1 cells.[10,11]

The inactive phase is characterized by more stable proptosis, lid retraction, and restrictive strabismus, whereas signs of inflammation resolve. The disease generally enters the inactive

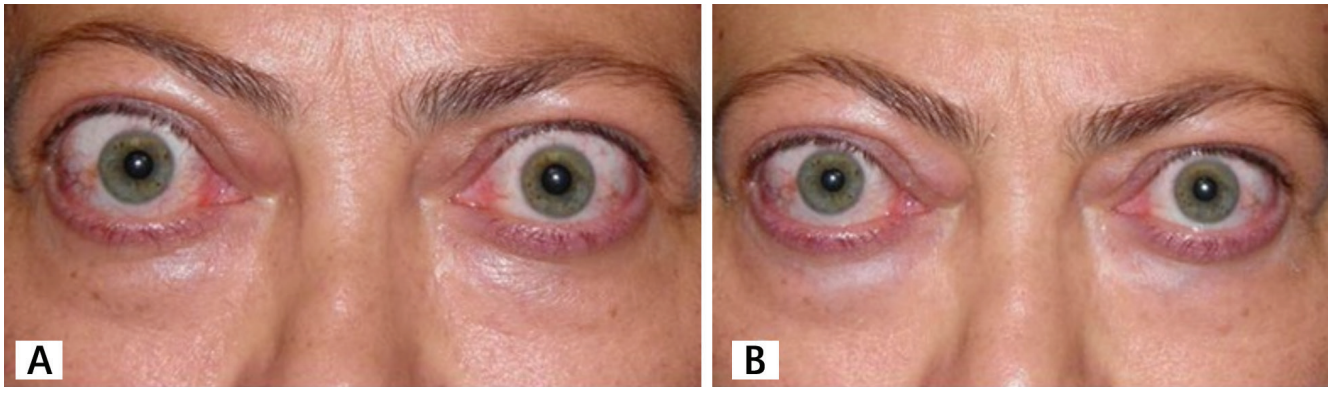

Figure 1. A) Pretreatment photograph showing bilateral proptosis which is more pronounced on the right, lid retraction, lid hyperemia and edema, conjunctival hyperemia, and right caruncular edema; B) posttreatment photograph showing bilateral improvement in lid edema, hyperemia, lid retraction, and conjunctival hyperemia

phase an average of 18-24 months after onset.[3] The cytokines involved in this phase originate from T helper-2 (Th2) cells and are predominantly interleukin-4, 5 and 10.[11]

In addition to T cells, B cells also play a role in the pathogenesis of GO. It has been demonstrated that B cells are abundant in the orbits of GO patients and that they produce autoantibodies against TSHR and IGF-1R. Aside from producing antibodies, B cells present antigens to T cells and mediate their activation via cytokines.[12] Therefore, agents that are effective against both T cells and B cells are now used in the management of GO.[13]

Currently, the most common therapeutic approaches to GO are corticosteroids, radiotherapy, and decompression surgery.[13,14] Long-term corticosteroid use can lead to hypertension, hyperglycemia, diabetes, osteoporosis, cushingoid appearance, proximal myopathy, peptic ulceration, increased susceptibility to infections, and psychiatric disorders.[15] External-beam radiotherapy can cause temporary exacerbation of ocular symptoms and cataract. Furthermore, it is not generally recommended for diabetic and hypertensive patients due to the risk of radiation retinopathy, a rare but sight-threatening complication. It is also not recommended for patients under 35 years of age because it can precipitate carcinogenesis.[16,17] Orbital decompression surgery is performed in the active phase when there is a threat to optic disc function, or for cosmetic purposes in the inactive phase. The procedure requires an experienced surgical team.[13,14,18] Due to the limitations of these therapeutic modalities, the search for effective treatment for GO is ongoing. The efficacy of rituximab in other autoimmune diseases such as rheumatoid arthritis suggested that it may also be effective in the management of GO.

Rituximab is a monoclonal antibody against the transmembrane protein CD20, which is expressed in both mature and immature B cells. The CD20 antigen enables the

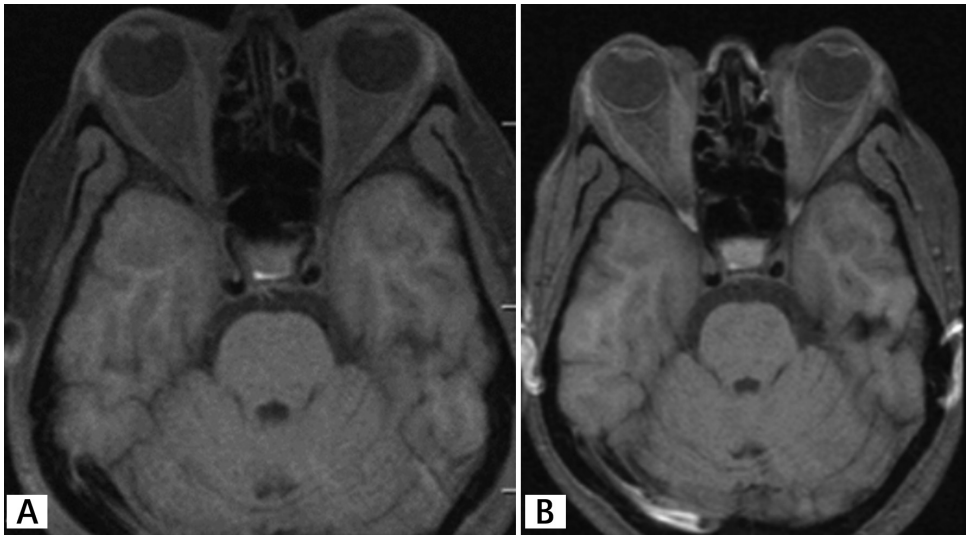

Figure 2. Orbital magnetic resonance imaging showing A) pretreatment fusiform thickening of the extraocular muscles and B) posttreatment regression of the extraocular muscle thickening

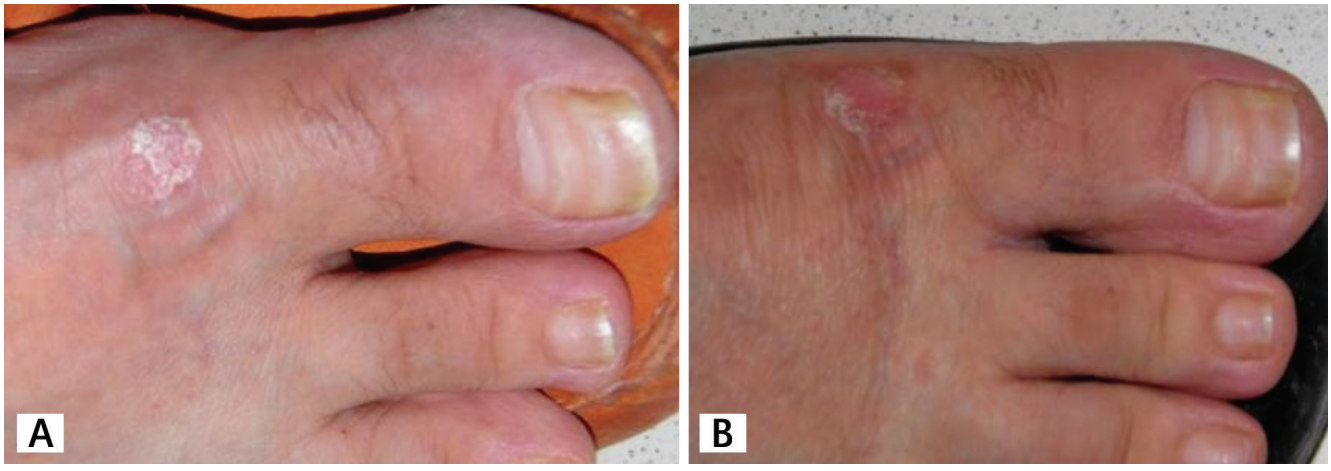

Figure 3. A) Pretreatment photograph showing a light-colored psoriatic lesion on the top of the foot; B) posttreatment photograph showing regression of the psoriatic lesion

activation and differentiation of B cells. As CD20 is absent in plasma and stem cells, rituximab can prevent B cell activation and differentiation without disrupting the immunoglobulin structure or B cell regeneration. In GO, which primarily involves T cells, rituximab also disrupts B cells' antigen-presenting function.[19,20] Rituximab has been shown to deplete B cells for 4-6 months and reduce signs associated with active GO. The earliest study related to this was presented by Salvi et al.,[6] who reported an extremely rapid (within hours) regression of proptosis and clinical signs after rituximab treatment.

To date, most relevant studies are case reports or small case series; no controlled clinical studies have been conducted yet. Khanna et al.[21] administered rituximab to 6 patients whose active GO was unresponsive to steroid therapy and orbital decompression surgery. All of the patients showed improved CAS and reduced orbital inflammation, but proptosis and strabismus remained unchanged. The authors concluded that rituximab does not offer a cure for GO but can be considered as a salvage therapy, particularly in cases of serious complications like optic neuropathy. Similarly, our case did not show improvement in proptosis or eye movement restriction despite regression of signs related to soft tissue involvement. The presence of another autoimmune disease, normal baseline B lymphocyte levels, or having previously underwent 8 cycles of adalimumab therapy for psoriasis may explain why our patient did not exhibit rapid improvement following rituximab treatment. Furthermore, patients in other studies of rituximab were administered combined therapy with corticosteroids. We did not use that approach due to our patient's contraindication for steroid use. In a study evaluating patients treated with rituximab, it was noted that 2 of the 3 patients who did not respond to treatment had received only rituximab, whereas all of the responsive patients had been treated with both rituximab and corticosteroids. Combined use of the two agents may have provided a quicker effect and greater improvement of symptoms.[22] A case showing transient improvement after rituximab therapy with later recurrence has also been reported.[23] Based on our experience with the present case, we believe that rituximab treatment was effective against some factors involved in the pathogenesis of GO, but the disease still showed progression due to other pathogenetic mechanisms.

GO is an autoimmune disease and may manifest with other autoimmune diseases, the most common of which are rheumatoid arthritis and type 2 diabetes. Comorbid dermatologic disorders such as pemphigus vulgaris and acquired ichthyiosis have also been reported.[24] A search of the literature yielded no other cases like our own, with GO and coexisting psoriasis. The Th1 inflammatory cytokines involved in the active phase of GO are also responsible for the pathogenesis of psoriasis.[25] The effect of rituximab on psoriasis is controversial. There are reports of patients developing psoriasis after rituximab therapy, but there are also cases whose cutaneous lesions and psoriatic arthritis partially improved after taking rituximab.[26,27] Interleukin-10-secreting regulatory B cells mediate the suppression of autoimmune and inflammatory diseases by inhibiting Th1 and Th2 cytokine polarization, antigen presentation, and proinflammatory cytokine production by monocytes and macrophages. B cell depletion after treatment with drugs like rituximab may result in exacerbation of autoimmune diseases like ulcerative colitis and psoriasis.[28,29] The proposed mechanism by which rituximab causes psoriasis is that the depletion of B cells eliminates their regulatory effect over T cells, resulting in an abnormal T cell response or subclinical infection which triggers psoriasis.[26] Rituximab treatment has also been reported to bring about partial amelioration of psoriatic lesions, but those patients were under rituximab therapy for lymphoma or other hematologic diseases and had coexisting psoriasis. The improvement of psoriatic plaques in these patients has been associated with the effect of rituximab on immune complexes that mediate the production of tumor necrosis factor alpha (TNF-α).[27] TNF-α blockers are used in the management of psoriasis.

