ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 20 • ISSUE 3 • MAY 2019

Original Articles

istanbulmedicaljournal.org

galenos yayınevi

İstanbul Medical Journal / İstanbul Tıp Dergisi Volume: 20 Issue: 3 May 2019 Page: 176-272

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

galenos yayınevi

Galenos Publishing House Owner and Publisher
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Project Coordinators
Eda Kolukısa
Esra Semerci
Hatice Balta
Zeynep Altındağ

Project Assistants
Duygu Yıldırım
Gamze Aksoy
Melike Eren
Nurcan Acarçağ
Pelin Bulut
Saliha Tuğçe Güdücü

Finance Coordinator
Sevinç Çakmak

Research&Development
Kerim Sancar Ölmez
Mert Can Köse

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: Üniform Basım San. ve Turizm Ltd. Şti.
Matbaacılar Sanayi Sitesi 1. Cad. No: 114 34204 Bağcılar, İstanbul, Turkey
Phone: +90 (212) 429 10 00
Certificate Number: 42419
Printing Date: May 2019
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

AIMS AND SCOPE

İstanbul Medical Journal is the scientific, peer reviewed, open access publication of İstanbul Training and Research Hospital. The journal is printed six times in a year; on January, March, May, July, September, November and its publication language is Turkish and English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all fields of medicine. Reviews comprising the latest research findings, reports on rare and educative cases and letters to the editor are also published.

The target population of the journal includes specialists in all fields of medicine, academicians and relevant health care professionals.

The İstanbul Medical Journal is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO and GALE.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.istanbulmedicaljournal.org. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the İstanbul Training and Research Hospital. Potential advertisers should contact the Editorial Office. The journal does not publish advertisement.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the İstanbul Training and Research Hospital, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.istanbulmedicaljournal.org. Printed copies of the journal are distributed to the members of İstanbul Training and Research Hospital as well as the members of the editorial board and the journal's reviewers, free of charge.

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.

Editor: Tevfik Fikret ÇERMİK

Address: Clinic of Nuclear Medicine, Health Sciences University İstanbul Training and Research Hospital, İstanbul, Turkey

Fax: +90 (212) 530 80 55 E-mail: tevfik.cermik@sbu.edu.tr

Publisher : GALENOS PUBLISHING HOUSE

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 Fındıkzade 34093 İstanbul, Turkey

Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27 E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr

OPEN ACCESS

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to İstanbul Medical Journal will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. 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. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

İstanbul Medical Journal requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.istanbulmedicaljournal.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

İstanbul Medical Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to İstanbul Medical Journal, authors accept to assign the copyright of their manuscript to İstanbul Training and Research Hospital. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. İstanbul Medical Journal requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.istanbulmedicaljournal.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in İstanbul Medical Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.istanbulmedicaljournal.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.istanbulmedicaljournal.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Report, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed “Response to the reviewers” that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer’s comment, followed by the author’s reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal’s webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor : Tevfik Fikret ÇERMİK

Address: University of Medical Sciences, Istanbul Training and Research Hospital, Clinic of Nuclear Medicine, Samatya, Fatih, İstanbul, Türkiye

Phone: +90 212 459 64 53

Fax: +90 212 530 80 55

E-mail: tevfik.cermik@sbu.edu.tr

Publisher : GALENOS PUBLISHING HOUSE
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 Fındıkzade 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

İstanbul Med J 2019; 20(3): 176-87
DOI: 10.4274/imj.galenos.2018.79837

Assessment of the Efficacy of Interventions for the Treatment of Sleep Respiratory Disorder in Chronic Heart Failure Patients: A Systematic Review

Kronik Kalp Yetersizliği Hastalarında Uykuda Solunum Bozukluğunun Tedavisi İçin Kullanılan Girişimlerin Etkinliğinin Değerlendirilmesi: Sistematik Derleme

Hilal Uysal[1], Hanım Büşra Oruçoğlu[2]