Our patient was also administered the TNF-α blocker adalimumab for psoriasis prior to rituximab therapy. After rituximab, she exhibited no increase in psoriatic lesions and in fact a partial improvement was observed. This may be attributed to the effect of rituximab on TNF-α. Our patient exhibited no side effects related to rituximab therapy during the 4 months of follow-up. Potential short-term side effects such as hypotension, sinus tachycardia, and serum sickness have been reported in the literature. Rare instances of polyarthritis, ulcerative colitis, urinary system infections, cardiac arrest and pneumonia have been reported in the long-term.[22] The low incidence of serious side effects makes rituximab therapy advantageous.

Smoking is another important issue in the management of GO, and patients who smoke are strongly advised to quit. Cigarette use is proven to increase the prevalence and severity of GO. Moreover, smoking is a cause of poor treatment response. Smoking has been shown to increase the synthesis of hyaluronic acid by orbital fibroblasts in adipose tissue; furthermore, tissue hypoxia induced by smoking results in the generation of free radicals, which in turn induce the proliferation of orbital fibroblasts and stimulate glycosaminoglycan synthesis and adipogenesis.[30,31] Our patient also had a smoking history. We believe this had a negative impact on her recovery and resulted in only partial resolution of her symptoms.

Although thyroid function is not associated with GO severity, the treatment of hyperthyroidism is undeniably important. GO is more severe in the presence of persistent hyper- or hypothyroidism; therefore, it is recommended to maintain a state of euthyroidism in these patients. Due to higher incidence and severity of GO with radioactive iodine therapy, this treatment is not recommended for high-risk patients.[3]

Conclusion

Although GO is rarely severe, its management is still of substantial importance due to possible sight-threatening complications and resultant esthetic issues and reduced quality of life. Because of the many factors involved in the pathogenesis, a single therapeutic approach may not be effective and different treatment protocols may be necessary. In our case, IV rituximab

therapy prevented serious complications by arresting disease progression and effecting partial resolution of symptoms, indicating that IV rituximab is a possible alternative therapy for patients with contraindication for steroids or other treatment approaches. Randomized, controlled clinical studies are needed to evaluate the efficacy and safety of this treatment method.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tülay Şimşek, Nilgün Yıldırım, Concept: Tülay Şimşek, Belgin Efe, Nilgün Yıldırım, Design: Tülay Şimşek, Nur Kebapçı, Nilgün Yıldırım, Data Collection or Processing: Tülay Şimşek, Nur Kebapçı, Analysis or Interpretation: Tülay Şimşek, Belgin Efe, Literature Search: Tülay Şimşek, Nur Kebapçı, Writing: Tülay Şimşek.

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. European Group of Graves' Orbitopathy, Perros P, Baldeschi L, Boboridis K, Dickinson AJ, Hullo A, Kahaly GJ, Kendall-Taylor P, Krassas GE, Lane CM, Lazarus JH, Marcocci C, Marino M, Mourits MP, Nardi M, Orgiazzi J, Pinchera A, Pitz S, Prummel MF, Wiersinga WM. A questionnaire survey on the management of Graves' orbitopathy in Europe. Eur J Endocrinol. 2006;155:207-211.
2. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726-738.
3. Naik VM, Naik MN, Goldberg RA, Smith TJ, Douglas RS. Immunopathogenesis of thyroid eye disease: Emerging paradigms. Surv Ophthalmol. 2010;55:215-226.
4. Douglas RS, Naik V, Hwang CJ, Afifiyan NF, Gianoukakis AG, Sand D, Kamat S, Smith TJ. B cells from patients with Graves' disease aberrantly express the IGF-1 receptor: Implications for disease pathogenesis. J Immunol. 2008;181:5768-5774.
5. Hasselbalch HC. B-cell depletion with rituximab- a targeted therapy for Graves' disease and autoimmune thyroiditis. Immunol Lett. 2003;88:85-86.
6. Salvi M, Vannucchi G, Campi I, Curro N, Dazzi D, Simonetta S, Bonara P, Rossi S, Sina C, Guastella C, Ratiglia R, Beck-Peccoz P. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. Eur J Endocrinol. 2007;156:33-40.
7. Khanna D, Chong KKL, Afifiyan NF, Hwang CJ, Lee DK, Garneau HC, Goldberg RA, Darwin CH, Smith TJ, Douglas RS. Rituximab treatment of patients with severe, corticosteroid resistant thyroid associated ophthalmopathy. Ophthalmology. 2010;117:133-139.
8. Salvi M, Vannucchi G, Curro N, Introna M, Rossi S, Bonara P, Covelli D, Dazzi D, Guastella C, Pignataro L, Ratiglia R, Golay J, Beck-Peccoz P. Small dose of rituximab for Graves Orbitopathy: new insights into the mechanism of action. Arch Ophthalmol. 2012;130:122-124.
9. Bahn RS. Clinical review157: pathophysiology of Graves' Ophthalmopathy: the cycle of disease. J Clin Endocrinol Metab. 2003;88:1936-1946.
10. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. N Engl J Med. 1993;329:1468-1475.
11. Aniszewski JP, Valyasevi RW, Bahn RS. Relationship between disease duration and predominant orbital T cell subset in Graves' ophthalmopathy. J Clin Endocrinol Metab. 2000;85:776-780.
12. Zha B, Huang X, Lin J, Liu J, Hou Y, Wu G. Distribution of lymphocyte subpopulations in thyroid glands of human autoimmune thyroid disease. J Clin Lab Anal. 2014;28:249-254.
13. Briceno CA, Gupta S, Douglas RS. Advances in the management of thyroid eye disease. Int Ophthalmol Clin. 2013;53:93-101.
14. Onaran Z, Konuk O, Oktar SÖ, Yücel C, Unal M. Intraocular pressure lowering effect of orbital decompression is related to increased venous outflow in Graves orbitopathy. Curr Eye Res. 2014;39:666-672.
15. Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, Bournaud C, Stahl M, Sassi L, Veronesi G, Azzolini C, Boboridis KG, Mourits MP, Soeters MR, Baldeschi L, Nardi M, Curro N, Boschi A, Bernard M, von Arx G; European Group on Graves' Orbitopathy. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab. 2012;97:4454-4463.
16. Wakelkamp IM, Tan H, Saeed P, Schlingemann RO, Verbraak FD, Blank LE, Prummel MF, Wiersinga WM. Orbital irradiation for Graves' ophthalmopathy: is it safe ? A long-term follow-up study. Ophthalmology. 2004;111:1557-1562.
17. Viebahn M, Marricks ME, Osterloh MD. Synergism between diabetic and radiation retinopathy: case report and review. Br J Ophthalmol. 1991;75:29-32.
18. Wiersinga WM. Grave's orbitopathy: Management of difficult cases. Indian J Endocrinol Metab. 2012;16:150-152.
19. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994;83:435-445.
20. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Ann Oncol. 2003;14:520-535.
21. Khanna D, Chong KKL, Afifiyan NF, Hwang CJ, Lee DK, Garneau HC, Goldberg RA, Darwin CH, Smith TJ, Douglas RS. Rituximab treatment of patients with severe, corticosteroid resistant thyroid associated ophthalmopathy. Ophthalmology. 2010;117:133-139.
22. Shen S, Chan A, Sfikakis PP, Hsiu Ling AL, Detorakis ET, Boboridis KG, Mavrikakis I. B cell targeted therapy with rituximab for thyroid eye disease: Closer to the clinic. Surv Ophthalmol. 2013;58:252-265.
23. Salvi M, Vannucchi G, Campi I, Curro N, Simonetta S, Covelli D, Pignataro L, Guastella C, Rossi S, Bonara P, Dazzi D, Ratiglia R, Beck-Peccoz P. Rituximab treatment in a patient with severe thyroid-associated ophthalmopathy: effects on orbital lymphocytic infiltrates. Clin Immunol. 2009;131:360-365.
24. Kirby JS, James WD. Dermatologic disorders associated with thyroid disease. In Warren R Heymann eds. Thyroid disorders with cutaneous manifestations (first ed). London; Springer-Verlag. 2008:157-180.
25. Bos JD, Hulsebosch HJ, Krieg SR, Bakker PM, Cormane RH. Immunocompetent cells in psoriasis: in situ immunophenotyping by monoclonal antibodies. Arch Dermatol Res. 1983;275:181-189.
26. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. Arthritis Rheum. 2007;56:2715-2718.
27. Moberg P, Charles JF, Respicio G, Venna SS, Rooney T. İmprovment in psoriasis during rituksimab therapy for mixed cryoglobulinemia type II. Cutis. 2010;86:133-135.
28. Guidelli GM, Fioravanti A, Rubegni P, Feci L. Induced psoriasis after rituximab therapy for rheumatoid arthritis: a case report and review of the literature. Rheumatol Int. 2013;33:2927-2930.
29. Ardelean DS, Gonska T, Wires S, Cutz E, Griffiths A, Harvey E, Tse SM, Benseler SM. Severe ulcerative colitis after rituximab therapy. Pediatrics. 2010;126:e243-246.
30. Şimşek T, Acaroğlu G, Çıtırık M, Elgin U, Çankaya AB, Kabataş N. Incidence and Risk Factors of Secondary Glaucoma in Patients with Thyroid-Associated Orbitopathy. Turk J Ophthalmol. 2009;39:387-392.
31. Shine B, Fells P, Edwards OM, Weetman AP. Association between Graves' ophthalmopathy and smoking. Lancet. 1990;335:1261-1263.

DOI: 10.4274/tjo.93824
Turk J Ophthalmol 2017;47:47-51

Case Report

Anterior Segment Ischemia after Strabismus Surgery

Emine Seyhan Göçmen, Yonca Atalay, Özlem Evren Kemer, Hikmet Yavuz Sarıkatipoğlu
Ankara Numune Training and Research Hospital, Ophthalmology Clinic, Ankara, Turkey

Abstract

A 46-year-old male patient was referred to our clinic with complaints of diplopia and esotropia in his right eye that developed after a car accident. The patient had right esotropia in primary position and abduction of the right eye was totally limited. Primary deviation was over 40 prism diopters at near and distance. The patient was diagnosed with sixth nerve palsy and 18 months after trauma, he underwent right medial rectus muscle recession. Ten months after the first operation, full-thickness tendon transposition of the superior and inferior rectus muscles (with Foster suture) was performed. On the first postoperative day, slit-lamp examination revealed corneal edema, 3+ cells in the anterior chamber and an irregular pupil. According to these findings, the diagnosis was anterior segment ischemia. Treatment with 0.1/5 mL topical dexamethasone drops (16 times/day), cyclopentolate hydrochloride drops (3 times/day) and 20 mg oral fluocortolone (3 times/day) was initiated. After 1 week of treatment, corneal edema regressed and the anterior chamber was clean. Topical and systemic steroid treatment was gradually discontinued. At postoperative 1 month, the patient was orthophoric and there were no pathologic symptoms besides the irregular pupil. Anterior segment ischemia is one of the most serious complications of strabismus surgery. Despite the fact that in most cases the only remaining sequel is an irregular pupil, serious circulation deficits could lead to phthisis bulbi. Clinical properties of anterior segment ischemia should be well recognized and in especially risky cases, preventative measures should be taken.
Keywords: Anterior segment ischemia, Foster, sixth nerve palsy, transposition surgery

Introduction

Anterior segment ischemia is a rare but well documented complications of strabismus surgery. It generally manifests within 24 hours of surgery with blurred vision, lid and corneal edema, anterior segment cells, and hypotony.[1] Advanced age, procedures involving multiple muscles, procedures on vertical muscles, hyperviscosity, and systemic vascular diseases are among the risk factors for anterior segment ischemia.[2] In order to prevent this possible sight-threatening complication, surgical procedures which spare the anterior ciliary artery should be favored, especially in patients with risk factors.[3] In this report, we discuss the precipitating factors, clinical features, and management of a case of anterior segment ischemia following full-thickness tendon transposition (with Foster suture).