[1]İstanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, Department of Internal Medicine Nursing, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, İstanbul, Turkey

ABSTRACT

One of the most important problems of heart failure (HF) patients is sleep disturbance. In HF patients with obstructive and central sleep apnea, hypoxia, hypercapnia and over-excitation of the sympathetic system are observed. As a result, negative intrathoracic pressure and left ventricular afterload increase. Treatment of sleep respiratory disorders in chronic HF patients is important for the prognosis of the disease. Therefore, in this systematic review, we aimed to evaluate the efficacy of interventions used for the treatment of sleep respiratory disorder in chronic HF patients.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, Turkey Citation Index and EBSCO databases were searched for studies between June 2017-August 2018. When all studies were examined, out of 2.691.006 studies published between 2007-2017, 16 randomized controlled trials that met inclusion criteria were included in the study. In these studies, treatment interventions for treatment groups with sleep respiratory disorder included continuous positive airway pressure (CPAP), bi-level positive airway pressure, adaptive servo-ventilation (ASV), atrial overdrive pacing, home oxygen therapy, slow breathing exercise device and structured physical exercise. When the study results are examined, CPAP treatment improved daytime sleepiness and left ventricular ejection fraction (LVEF) but did not provide significant improvement on quality of life, and that ASV treatment reduced apnea-hypopnea index, provided improvement in LVEF and cardiac function, and reduced ventricular ejection fraction. However, further research is needed to fully demonstrate the efficacy of interventions for the treatment of sleep respiratory disorder in chronic HF patients.

Keywords: Sleep apnea, obstructive sleep apnea, central sleep apnea, heart failure

ÖZ

Kalp yetersizliği hastalarının en önemli sorunlarından birisi uyku bozukluğudur. Obstrüktif ve santral uyku apnesi şikayeti olan kalp yetersizliği hastalarında hipoksi, hiperkapni ve sempatik sistemin aşırı uyarılması söz konusudur. Bunun sonucunda negatif intratorasik basınç ve sol ventrikül ard yükü artar. Kronik kalp yetersizliği hastalarında uyku bozukluğunun tedavisi hastalığın prognozu için önemlidir. Bu nedenle bu sistematik derleme çalışmasında, kronik kalp yetersizliği hastalarında uykuda solunum bozukluğunun tedavisi için kullanılan girişimlerin etkinliğinin değerlendirilmesi amaçlandı.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, Türkiye Atıf Dizini ve EBSCO'da yer alan çalışmalar Haziran 2017-Ağustos 2018 tarihleri arasında incelendi. Tüm çalışmalar incelendiğinde, toplam taranan 2.691.006 veriden 2007-2017 yılları arasında yayımlanmış, kronik kalp yetersizliği ve uykuda solunum bozukluğu olan (sol ventrikül ejeksiyon fraksiyon ≤%45, apne-hipopne indeksi >10/saat), en az 3 ay takip edilmiş hastaların dahil edildiği 16 randomize kontrollü çalışma araştırmaya dahil edildi.

Çalışmalarda uykuda solunum bozukluğu olan girişim grubu için tedavi girişimleri olarak devamlı pozitif havayolu basıncı, iki seviyeli pozitif havayolu basıncı, adaptif servo-ventilasyon, overdrive pacemaker, evde oksijen tedavisi, yavaş solunum egzersizi cihazı ve yapılandırılmış fiziksel egzersiz girişimi uygulandığı tespit edildi. Çalışma sonuçları incelendiğinde, devamlı pozitif havayolu basıncı tedavisinin gündüz uykuluk durumunu ve sol ventrikül ejeksiyon fraksiyonu iyileştirdiği, ancak yaşam kalitesi üzerine anlamlı iyileşme sağlamadığı, adaptif servo-ventilasyon tedavisinin apne-hipopne indeksini azalttığı, sol ventrikül ejeksiyon fraksiyonda ve kardiyak fonksiyonlarda iyileşme sağladığı, ventrikül atım sayısını azalttığı tespit edilmiştir. Ancak kronik kalp yetersizliği hastalarında uykuda solunum bozukluğunun tedavisi için uygulanan girişimlerin etkisinin tam olarak ortaya konulabilmesi için daha fazla araştırmaya ihtiyaç olduğu ortaya çıkmaktadır.