Case Report

A 46-year-old male patient presented to our clinic with an approximately 18-month history of esotropia in his right eye and diplopia. The patient had no systemic diseases and it was learned that his symptoms developed following a car accident. The patient's visual acuity was measured by Snellen chart as 20/20 in both eyes with refractive correction of -1.50 -1.00x95 on the right and -1.75 -0.50x120 on the left. Anterior and posterior examinations were normal. The patient had esotropia of 40 prism diopters and right eye abduction was graded as -4 (completely limited). Cranial tomography conducted 6 months earlier had revealed no pathology. Based on the findings, the patient was diagnosed with sixth nerve palsy and 18 months after the trauma he underwent 6 mm recession of the right medial rectus muscle. In postoperative follow-up, the patient's esotropia in primary position continued and right eye abduction

Address for Correspondence: Emine Seyhan Göçmen MD, Ankara Numune Training and Research Hospital, Ophthalmology Clinic, Ankara, Turkey
Phone: +90 533 310 89 41 E-mail: esgocmen@yahoo.com **Received:** 19.10.2014 **Accepted:** 21.04.2015

remained -3 limited. Ten months after the initial surgery, he underwent a full-thickness transposition of the superior and inferior rectus muscles to the lateral rectus muscle and a 5/0 multifilament nonabsorbable lateral fixation suture (Foster) was placed in the sclera 8 mm posterior to the lateral rectus insertion incorporating the superior rectus and one fourth of the lateral rectus muscle. Another 5/0 multifilament nonabsorbable lateral fixation suture was placed in the sclera 8 mm posterior to the lateral rectus insertion incorporating the inferior rectus and one fourth of the lateral rectus muscle. On postoperative day 1, biomicroscopic examination revealed corneal edema, Descemet's membrane folds, mild hypotony, 3+ cells in the anterior chamber, and irregular mid-dilated pupil. The lens was not cataractous and fundus examination was normal. Visual acuity had declined to 20/40 on Snellen chart. Based on the findings, the diagnosis was anterior segment ischemia. Treatment with 0.1/5 mL topical dexamethasone drops (16 times/day), cyclopentolate hydrochloride drops (3 times/day) and 20 mg oral fluocortolone (3 times/day) was initiated the same day. After 1 week of treatment, the corneal edema had regressed and the anterior chamber was free of cells, but the pupil irregularity persisted. Visual acuity had improved to 20/28. Intraocular pressure was normal. The oral fluocortolone and topical dexamethasone were gradually discontinued over the course of 1 month. The patient's visual acuity improved to 20/20, diplopia completely resolved and at postoperative 1 month, there were no remaining pathologic signs other than pupil irregularity. The patient was orthophoric in primary position and there was -1 limitation in right eye movement (Figures 1-4).

Discussion

Circulation to the anterior segment is provided by seven anterior ciliary arteries and two posterior ciliary arteries. One anterior ciliary artery supplies the lateral rectus muscle and two supply each of the other extraocular muscles.[1] The vertical rectus muscle in particular has a major impact on anterior segment circulation.[2] Various authors have reported anterior segment ischemia due to damage to this vascular network during strabismus surgery at rates ranging from 1/13,000 to 1/30,000.[3] Anterior segment ischemia occurs as a result of interruption to the blood supply to the anterior segment following strabismus surgery. Permanent detachment of the rectus muscles cuts blood flow in the anterior ciliary arteries. Intravascular coagulative hematologic abnormalities and local or systemic factors impairing ocular circulation may also contribute to reduced blood flow.[4] Advanced age, systemic vascular disease, hyperviscosity, diabetes mellitus, dysthyroid ophthalmopathy, and 360° scleral buckling surgery due to retinal detachment are among the risk factors associated with this complication.[5] Anterior segment ischemia has been reported as a result of strabismus surgery in patients with a history of radiotherapy to treat tumors of the head and neck.[6] As a general rule, including more than three rectus muscles in a single operation and performing a second rectus muscle

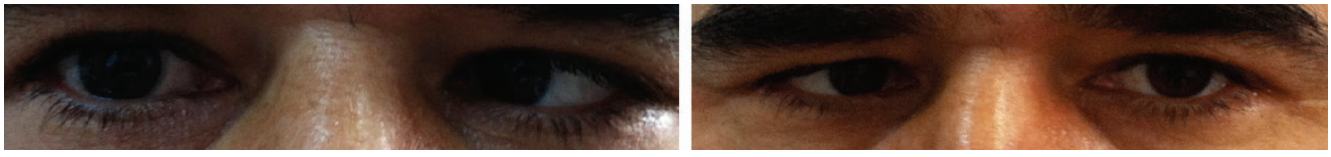

Figure 1. Right esotropia is evident preoperatively in primary position. Abduction is -4 limited

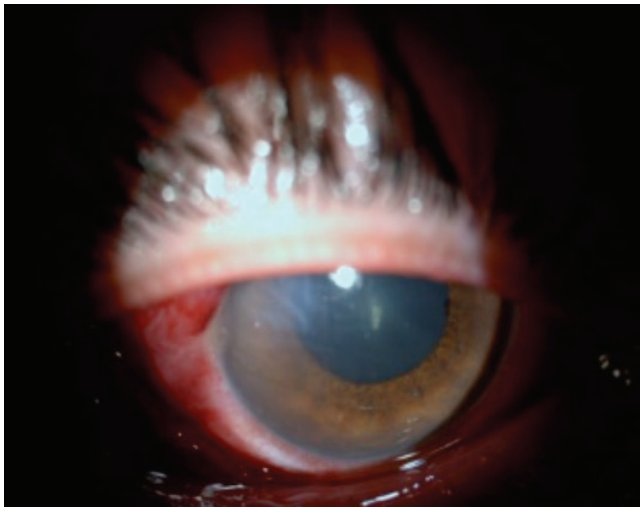

Figure 2. On postoperative day 1, corneal edema, Descemet membrane folds, irregular pupil and 3+ anterior segment cells are evident

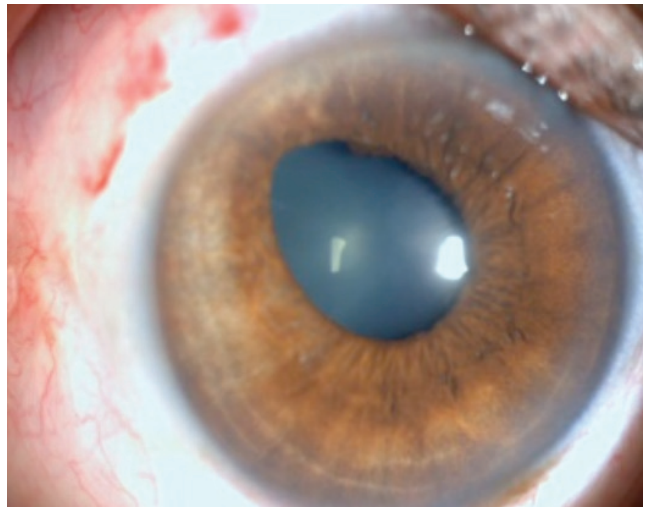

Figure 3. At postoperative 1 month, there are no pathologic signs other than pupil irregularity

surgery within six months of a previous rectus muscle surgery substantially increase the risk of anterior segment ischemia.[2] Olver and Lee[7] graded anterior segment ischemia as follows: Grade I: decreased iris perfusion; Grade II +pupil signs; Grade III: +uveitis; and Grade IV: +keratopathy. Although most patients' iris circulation returns to baseline levels within 2 weeks after surgery, the recovery can last up to 12 weeks in some cases. Grade IV anterior segment ischemia in particular can lead to permanent vision loss due to cataract, corneal scar and macular changes. The condition is marked by blurred vision and edema of the eyelids, conjunctiva and cornea which usually appear the first day after strabismus surgery. The pupil is often mid-dilated and light reaction is weak. There may be a high concentration of cells in the anterior chamber, but intraocular pressure is low due to reduced circulation.[8] Anterior segment angiography reveals diffuse iris leakage in acute-onset ischemia, versus pupil margin leakage and nodule-like vascular dilations in gradual-onset ischemia. In ischemias that cause iris atrophy, the areas of ischemia have distinct margins.[9] Arterial circulation often recovers in the long term but in some patients, iris atrophy and pupil irregularity may persist.[1] Kaeser and Klainguti[10] noted relative iris ischemia in 4 of 10 patients that had previously undergone horizontal rectus muscle.

It is generally recommended to avoid procedures involving more than three rectus muscles in order to prevent anterior segment ischemia.[8] Girard and Beltranena[11] reported mild anterior segment necrosis due to impaired anterior ciliary artery circulation after tenotomy of three or more rectus muscles. In an experimental study on monkey eyes by Virdi and Hayreh,[12] it was determined that simultaneous recession of two or three rectus muscles can cause mild to moderate anterior segment ischemia, whereas procedures involving four muscles can lead to serious, permanent changes. Another surgical method developed to prevent anterior segment ischemia and which is currently especially used in paralytic strabismus surgery is the Hummelscheim procedure. In this technique, the muscle fibers attached to the lateral halves of the superior and inferior rectus tendons are fixated to the lateral rectus tendon. Many surgeons prefer this technique because it preserves the vasculature.[13] In 2001, Brooks et al.[14] proposed an adapted version of the Hummelsheim procedure in which the vertical rectus muscle is resected 4-5 mm prior to transposition (augmented Hummelsheim procedure). Couser et al.[15] performed medial rectus recession with the augmented Hummelsheim procedure in 9 patients and reported achieving orthophoria in primary position and improved abduction. None of their patients developed anterior segment ischemia. Klainguti et al.[16] performed posterior fixation of the contralateral medial rectus in addition to the Hummelsheim procedure in 2 patients with sixth nerve palsy and reported favorable results with this combination. Rectus muscle plication reduces the likelihood of ischemia in the lost muscle and anterior segment.[17] Oltra et al.[18] claimed that plication surgery is safe in patients at high risk of developing postoperative anterior segment ischemia and demonstrated that patients who underwent plication developed fewer filling defects on iris angiography. Vijayalakshmi et al.[19] performed left medial rectus muscle recession and vertical rectus muscle transposition to the lateral rectus augmented by lateral fixation sutures in a

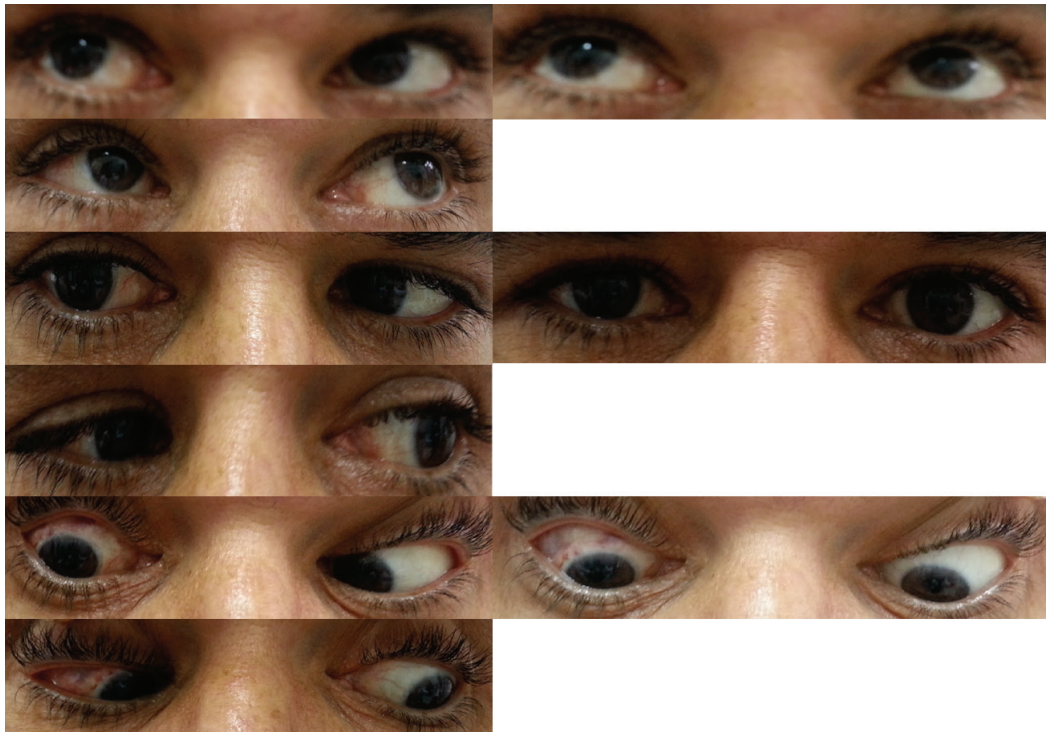

Figure 4. At postoperative 1 month, the patient is orthophoric in primary position. Abduction is -1 limited.