Anahtar Kelimeler: Uyku apnesi, obstrüktif uyku apnesi, santral uyku apnesi, kalp yetersizliği

Address for Correspondence/Yazışma Adresi: Hilal Uysal MD, İstanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, Department of Internal Medicine Nursing, İstanbul, Turkey
Phone: +90 212 440 00 00 **E-mail:** hilaluysal@gmail.com **ORCID ID:** orcid.org/0000-0003-3211-7011

Cite this article as/Atıf: Uysal H, Oruçoğlu HB. Assessment of the Efficacy of Interventions for the Treatment of Sleep Respiratory Disorder in Chronic Heart Failure Patients: A Systematic Review. İstanbul Med J 2019; 20(3): 176-87.

Received/Geliş Tarihi: 28.08.2018
Accepted/Kabul Tarihi: 12.11.2018

Introduction

Heart failure (HF) is defined as a structural or functional cardiac disorder that causes the heart not to provide enough oxygen to meet the metabolic needs of the tissues despite the normal filling pressures. Approximately 1-2% of the adult population in developed countries has HF. The prevalence of HF is reported to be 10% or more in individuals aged 70 years and older (1).

Sleep disorder is one of the most important problems of HF patients. Hypoxia, hypercapnia and over-excitation of the sympathetic system are present in HF patients with obstructive and central sleep apnea (CSA). As a result, negative intrathoracic pressure and left ventricular afterload increase. Determination of the degree of sleep disturbance by polysomnography (PSG) and administration of oxygen therapy, continuous positive airway pressure (CPAP), bi-level (BI) PAP for the treatment of obstructive sleep apnea (OSA) and adaptive servo-ventilation methods (ASV) for the treatment of nocturnal hypoxemia during the night are recommended in patients with HF (1).

The degree of SRD is determined by PSG and OSA and/or CSA classification is done. The hourly apnea-hypopnea index (AHI) between 5-15 is classified as mild OSA, between 15-30 as moderate OSA, and >30 as severe OSA. In the literature, it has been shown that patients with OSA with an AHI value of >20 have increased risk of morbidity and mortality if not treated (2). The diagnostic criteria of primary CSA syndrome are as follows: a) At least one of the following from frequent arousals and awakenings during sleep, excessive daytime sleepiness and awakening short of breath; b) PSG shows ≥5 central apneas per hour of sleep, representing >50% of total respiratory events in the AHI; and c) the disorder is not better explained by another current sleep disorder, a medical or neurologic disorder, medication use, or a substance use disorder. The diagnostic criteria of Cheyne-Stokes respiration (CSR) include ≥5 central apneas-hypopneas during sleep and monitoring crescendo-decrescendo cycle over a period of at least 10 minutes (3).

The gold standard treatment of OSA is PAP. The aim of the treatment of SRD is to ensure that the upper airway remains open during sleep and to regulate quality of breathing and sleep. However, the patient benefits from this treatment during the time she/he uses the device. For this reason, it is recommended that the patient should use the device over 70% and more than 4 hours during the night (2,3).

As reviewed in the literature, the treatment of sleep disturbance in chronic (C) HF patients is important for the prognosis of the disease. Therefore, the aim of this systematic review was to evaluate the efficacy of interventions for the treatment of SRD in CHF patients.

Methods

This systematic review was planned and carried out as a descriptive study to evaluate the efficacy of interventions used for the treatment of SRD in CHF patients. The following steps were used in systematic review. The framework of the study was based on (population, intervention, comparator, outcome and study design) (4). These steps are described in detail in Table 1.