patient with sixth nerve palsy. The patient developed anterior segment ischemia which resolved upon the removal of the lateral fixation sutures and administration of medical treatment. Risk of anterior segment ischemia is also markedly higher within the first six months after rectus muscle surgery. However, there are documented cases of patients developing anterior segment ischemia years after initial surgery.[20] Although surgeries that conserve the anterior ciliary arteries have been shown to reduce the risk of anterior segment ischemia, circulation may not always continue intra- and postoperatively in vessels believed to be saved. Ischemic complications may arise even after successful microvascular dissection and conservation. Cases have also been documented of patients developing anterior segment ischemia after vessel-sparing procedures.[21] Some authors argue that conjunctival incisions made at the fornix spare the conjunctiva-Tenon's capsule junction and are therefore less likely to cause ischemia than incisions made at the limbus.[22] The Jensen procedure (muscle joining technique) is known to preserve ciliary circulation to some degree, but it is not a definitive solution.[23] The minimally invasive strabismus surgery (MISS) technique described by Mojon[24] reduces the risk of anterior segment ischemia by sparing the perilimbal episcleral vessels. Nevertheless, the use of local anesthetics containing epinephrine can still lead to ischemia.[25] In patients at risk of anterior segment ischemia, intraocular pressure should be controlled preoperatively and local anesthesia without sympathomimetic activity should be used. Intraoperatively, peritomy of the conjunctiva should kept to a minimum, the rectus muscles should not be pulled excessively, and the long posterior ciliary arteries should be avoided.[5]

In the event of severe anterior segment ischemia, topical and systemic steroid therapy is used to suppress inflammation. Cycloplegic drugs can be used to prevent synechia; topical mannitol and 0.9% NaCl drops can be used to reduce corneal edema. Intraocular pressure should be controlled.[3]

In the present case, the patient could have been initially treated with a Botox injection to the medial rectus muscle and, considering the patient's age and the possibility that a procedure involving multiple rectus muscles would be required, the surgery initially performed could have been reserved as a secondary measure. Furthermore, evaluation of the patient by iris fluorescein angiography may have provided a warning of the possibility of anterior segment ischemia.

Conclusion

Anterior segment ischemia is one of the serious complications of strabismus surgery. Even though an irregular pupil is the only remaining sequel for many patients, serious circulation deficits can lead to outcomes as severe as phthisis bulbi. Ophthalmologists should be very familiar with the clinical features of anterior segment ischemia and take preventative measures in risky cases.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Emine Seyhan Göçmen, Concept: Emine Seyhan Göçmen, Özlem Evren Kemer, Hikmet Yavuz Sarıkatipoğlu, Design: Emine Seyhan Göçmen, Özlem Evren Kemer, Hikmet Yavuz Sarıkatipoğlu, Data Collection or Processing: Emine Seyhan Göçmen, Yonca Atalay, Analysis or Interpretation: Emine Seyhan Göçmen, Yonca Atalay, Literature Search: Emine Seyhan Göçmen, Yonca Atalay, Writing: Emine Seyhan Göçmen.

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. Sanaç Ali Şefik. Şaşılık ve Tedavisi. 2. Baskı 2002;75-121:208-209.
2. Diamond Gary R. Yanoff Oftalmoloji. 3. Baskı 2007; Bölüm 6 Şaşılık: 633.
3. Saunders RA, Bluestein EC, Wilson ME, Berland JE. Anterior segment ischemia after strabismus surgery. Surv Ophthalmol. 1994;38:456-466.
4. Erşanlı D, Gülecek O. Ön Segment İskemisi. Ret-Vit. 1999;7:248-252.
5. Wright KW. Color Atlas of Strabismus Surgery Strategies and Techniques. Edition 2007;100-101.
6. Yip WW, Yu CB, Fan DS, Yick DW, Rao SK, Lam DS. AnteriorSegment Ischemia After Two-Muscle Surgery in a Patient With Radiation-Treated Nasopharyngeal Carcinoma. J Pediatr Ophthalmol Strabismus. 2008;45:40-42.
7. Olver JM, Lee JP. Recovery of anterior segment circulation after strabismus surgery in adult patients. Ophthalmology. 1992;99:305-315.
8. Helveston E. Surgical Management of Strabismus 5th Edition. 2005;469.
9. Easty DL, Chignell AH. Fluorescein angiography in anterior segment ischemia. Br J Ophthalmol. 1973;57:18-26.
10. Kaeser PF, Klainguti G. Anterior segment angiography in strabismus surgery. Klin Monbl Augenheilkd. 2012;229:362-364.
11. Girard LJ, Beltranena F. Early and late complications of extensive muscle surgery. Arch Ophthalmol. 1960;64:576-584.
12. Virdi PS, Hayreh SS. Anterior segment ischemia after recession of various recti: an experimental study. Ophthalmology. 1987:94;1258-1271.
13. Hendler K, Pineles S, Demer J, Yang D, Velez. Adjustable Augmented Rectus Muscle Transposition Surgery with or Without Ciliary Vessel Sparing for Abduction Deficiencies. Strabismus. 2014;22:74-80.
14. Brooks SE, Olitsky SE, Ribeiro G. Augmented Hummelsheim procedure for paralytic strabismus. J Pediatr Ophthalmol Strabismus. 2000;37:189-195.
15. Couser NL, Lenhart PD,Hutchinson AK. Augmented Hummelsheim procedure to treat complete abducens nerve palsy. J AAPOS. 2012;16:331-335.
16. Klainguti G, Gianoli F, Mataftsi A. Retro-equatorial myopexy following Hummelsheim transposition in treatment of 6th cranial nerve paralysis. Klin Monbl Augenheilkd. 2003;220:170-175.
17. Velez FG, Demer JL, Pihlblad MS, Pineles SL. Rectus muscle plication using an adjustable suture technique. J AAPOS. 2013;17:480-483.
18. Oltra EZ, Pineles SL, Demer JL, Quan AV, Velez FG. The effect of rectus muscle recession, resection and plication on anterior segment circulation in humans. Br J Ophthalmol. 2015;99:556-560.
19. Vijayalakshmi P, Muralidhar R, Shetty S, Sane M. Resolution of anterior segment ischemia after the removal of lateral fixation sutures. J AAPOS. 2008;12:531-532.
20. Raizman MB, Beck RW. Iris ischemia following surgery on two rectus muscles. Arch Ophthalmol. 1985;103;1783-1787.
21. Murdock Todd J, Mills Monte D. Anterior segment Ischemia After Strabismus Surgery With Microvascular Dissection. J AAPOS. 2000;4:56-57.

22. Wright KW. Complex strabismus: restriction, paresis,dissociated strabismus and torticollis. In: Wright KW, Spiegel PH, editors. Pediatric Ophthalmology and Strabismus. Springer-Verlag: New York, 2003:287-288.
23. Frey T. Anterior segment ischemia caused by Jensen's procedure. J Ocular Ther Surg. 1985;3:242-245.
24. Mojon DS. Comparison of a new, minimally invasive strabismus surgery (MISS) technique with the usual limbal approach for rectus muscle recession and plication. Br J Ophthalmol. 2007;91:76-82.
25. Ryan SJ, Goldberg MF. Anterior segment ischemia following scleral buckling in hemoglobin SC disease. Am J Ophthalmol. 1971;72:35-50.

DOI: 10.4274/tjo.32448
Turk J Ophthalmol 2017;47:52-55

Case Report

Eye Injuries from Pencil Lead: Three Cases

Ceyhun Arıcı*, Osman Şevki Arslan*, Burcu Görgülü*, Rengin Yıldırım*, Umut Onur**
*İstanbul University Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
**Bakırköy Dr. Sadi Konuk Training and Research Hospital, Ophthalmology Clinic, İstanbul, Turkey

Abstract
Corneal stromal and/or penetrating ocular injuries from pencils and pencil lead are more common in childhood and may lead to intraocular infection or severe intraocular sterile inflammatory reaction. Herein we report 3 children with ocular trauma due to pencil lead injuries. The first case had corneal stromal injury caused by a pencil. In the second case, a pencil perforated the cornea and contacted the iris. In the third case, pencil lead perforated both the cornea and iris and reached the vitreous through the lens zonules. Intracameral triamcinolone (2 mg/0.05 mL) was injected after the pencil lead was removed from the eyeball. Topical anti-inflammatory and cycloplegic drops were prescribed. In conclusion, corneal and especially penetrating ocular injuries from pencil lead may have a good prognosis with the use of appropriate anti-inflammatory and prophylactic antibiotic treatment and follow-up.
Keywords: Intraocular inflammation, pencil lead, intraocular foreign body

Introduction

Organic intraocular foreign bodies generally cause serious inflammatory reaction and infection. The inflammatory reaction induced by inorganic foreign bodies is related to the composition of the object.[1] There are few cases in the literature of intracorneal carbon particles[2,3] and intraocular penetrating injuries[4,5,6,7,8] due to pencil lead. Although it has been reported that the carbon particles from pencil lead may remain dormant in the eye without inducing inflammation for long periods of time,[2,3] they have also been reported to cause severe endophthalmitis[5] or endothelial dysfunction and corneal edema.[6] In this report we share three cases of pencil lead injury, one with corneal stromal injury and two with intraocular penetrating injuries.

Case Reports

Case 1

An 8-year-old boy was admitted to our urgent ophthalmology clinic the same day of a pencil injury to his left eye. His visual acuity was 20/20 bilaterally. Slit-lamp examination of the left eye revealed intact corneal epithelium and intrastromal silver-gray carbon particles in the inferonasal quadrant of the cornea. The conjunctiva was mildly hyperemic. There was no sign of anterior chamber reaction. Anterior segment examination of the right eye was normal. Intraocular pressure measured by applanation tonometry was 14 mmHg in the right and 17 mmHg in the left eye. Fundus examination was normal in both eyes. The patient was administered moxifloxacin ophthalmic drops (Vigamox 0.5%; Alcon Laboratories Inc., Fort Worth, TX, USA) 4 times a day for 3 weeks and preservative-free artificial tears (Tears Naturale Free; Alcon Laboratories Inc., Fort Worth, TX, USA) 4 times a day for 4 weeks. No signs of inflammatory reaction or injection were observed in follow-up examinations at 1 week and 1, 4, and 6 months (Figures 1A and 1B).

Case 2

A 13-year-old patient presented after being poked in the right eye by a pencil. The patient's visual acuity was counting fingers (CF) from 0.5 m in the right eye and 20/20 in the left eye. On slit-lamp examination, a fragment of pencil lead was found lodged in the inferonasal (at 5 o'clock) paracentral cornea of the right eye. Seidel test was negative. Anterior chamber examination revealed +2 cells in the right eye and was normal in the left eye.