Inclusion criteria were RCTs published between 2007-2017, including patients with CHF and RSD (OSA, CSA) (left ventricular ejection fraction (LVEF) ≤45%, AHI >10/hour) followed for at least 3 months (Table 1).

All of the RCTs included in the study were evaluated by two researchers using an appropriate quality assessment checklist (5). The results of the evaluation were discussed and the publications prepared according to the RCT criteria were included in the study.

In data extraxtion analysis, one of the researchers first examined the researches included and collected data on the findings and characteristics of the research. The second researcher then checked the accuracy of this data. Data extraction steps were carried out by the authors. The data extraction steps and the findings are explained in detail in Table 2.

In this study, the answer to the question "Which interventions are effective in the treatment of SRD in patients with CHF?" was investigated.

No funding was received during the research. Researchers used their own means throughout the study. The researchers took part in each phase of the study according to the timetable. The timetable of the study was carried out as follows:

1. Preparation of the research protocol: 07/06/2017

2. Scanning period: June-September 2017

3. Analysis: October 2017-March 2018

4. Article writing: April-August 2018

In the study, keywords were selected in accordance with the research topic (Figure 1) and electronic scanning was performed. In the selection of keywords, attention was paid to the scanning of the full text of RCTs, in which the effectiveness of interventions used in the treatment of CHF patients diagnosed with SRD.

Cochrane Library, Scopus, Springer Link, Science Direct, Clinical Key, PubMed, EBSCO and Turkey Citation Index electronic databases were used for scanning. Medline, EMBASE, Ovid and CINAHL databases were not used because they could not be accessed. When all the studies recorded according to inclusion criteria were examined, 16 publications from total scanned 2.691.006 data were included in our study (Figure 1) (6).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
- Published between 2007-2017
- Followed for at least 3 months
- Randomized controlled trials
- Diagnosed with chronic heart failure
- LVEF ≤45%
- Diagnosed with CSA and/or OSA
- AHI >10/hour
- Diagnosis of sleep respiratory disorder by polysomnography
- Research in English and Turkish
- Full texts
- Studies on specified keywords
Exclusion criteria
- Studies not published in Turkish and English
- Unpublished thesis studies
- Reviews
- Abstracts
- Conference summaries, protocols, case reports, *in vitro* studies
- Ongoing study findings

LVEF: left ventricular ejection fraction, CSA: central sleep apnea, OSA: obstructive sleep apnea, AHI: apnea-hypopnea index

<table>
<tr><td colspan="2">Number of articles scanned by keywords: 2.691.006</td></tr>
<tr><td>Keywords
English: Heart failure, chronic heart failure, polisomnography, sleep disorders, sleep apnea, sleep quality, obstructive sleep apnea, central aleep apnea.
Turkish: Kalp Yetersizliği, kronik kalp yetersizliği, polisomnografi, uyku uyku bozukluğu, uyku apnesi, uyku kalitesi, obstruktif uyku apnesi, santral uyku apnesi.</td><td>Number of articles scanned by words in databases
CLINICAL KEY: 95.666
COCHRANE LIBRARY: 573
EBSCO: 1098
SCIENCE DIRECT: 1.071.673
SCOPUS: 530.056
SPRINGER LINK: 705.691
PUBMED: 286.854
TURKIYE CITATION INDEX: 803</td></tr>
<tr><td rowspan="2">Therapy initiatives for sleep-disordered breathing included in the study: CPAP, BIPAP, Adaptive Servo Ventilation (ASV), atrial overdrive pacemaker, oxygen therapy at home (HOT), slow breathing exercise device (RESPERATE) and physical exercise therapy: 16</td><td>Exclusion criteria
Unpublished and not followed for at least 3 months between 2007 and 2017: 13.454
Other than randomized controlled study: 18.802.898
Patients without a diagnosis of chronic heart failure: 161.479
Patients without AHI> 10 / s: 26.908
Studies other than Turkish and English: 20.212
Unpublished thesis studies: 47.089
Reviewes: 316.200
Conference etc. abstracts, protocols, case reports, in-vitro studies: 282.565
Ongoing studies: 20.181</td></tr>
<tr><td>A study that was evaluated for 4 weeks was removed. (Staniforth et al. 1998)</td></tr>
<tr><td colspan="2">Studies in accordance with the inclusion criteria: 16</td></tr>
</table>