Address for Correspondence: Ceyhun Arıcı MD, İstanbul University Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 212 572 26 42 E-mail: ceyhundr@gmail.com **Received:** 27.01.2015 **Accepted:** 05.05.2015

No signs of pathology were observed in fundus examination of either eye. The patient was admitted for surgical removal of the foreign body. The pencil lead fragment lodged in the cornea was removed using forceps and viscoelastic to support the anterior chamber. The corneal laceration was closed with 4 sutures using 10/0 nylon suture. After the procedure, 2 mg/0.05 mL triamcinolone and 0.25 mg/0.05 mL moxifloxacin were injected into the anterior chamber. On postoperative day 1, treatment was initiated with moxifloxacin drops (6 times a day for 1 week, then reduced to 4 times a day for 2 weeks). Dexamethasone ophthalmic drops (Maxidex, 0.1%; Alcon Laboratories Inc., Fort Worth, TX, USA) were started at 8 times a day for 5 days, then reduced to 6/day for 1 week, then reduced to 4/day for 1 week and tapered by 1 application/day each week until discontinuation. On postoperative day 3, visual acuity on Snellen chart was 20/25 (with or without correction). No inflammatory reaction was observed on anterior segment examination. The corneal sutures were removed at 3-month follow-up. At 7 months, the patient's visual acuity was 20/20 bilaterally (Figure 2). Corneal scar and a few isolated carbon particles were observed in the inferonasal paracentral cornea of the right eye. There were no further changes noted at 1-year follow-up.

Case 3

A 15-year-old male patient whose right eye was stabbed with pencil lead was referred from outside the city to our clinic on the second day after the trauma. His visual acuity was CF from 0.5 m on the right and 20/20 on the left. Slit-lamp examination revealed pencil lead in the right temporal cornea (between 8-9 o'clock) that had perforated the cornea and iris near the limbus. Cyclitic membrane was noted around the pupillary region and hypopyon was present (Figure 3A). The left eye appeared normal. Fundus examination could not be performed in the right eye, but was normal in the left eye. The vitreous and retina appeared normal on B-mode ultrasonography of the right eye. The patient was admitted for surgery to remove the foreign body. Under viscoelastic support of the anterior chamber, microforceps were used to remove a foreign body approximately 5.5 mm long and 1 mm in diameter (Figure 3B). After the procedure, 2 mg/0.05 mL triamcinolone and 0.25 mg/0.05 mL moxifloxacin were injected into the anterior chamber. On postoperative day 1, treatment was initiated with moxifloxacin drops (6 times a day for 1 week, then reduced to 4 times a day for 2 weeks); dexamethasone ophthalmic drops were initiated at 8 times a day for 5 days, then reduced to 6/day for 1 week, then 4/day, and finally tapered by 1 application/day each week until discontinuation. The patient's visual acuity was 20/20 on postoperative day 5. His visual acuity was still 20/20 at 1-year follow-up. On slit-lamp examination, corneal scar tissue and intrastromal carbon particles were noted in the right temporal area. No anterior chamber reaction was observed (Figure 3C).

Discussion

Pencil lead is made of a mixture of carbon, clay and animal fat and is surrounded by a wooden sheath. The main component, carbon, is known to usually remain inert in the eye. However, potential toxicity due to the other components is controversial.[5,9] The first reported case of intracorneal carbon particles was presented by Jeng et al.[2] The patient presented due to a chemical injury to the right eye and silver-gray crystalline opacities were observed in the corneal stroma. It was learned that the patient had sustained a pencil injury to the left eye 8 years earlier. However, the patient's medical records indicated that the injury had in fact been to the right eye. Slit-lamp examination revealed intact corneal epithelium and silver carbon particles in the inferonasal stroma. This demonstrated that carbon particles in the corneal stroma were well tolerated in the long term. Philip et al.[3] reported a case in which intracorneal carbon particles were observed during routine eye examination in a patient who had sustained a pencil injury to the same eye 3 years earlier. Slit-lamp examination of the right eye revealed anterior stromal scar, though no signs of previous or current inflammation were detected in the intraocular structures.

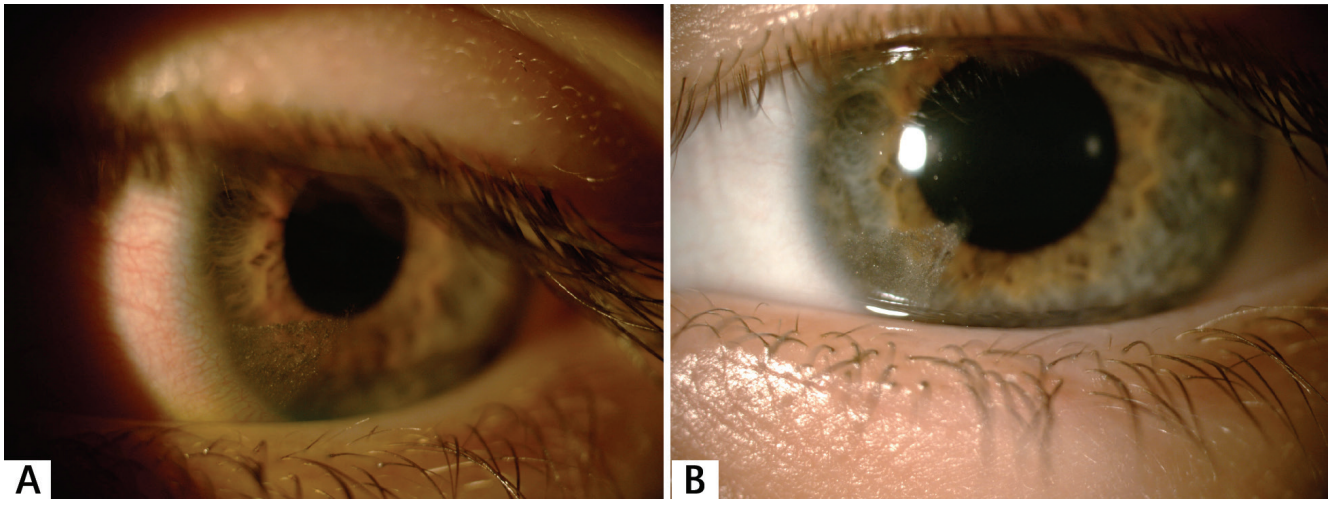

Figure 1. A) Intrastromal carbon particles observed at presentation; B) at four months, the carbon particles are still present but are inert.

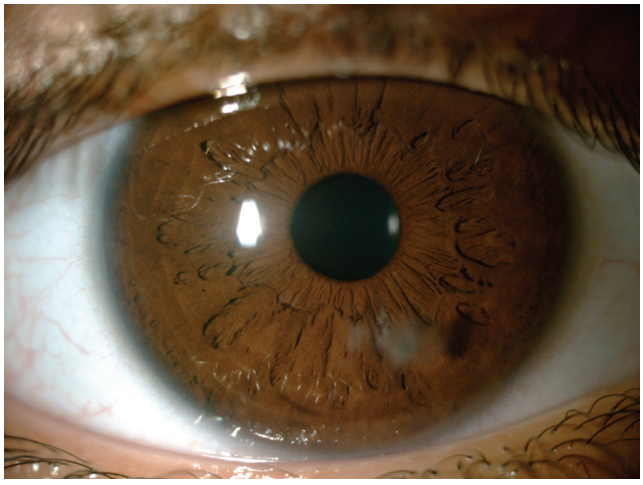

Figure 2. No signs of ocular toxicity are observed in examination at postoperative 7 months

There are also reports in the literature of pencil lead causing severe inflammatory reaction and endophthalmitis. One reported case underwent corneal suturation and lens extraction following a pencil injury to the right eye. Pencil lead fragments were noted in the vitreous and on the second postoperative day the patient developed endophthalmitis. Although bacterial endophthalmitis was suspected based on clinical findings, a vitreal sample taken during pars plana vitrectomy was culture negative. It was proposed that the wood and aluminum found in pencils may have caused a severe inflammatory reaction.[5] In another case with a history of pencil injury, a suspected conjunctival melanoma was excised and the histopathologic report indicated granulomatous reaction due to carbon particles.[10]

Another patient who had sustained a pencil injury to the left eye 4 months earlier presented to an ophthalmologist with a complaint of pain in the left eye for 2 days. Examination revealed a full-thickness corneal scar, a small area of iris atrophy, and a black foreign body resembling pencil lead in the anterior

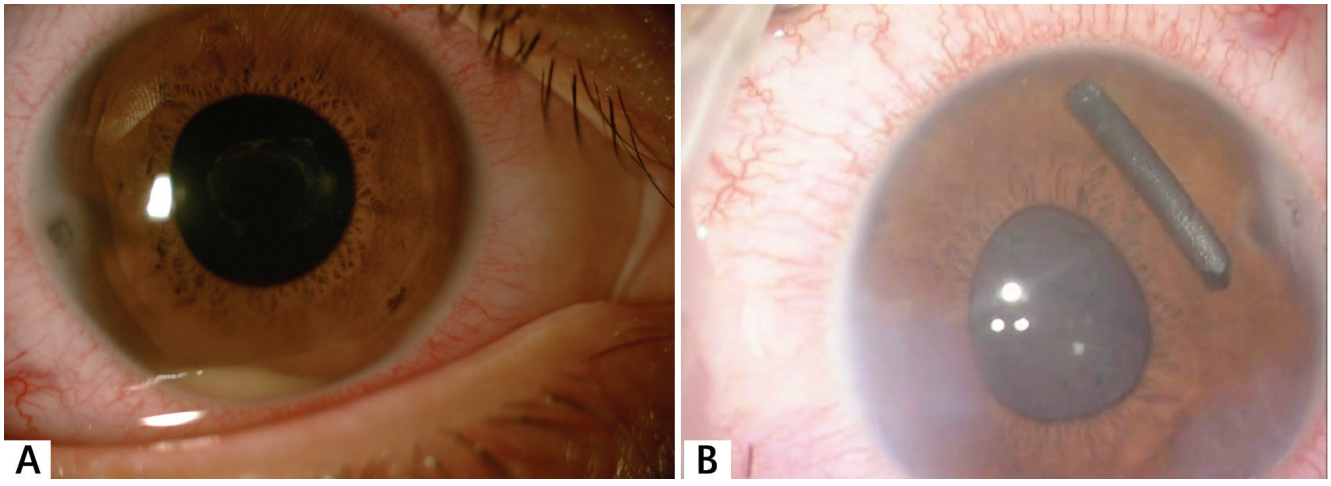

Figure 3. A) At presentation, a foreign body is observed penetrating the cornea in the temporal quadrant. Cyclitic membrane and hypopyon are apparent in the pupillary region; B) a pencil lead fragment that paralimbally perforated the cornea and iris and reached the vitreous through the lens zonules is brought into the anterior chamber during the extraction procedure