Figure 1. Flow Chart

Staniforth et al. (6) European Heart Journal 1998; 19: 922-8.

In the studies, CPAP, BIPAP, ASV, overdrive pacemaker, home oxygen therapy (HOT), slow breathing exercise device (RESPERATE) and structured physical exercise interventions were applied as treatment interventions for the group with SRD (Tables 2, 3). In addition, in the studies evaluated, it was found that symptom evaluation scales such as Epworth Sleepiness Scale (ESS), Pittsburg Sleep Quality Index (PSQI), Fatigue Severity Scale, and disease-specific quality of life scales such as Minnesota Living with HF Questionnaire (MLHFQ) and Chronic HF Questionnaire (Q), and SF-36 general quality of life scale, mental status and motor function assessment tools were used (Table 2).

Results

The randomized controlled trials included in the study were mostly conducted with male CHF patients who were 60 years of age and over and who had a diagnosis of OSA and CSA (AHI >10/hr., LVEF ≤45%) (Table 2).

In a study evaluating the effect of CPAP therapy on cardiac functions in CHF patients with OSA, it was reported that CPAP treatment improved LVEF compared to those treated with fake-CPAP (placebo) treatment. However, no significant difference was found in the cardiological variables and quality of life of patients in both the intervention and placebo groups. The authors stated that the improvement in LVEF would not necessarily improve cardiological symptoms (7). However, Khayat et al. (8) stated that, contrary to this study, BIPAP treatment was more effective on improvement in LVEF than CPAP. Bradley et al. (9) reported that CPAP treatment, in addition to medical treatment, improved the CSA and nocturnal oxygenation compared to medical treatment only, and that the CPAP group had more improvement in their functional capacity (six minutes walking distance-6MWD) (p=0.016) (Table 2).

In the study of O'Connor et al. (10), in which the effectiveness of ASV therapy was evaluated, it was found that ASV treatment added to the optimal medical therapy in patients with moderate-to-severe sleep apnea did not improve cardiovascular (CV) outcomes over 6 months, and that functional capacity in both control and intervention group did not differ. However, Arzt et al. (11) reported that ASV treatment added to medical therapy was an effective treatment for CSA and OSA, and that it improved cardiac function compared to medical therapy only in patients with sleep apnea. Similarly, in another study conducted in 2012, it was found that ASV significantly reduced central, periodical various respiratory disorders (12). In another study, it was found that ASV treatment at home caused a mild improvement in sleep fragmentation and improved sleep efficiency in CHF patients with CSA or OSA (13). However, Cowie et al. (14) stated that ASV treatment in addition to medical therapy did not improve outcomes, increased risk of CV death, and had no beneficial effect on quality of life and HF symptoms (Table 2).

Kasai et al. (15) found a significant increase in functional capacity (6MWD) in the ASV-mode group compared to the CPAP-mode group. Priefert et al. (16) found that ASV therapy for patients with EF <40% lower ejection fraction (HFrEF) and SRD provided significant improvement in AHI at 12 weeks compared to the group treated with medical therapy only. In the same study, it was found that ASV treatment had an effect on nocturnal ventricular and supraventricular arrhythmias and the number of ventricular beats was less in the ASV treated group compared to the control group (Table 2).