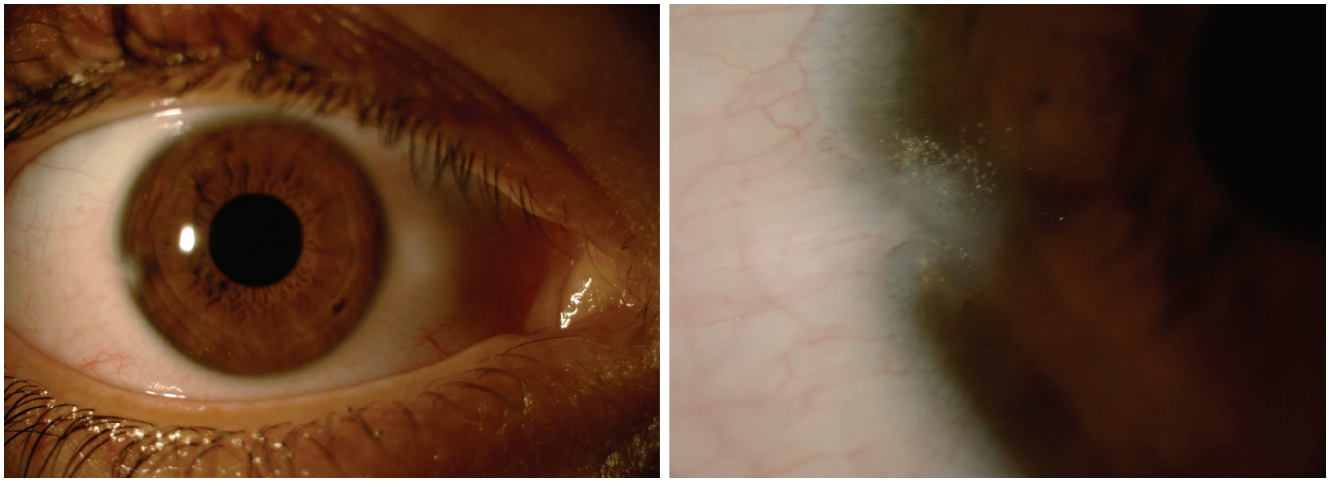

Figure 3C. At 1 year, the intrastromal carbon particles are found to be inert and there are no signs of ocular toxicity

chamber. No inflammatory reaction was observed in the anterior chamber and surgery was performed to remove the foreign body.[9] No anterior chamber inflammation occurred during the 1-month follow-up period (with tapering topical steroid and cycloplegic agent as medical therapy). A case reported by Gül et al.[8] presented with severely reduced vision (CF at 2 m) following ocular trauma by pencil. On slit-lamp examination, corneal perforation and fragments of pencil lead were observed at the wound site. The +4 anterior chamber reaction observed preoperatively continued after corneal suturation and foreign body extraction. Examination on the same day revealed linear carbon accumulation on the endothelial surface, and a pencil lead fragment was visible on the lens after pupil dilation. With hourly steroid therapy, the anterior chamber reaction resolved and the endothelial accumulation and material on the lens disappeared. Han et al.[6] reported a patient with a pencil injury 12 years earlier who presented with stromal keratitis. Antiviral and anti-inflammatory therapy was initiated for a preliminary diagnosis of herpetic stromal keratitis. The patient showed improvement of clinical findings, but at 3-month follow-up, a previously unnoticed foreign body was observed at the anterior chamber angle. The authors believed that the previously inert pencil lead fragment came into contact with the endothelium when it moved, thus triggering an inflammatory reaction. Pencil lead perforated the cornea in our second case and in the third case it perforated both the cornea and iris, reaching the vitreous through the zonules. To prevent a possible inflammatory reaction induced by pencil lead in these patients, triamcinolone was injected into the anterior chamber at the end of surgery, which may be considered possibly beneficial in such cases.

Conclusion

It can be concluded that carbon particles in the cornea are well tolerated in the long term, and that a good prognosis can be achieved in cases of intraocular pencil lead injury with anti-inflammatory therapy, prophylactic antibiotic therapy, and monitoring.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ceyhun Arıcı, Osman Şevki Arslan, Burcu Görgülü, Concept: Ceyhun Arıcı, Osman Şevki Arslan, Burcu Görgülü, Design: Ceyhun Arıcı, Osman Şevki Arslan, Data Collection or Processing: Ceyhun Arıcı, Osman Şevki Arslan, Burcu Görgülü, Analysis or Interpretation: Ceyhun Arıcı, Osman Şevki Arslan, Burcu Görgülü, Rengin Yıldırım, Umut Onur, Literature Search: Ceyhun Arıcı, Burcu Görgülü, Writing: Ceyhun Arıcı, Burcu Görgülü

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. Lit ES, Young LH. Anterior and posterior segment intraocular foreign bodies. Int Ophthalmol Clin. 2002;42:107-120.
2. Jeng BH, Whitcher JP, Margolis TP. Intracorneal graphite particles. Cornea. 2004;23:319-320.
3. Philip SS, John D, John SS. Asymptomatic Intracorneal Graphite Deposits following Graphite Pencil Injury. Case Rep Ophthalmol Med. 2012;2012:720201.
4. Paine DA, Pruett PB, Randleman JB. Occult Perforating Corneal Injury from Mechanical Pencil Graphite. Ophthalmic Surg Lasers Imaging. 2010:1-3.
5. Hamanaka N, Ikeda T, Inokuchi N, Shirai S, Uchihori Y. A case of an intraocular foreign body due to graphite pencil lead complicated by endophthalmitis. Ophthalmic Surg Lasers. 1999;30:229-231.
6. Han ER, Wee WR, Lee JH, Hyon JY. A case of retained graphite anterior chamber foreign body masquerading as stromal keratitis. Korean J Ophthalmol. 2011;25:128-131.
7. Kelly SP, Reeves GM. Penetrating eye injuries from writing instruments. Clin Ophthalmol. 2012;6:41-44.
8. Gül A, Can E, Yücel OE, Niyaz L, Akgün Hİ, Arıtürk N. Suspected endothelial pencil graphite deposition. Case Rep Ophthalmol Med. 2013;2013:369374.
9. Amritanand A, John SS, Philip SS, John D, David S. Unusual case of a graphite foreign body in the anterior chamber. Clin Pract. 2011;1:e73.
10. Guy JR, Rao NA. Graphite foreign body of the conjunctiva simulating melanoma. Cornea. 1985-1986;4:263-265.

DOI: 10.4274/tjo.57614
Turk J Ophthalmol 2017;47:56-58

Case Report

Spontaneous Regression of Optic Disc Pit Maculopathy in a Six-Year-Old Child

Sezin Akça Bayar*, Almila Sarıgül Sezenöz*, Eylem Yaman Pınarcı**, Gürsel Yılmaz*
*Başkent University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
**Başkent University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

Abstract
A 6-year-old boy with a complaint of blurred vision for two months was referred to our clinic. His visual acuity was 20/32 in the right eye and 20/20 in the left eye. Optical coherence tomography (OCT) revealed optic disc pit maculopathy in the right eye. The patient was followed for 6 months without any treatment. At the end of the 6-month period, the patient's visual acuity was 20/20 in both eyes. The OCT imaging showed spontaneous regression of the optic disc pit maculopathy. In this case report, it is concluded that in children, spontaneous regression of the optic pit maculopathy with full recovery of visual acuity is possible. The development of optic pit maculopathy in childhood is rare and there are not enough studies on the treatment methods. Therefore, our case report may be helpful in the management of similar cases of pediatric optic disc maculopathy.
Keywords: Optic pit maculopathy, optic pit, spontaneous regression

Introduction

Optic disc pit (ODP) is a rare congenital optic disk abnormality with an incidence of 1/11,000. ODPs are hypopigmented, yellowish, gray-white, oval or round depressions that are usually located unilaterally at the temporal part of the optic disc.[1,2,3] ODPs are usually asymptomatic and noticed during routine eye examinations. However, some patients with ODP demonstrate significant macular changes, resulting in irreversible central visual field defects and reduced central visual acuity. These macular changes, including serous macular detachment, cystic degeneration, and degenerative pigment changes, are defined as ODP-induced maculopathy (ODP-M).[1] The great majority of ODP-Ms become symptomatic in the third or fourth decade of life.[1] Twenty-five percent of ODP-Ms resolve spontaneously, but the final outcomes of these cases are shown to be poor.[1] Therefore, different treatment modalities such as vitreoretinal surgery or laser photocoagulation may be preferable over conservative management. In the literature, there are only a few cases of childhood-onset ODP-M that showed spontaneous resolution.[2,4,5] In this report we present a case of a 6-year-old-boy with ODP-M. To our knowledge, this is the first case of ODP-M in children which spontaneously regressed with full recovery of visual acuity.

Case Report

A previously healthy 6-year-old boy who had a complaint of blurry vision in his right eye for two months was referred to the retina department. His best-corrected visual acuity (BCVA) measured with Snellen chart was 20/32 in the right eye and 20/20 in the left eye. Anterior segment findings and intraocular pressures of both eyes were normal. Refraction results were +0.75 D in the right eye, and +0.50 D in the left eye. On fundoscopic examination a temporally located ODP associated with cystic changes in the macular area was detected in the right eye, while no pathological changes were seen in the left eye (Figure 1A). High-resolution (HR) optical coherence tomography (OCT) (Cirrus, Carl Zeiss Meditec. Inc.) imaging revealed a schisis cavity due to the optic pit and cystoid changes due to fluid collection under the internal limiting membrane in the right eye (Figure 1B). The patient had no family history or known macular disorder. As the patient's visual acuity was 20/32, we opted for a conservative approach and the patient was followed for 6 months

Address for Correspondence: Sezin Akça Bayar MD, Başkent University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey
Phone: +90 312 212 68 68 E-mail: sezinakca@gmail.com **Received:** 24.01.2015 **Accepted:** 06.03.2015

without any treatment. In the ophthalmologic examination at the end of the 6-month period, the patient's BCVA was 20/20 in both eyes. The maculopathy had resolved, leaving some residual pigment epithelial changes (Figure 2A). OCT images showed regression of the previous findings of ODP-M in the right eye (Figure 2B).

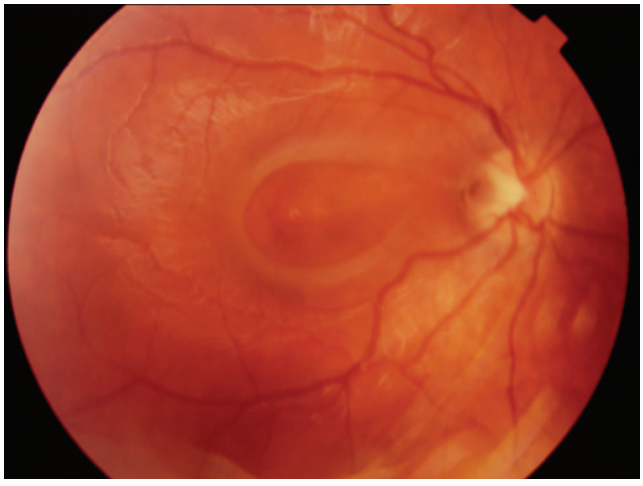

Figure 1A. Fundus photograph of the right eye showing the optic disc pit and maculopathy

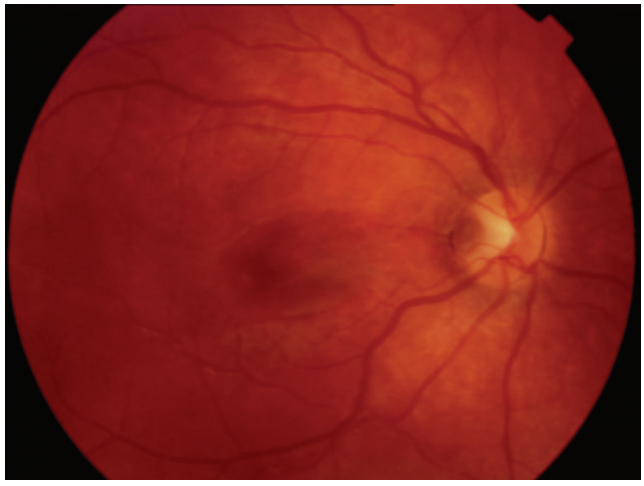

Figure 2A. Fundus photoghraph of the right eye showing resolution of the optic disc pit maculopathy

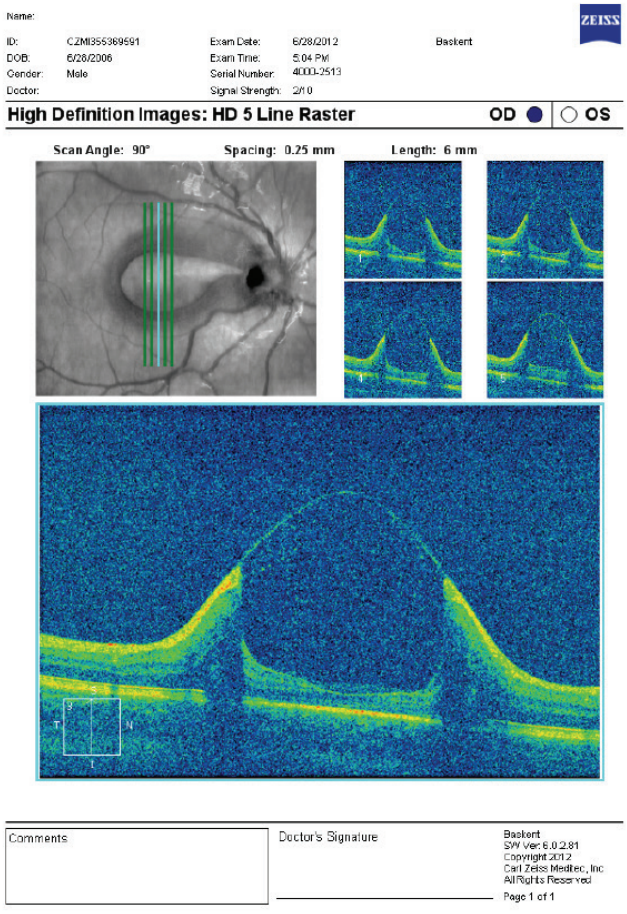

Figure 1B. Optical coherence tomography image of the macula of the right eye taken at presentation

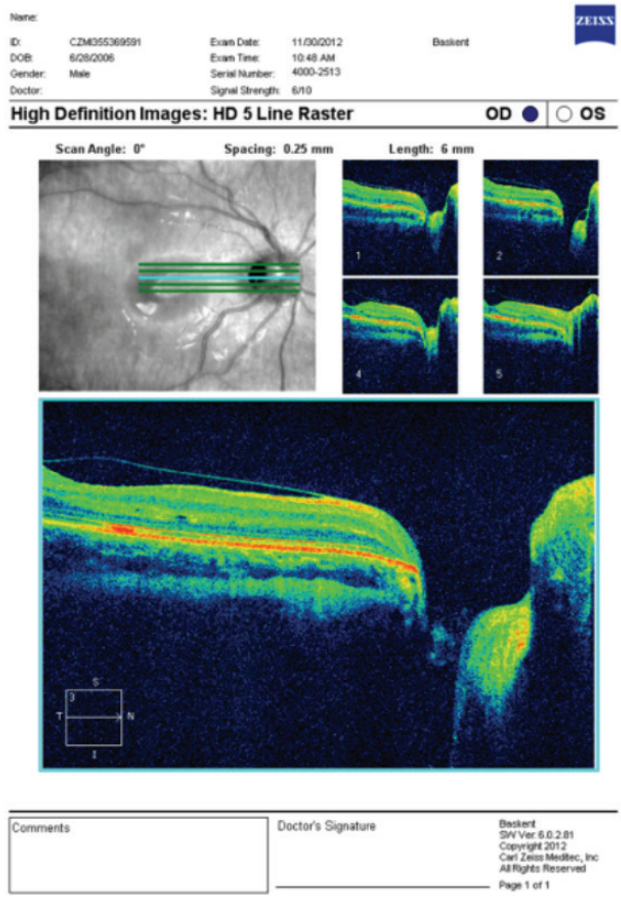

Figure 2B. Optical coherence tomography image of the right eye taken at final examination

Discussion

Although spontaneous resolution of ODP-M with improvement of visual acuity has been reported, the prognosis remains poor in approximately 25% to 75% of the patients.[2,4] A few cases of spontaneous regression of ODP-M in children have been previously reported in the literature.[2,4,5] Yuen and Kaye[2] noted a case with spontaneous resolution in which the visual acuity of an 8-year-old patient improved from light perception to 2/30. Sugar[4] reported a 4-year-old child whose vision recovered after spontaneous regression of the subretinal fluid within 18 months. Schatz and McDonald[5] reported a 6-year-old child with spontaneous near-complete reattachment of the macula within 5 months. In these studies, conservative management was preferred as 25% of ODP-Ms resolve spontaneously.[2,4]

In our case, visual improvement started within 3 months. At the end of the sixth month, unlike other cases in the literature, full anatomical and functional recovery was obtained without any need for additional interventions.

Though not seen in our case, fluid accumulation between retinal layers is a common finding in ODP-M. In a recent study of 16 patients with ODP, it was shown by HR-OCT that fluid can move directly from the optic pit to the subinternal limiting membrane space, ganglion cell layer, inner and outer nuclear layers, or subretinal space.[6] In our case, HR-OCT revealed a schisis cavity due to the optic pit and cystoid changes due to fluid accumulation under the internal limiting membrane. Despite numerous case reports offering different treatment modalities, the best method has not yet been determined for pediatric cases. In previous years, laser photocoagulation was used in cases that did not show spontaneous improvement within three months. Now, however, the presence of vitreous traction is the most important determining factor in treatment decisions. Most retina specialists recommend the combined use of laser photocoagulation of the peripapillary region and vitrectomy with or without ILM-peeling.[1,7] However, particularly in pediatric cases, 3-6 months of follow-up before any surgical and invasive procedures is appropriate.

Conclusion

In the management of ODP-M cases, it must be kept in mind that spontaneous regression is possible, especially in pediatric cases such as ours. Therefore, a more conservative approach may be beneficial in the treatment of young patients.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Concept: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Design: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Data Collection or Processing: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Analysis or Interpretation: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Literature Search: Sezin Akça Bayar, Almila Sarıgül Sezenöz, Eylem Yaman Pınarcı, Gürsel Yılmaz, Writing: Sezin Akça Bayar, Almila Sarıgül Sezenöz.

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. Georgalas I, Ladas I, Georgopoulos G, Petrou P. Optic disc pit: a review. Graefes Arch Clin Exp Ophthalmol. 2011;249:1113-1122.
2. Yuen CHW, Kaye SB. Spontaneous Resolution of Serous Maculopathy Associated With Optic Disc Pit in a Child: A Case Report. J AAPOS. 2002;6:330-331.
3. Theodossiadis GP, Grigoropoulos VG, Liarakos VS, Rouvas A, Emfietzoglou I, Theodossiadis PG. Restoration of the photoreceptor layer and improvement of visual acuity in successfully treated optic disc pit maculopathy: a long follow-up study by optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2012;250:971-979.
4. Sugar HS. Congenital pits of the optic disc. Am J Ophthalmol. 1967;63:298-307.
5. Schatz H, McDonald R. Treatment of sensory retinal detachment associated with optic nerve pit or coloboma. Ophthalmology. 1988;95:178-186.
6. Imamura Y, Zweifel SA, Fujiwara T, Freund KB, Spaide RF. High resolution optical coherence tomography findings in optic pit maculopathy. Retina. 2010;30:1104-1112.
7. Georgalas I, Kouri A, Ladas I, Gotzaridis E. Optic disc pit maculopathy treated with vitrectomy, internal limiting membrane peeling, and air in a 5-year-old boy. Can J Ophthalmol. 2010;45:189-191.

DOI: 10.4274/tjo.27482
Turk J Ophthalmol 2017;47:59-62

Case Report

Evaluation of Retinal Changes Using Optical Coherence Tomography in a Pediatric Case of Susac Syndrome

Mehmet Kola, Hidayet Erdöl, Sevil Ertuğrul Atasoy, Adem Türk
Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey

Abstract

Susac syndrome is a rare occlusive vasculopathy affecting the retina, inner ear and brain. The cause is unknown, although it generally affects young women. This syndrome can be difficult to diagnose because its signs can only be revealed by detailed examination. These signs are not always concomitant, but may appear at different times. This report describes a pediatric case who was diagnosed with Susac syndrome when retinal lesions were identified in the inactive period with the help of optical coherence tomography (OCT). The purpose of this case report is to emphasize the importance of OCT in clarifying undefined retinal changes in Susac syndrome.

Keywords: Optical coherence tomography, retina, retinal artery occlusion, Susac syndrome, diagnosis

Introduction

Susac syndrome (SS) is a relatively rare disorder characterized by the triad of encephalopathy, sensorineural hearing loss, and branch retinal artery occlusion (BRAO).[1] It was first described in 1979 by Susac, and Hoyt further refined its description in 1986.[2,3] The condition usually affects females in the mid-teen age group, though it can reportedly develop in individuals between 7 and 70 years old. To date, approximately 300 cases have been reported worldwide, but the prevalence of the disease is not exactly known.[1] BRAO, one of the ocular signs of SS, is a common pathology; it generally develops bilaterally and affects multiple retinal fields. In the active stage, BRAO is best assessed by fundus fluorescein angiography (FFA), in which it typically appears as multifocal fluorescence in the arteriole walls.[4] However, in the inactive stage, FFA is not particularly useful in diagnosing earlier retinal pathologies.[2] This case report is presented to highlight the importance of optical coherence tomography (OCT) in the evaluation of inactive retinal changes in the inactive stage of SS.

Case Report

A 14-year-old female patient with a 2-year history of headaches and subsequent hearing loss was referred to our clinic for further testing and treatment for visual symptoms that had worsened over recent months. The patient's history included visual complaints accompanied by clumsiness and difficulty walking which started about 3 months prior to her presentation to our clinic. Cranial magnetic resonance imaging (MRI) revealed lesions in the corpus callosum consistent with chronic infarct. Furthermore, odiometric analysis showed bilateral sensorineural hypoacusis (Figure 1).

Visual acuity was 20/20 in both eyes and intraocular pressure was 16 mmHg in the right eye and 17 mmHg in the left eye. Anterior and posterior biomicroscopic examination findings were normal. No clear pathology was apparent on FFA examination, but a partial defect was noted on visual field analysis (Figure 1). In both eyes, cross-sectional OCT revealed pronounced atrophic changes in the inner retinal layers corresponding to the areas of visual field loss (Figure 2). These findings were considered sequelae to previous BRAO. Taken together with her clinical signs, the patient was diagnosed with SS. The patient was followed without any treatment for about 1 year, during which no new active findings were observed.

Discussion

The etiology of SS is still not fully understood. It is believed to be an immunologic endotheliopathy that affects the

Address for Correspondence: Adem Türk MD, Karadeniz Technical University Faculty of Medicine, Department of Ophthalmology, Trabzon, Turkey
Phone: +90 462 377 10 45 E-mail: doktorademturk@yahoo.com **Received:** 09.02.2015 **Accepted:** 15.05.2015

microvasculature of the brain, retina, and inner ear. However, other unsupported theories such as vasospastic phenomena, coagulation disorders, and viral infections have also been implicated in its development.[2,5,6] The disease tends to affect precapillary arterioles, and encephalopathy is usually the first clinical sign. The other clinical signs may emerge at various times after the development of encephalopathy. In about 10% of cases, disease onset occurs during pregnancy.[1,7]

Various clinical examinations and analyses are useful in the diagnosis of SS. Cranial MRI of SS patients performed due to neurological symptoms reveals infarct in the corpus callosum.[8,9] Areas of infarct in the corpus callosum were also observed in the present case on MRI.

Odiologic tests which reflect inner ear involvement are also informative in SS patients.[6] In our case, odiologic test results indicated neurosensorial hypoacusis in both ears. Another common finding in SS is partial visual field defects. This sign occurs as a result of BRAO, which is often present in the syndrome. In addition to visual field loss, ophthalmoscopy in these patients may reveal signs of retinal vasculitis, BRAO and optic atrophy.[2,6,10] In the retinal vasculitis type, the refractive or nonrefractive yellowish Gass plaques which may be evident in the retinal arterioles are an important diagnostic finding for the disease. These plaques may sometimes be mistaken for embolism. On FFA examination, hyperfluorescent changes may also be observed in the retinal arterial walls in sections distant from areas of BRAO.[4,11,12,13]

BRAO seen in SS is generally bilateral and affects multiple retinal fields. In the active stage, BRAO is best recognized by FFA. In the chronic stage, however, the chance of overlooking retinal pathologies secondary to BRAO is fairly high, even in ophthalmologic examinations that include FFA.[2,4]

OCT enables retinal imaging comparable to histologic sections, and is currently used in the evaluation of many ophthalmologic conditions.[14,15,16] In retinal artery occlusion, OCT examination shows increased retinal layer thickness and reflectivity in the short term, and is used to follow atrophy in these retinal layers in the long term.[14,17,18] We also found in the current study that OCT examination provided useful information regarding retinal atrophic changes secondary to BRAO in SS. Brandt et al.[19] also utilized OCT to evaluate atrophic changes in the retina arising in SS. They reported that the morphologic changes revealed by retinal OCT examination may facilitate the differential diagnosis of SS and multiple sclerosis.[19]

There is currently no definitive treatment protocol for SS. General treatment approaches based on the autoimmune causes of

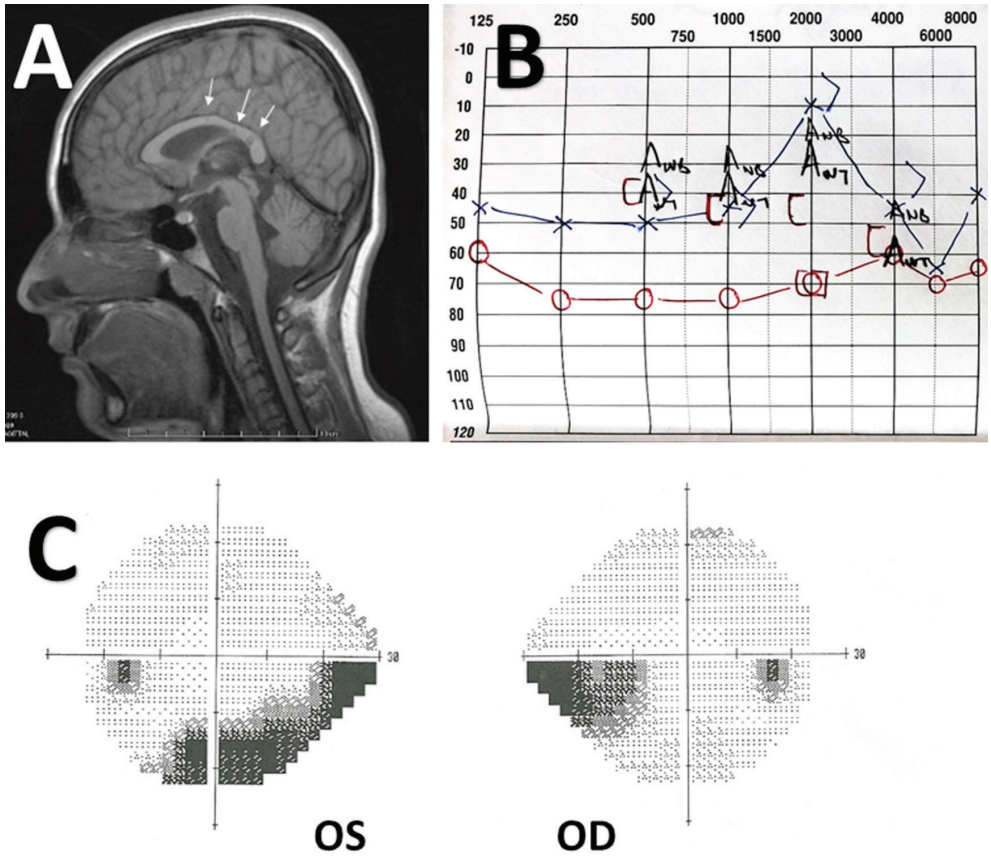

Figure 1. A pediatric Susac syndrome patient. A) T1-weighted magnetic resonance imaging shows hypointense corpus callosum lesions (arrows); B) odiometric analysis reveals bilateral sensorineural hypoacusis; C) visual field analysis shows bilateral scotoma secondary to previous branch retinal artery occlusion
OS: Oculus sinister, OD: Oculus dexter

SS heavily feature immunosuppressive and immunomodulatory agents in the active stage.[1,20] As the findings in the present case were considered chronic stage sequellae of SS, no treatment was administered.

Conclusion

The diagnosis of SS can be difficult because its clinical signs do not always manifest concurrently. Therefore, a detailed history and thorough systemic evaluation are mandatory. Cranial MRI, odiologic tests and retinal imaging are important in the diagnosis of this syndrome. Especially after an attack, retinal changes secondary to BRAO that are not evident in ophthalmoscopic examination or FFA can be diagnosed by a detailed OCT examination based on visual field analysis.

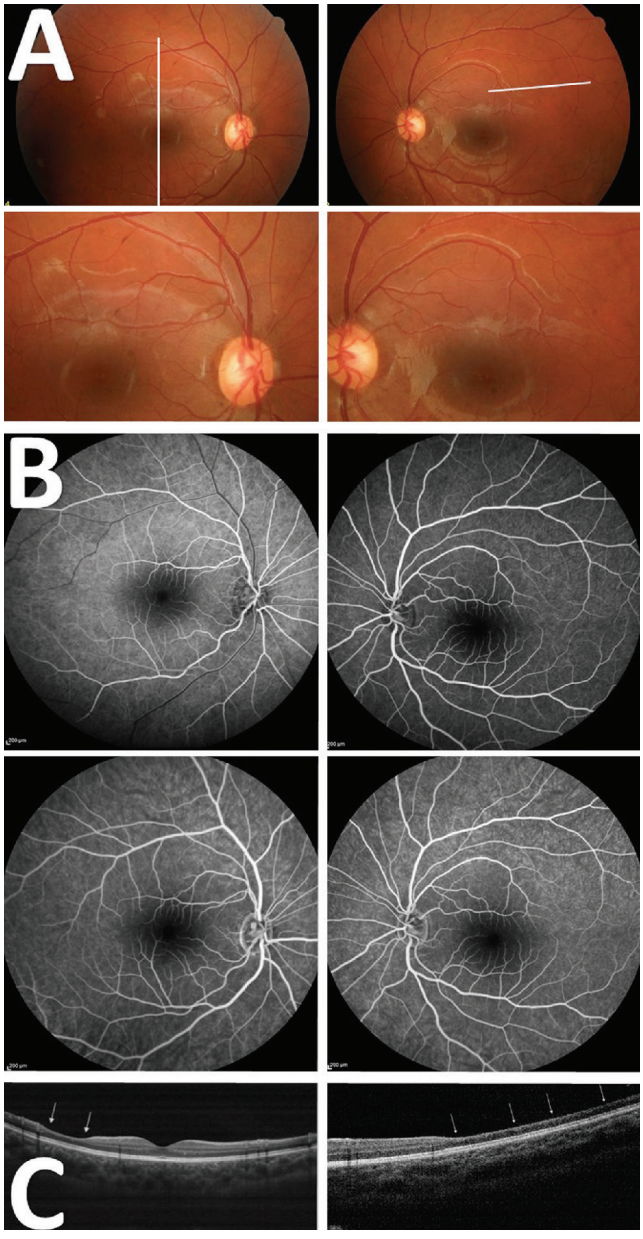

Figure 2. A pediatric Susac syndrome patient. A) Fundus photography; B) fundus fluorescein angiography images are normal in early and late phases; C) Optical coherence tomography sections taken from the areas marked with white lines on the fundus photographs. The arrows indicate atrophy of the inner retinal layers which emerged late secondary to branch retinal artery occlusion

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Kola, Hidayet Erdöl, Sevil Ertuğrul Atasoy, Concept: Mehmet Kola, Adem Türk, Design: Mehmet Kola, Adem Türk, Data Collection or Processing: Mehmet Kola, Hidayet Erdöl, Sevil Ertuğrul Atasoy, Adem Türk, Analysis or Interpretation: Mehmet Kola, Hidayet Erdöl, Adem Türk, Literature Search: Mehmet Kola, Adem Türk, Writing: Adem Türk.

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. Dörr J, Krautwald S, Wildemann B, Jarius S, Ringelstein M, Duning T, Aktas O, Ringelstein EB, Paul F, Kleffner I. Characteristics of Susac syndrome: a review of all reported cases. Nat Rev Neurol. 2013;9:307-316.
2. Susac JO, Egan RA, Rennebohm RM, Lubow M. Susac's syndrome: 1975-2005 microangiopathy/autoimmune endotheliopathy. J Neurol Sci. 2007;257:270-272.
3. Buelens T, Herode L, Nubourgh I, Caspers L, Willermain F, Postelmans L. Central retinal artery occlusion and Susac syndrome: a case report. Retin Cases Brief Rep. 2014;8:187-192.
4. Egan RA, Hills WL, Susac JO. Gass plaques and fluorescein leakage in Susac Syndrome. J Neurol Sci. 2010;299:97-100.
5. García-Carrasco M, Mendoza-Pinto C, Cervera R. Diagnosis and classification of Susac syndrome. Autoimmun Rev. 2014;13:347-350.
6. Greco A, De Virgilio A, Gallo A, Fusconi M, Turchetta R, Tombolini M, Rizzo MI, de Vincentiis M. Susac's syndrome--pathogenesis, clinical variants and treatment approaches. Autoimmun Rev. 2014;13:814-821.
7. Antulov R, Holjar Erlic I, Perkovic O, Miletic D, Antoncic I. Susac's syndrome during pregnancy - the first Croatian case. J Neurol Sci. 2014;341:162-164.
8. Susac JO, Murtagh FR, Egan RA, Berger JR, Bakshi R, Lincoff N, Gean AD, Galetta SL, Fox RJ, Costello FE, Lee AG, Clark J, Layzer RB, Daroff RB. MRI findings in Susac's syndrome. Neurology. 2003;61:1783-1787.
9. Ferrante E, Marazzi MR, Erminio C, Prone V, Protti A. Susac syndrome: an Italian case. Neurol Sci. 2013;34:2255-2257.
10. Milbratz GH, Marquardt FA, Guimaraes Neto HP, Marquardt DA, Souza ES. Retinal vasculitis in Susac syndrome: case report. Arq Bras Oftalmol. 2009;72:397-399.
11. Rennebohm R, Susac JO, Egan RA, Daroff RB. Susac's Syndrome--update. J Neurol Sci. 2010;299:86-91.
12. Susac JO, Hardman JM, Selhorst JB. Microangiopathy of the brain and retina. Neurology. 1979;29:313-316.
13. Egan RA, Ha Nguyen T, Gass JD, Rizzo JF, Tivnan J, Susac JO. Retinal arterial wall plaques in Susac syndrome. Am J Ophthalmol. 2003;135:483-486.
14. Türk A, Erdöl H, Akyol N, İmamoğlu Hİ. Retina arter tıkanıklıklarında görülen erken dönem optik koherens tomografi bulguları. Retina-Vitreus Dergisi. 2008;16:137-140.
15. Türk A, Esenülkü CM, Akyol N. Maküla kolobomundaki optik koherens tomografi bulguları. Turk J Ophthalmol. 2009;39:137-140.

16. Turk A, Kola M, Akyol N, Erdol H, Imamoglu HI. Optical coherence tomography findings of active ocular toxoplasmosis complicating with serous macular detachment. Turkiye Klinikleri J Med Sci. 2010;30:1409-1412.
17. Ahn SJ, Woo SJ, Park KH, Jung C, Hong JH, Han MK. Retinal and Choroidal Changes and Visual Outcome in Central Retinal Artery Occlusion: An Optical Coherence Tomography Study. Am J Ophthalmol. 2015;159:667-676.
18. Asefzadeh B, Ninyo K. Longitudinal analysis of retinal changes after branch retinal artery occlusion using optical coherence tomography. Optometry. 2008;79:85-89.
19. Brandt AU, Zimmermann H, Kaufhold F, Promesberger J, Schippling S, Finis D, Aktas O, Geis C, Ringelstein M, Ringelstein EB, Hartung HP, Paul F, Kleffner I, Dörr J. Patterns of retinal damage facilitate differential diagnosis between Susac syndrome and MS. PLoS One. 2012;7:e38741.
20. Seamone ME, Fielden M. A case of isolated Susac occlusive retinal vasculitis. J Neuroophthalmol. 2013;33:260-262.