Kawecha-Jaszcz et al. (17) found that the use of slow breathing device at home in patients with stable chronic systolic HF tended to reduce sleep disturbance and predominantly narrow central apnea, improve functional capacity and systolic left ventricular function. In one study, the authors stated that CPAP treatment titrated automatically at night in patients with OSA and CHF improved the daytime sleepiness, but did not improve other quality of life measures or severe CHF markers (Table 2) (18).

In another study, daytime sleepiness was found to be better in the CPAP group than the BIPAP group. In the same study, quality of life, functional capacity and blood pressure (BP) changes were found to be better in the BIPAP group than in CPAP (8). Similarly, Egea et al. (7) reported that CPAP therapy did not show a significant improvement in cardiological changes and quality of life except daytime sleepiness (Table 2).

Nakao et al. (19) reported that nocturnal oxygen therapy for 12 weeks at home improved SRD and had a positive effect on functional capacity in chronic HF patients with CSA (Table 2).

Suna et al. (20) found that exercise training administered to the intervention group significantly improved poor sleep quality in patients with HF followed by a disease management program for 12 weeks (Table 2).

As a result of the studies, only one RCT evaluated the effect of atrial overdrive pacemaker treatment on SRD in systolic HF patients with OSA and the intervention was found to reduce AHI safely (Table 2) (21).

Table 2. Characteristics of the studies included in the systematic review

Source and sleep respiratory disorder type	Method-randomization	Gender-sampling	Duration	Other evaluation tools	Age	Findings	Results
Egea et al. (7) OSA	- RCT, multi-center, - Plasebo (fake-CPAP) (n=32) - CPAP (n=28)	- Mostly male - A total of 60 patients - OSA (AHI >10/h) - CHF (LVEF <45%)	3 months	- ESS - SF-36 - NYHA classification - Borg dyspnea scale - 6MWT	CPAP: 64 Fake-CPAP: 63 (mean)	- A 30% improvement in LVEF compared to baseline in the CPAP group, less than 30% improvement in placebo. - In contrast to the placebo group, significant improvement in AHI ($p<0.001$) and SaO_2 ($p=0.002$) in the CPAP group	- CPAP treatment has been shown to be beneficial in CHF patients with SRD. - No difference was found between the two groups except for ESS index in the cardiac variables and quality of life tests
Khayat et al. (8) OSA	- RCT pilot study, - BIPAP (n=13), CPAP (n=11)	- Female and male mixed group - Total 24 patients - Stable LV systolic dysfunction - NYHA class II-III, - CHF (LVEF LV 45%) - Not hospitalized in the last 3 months and medication was unchanged. - New OSA	3 months	- ESS - 6MWT - MLHFQ - Weekly device memory check for treatment compliance assessment	BIPAP=51.3 CPAP=54.8 (mean)	- AHI was not changed in both groups (p=0.24). - Compliance with the treatment device is slightly higher in the BIPAP group. In the CPAP group, the ESS score was higher (p=0.38). Heart rate changes in CPAP group more effective (p=0.42). - MLHF, 6MWD, SBP and DBP improved in the BIPAP group	BIPAP treatment was found to be more effective than CPAP in the treatment of LVEF in patients with LV dysfunction and OSA. Further studies have been proposed to evaluate the mechanisms behind this effect
Smith et al. (18) OSA	RCT, double blind, placebo control, diagonal design. - Automatically adjusted CPAP (at least 6 hours per night) - CPAP (n=12) - Fake-CPAP (n=11) (placebo) (1:1)	- Mainly male - Total 23 patients - NYHA class II-IV - Stable, symptomatic CHF (LVEF <45%) - OSA (AHI ≥15/h)	6 weeks	- Clinical evaluation - TTE - CPET - 6MWT - Neurohormonal markers - OSLER test - ESS - Quality of Life Assessment	61 (mean)	- In case of daily sleepiness with CPAP, there was no objective improvement (OSES p=0.63), there was improvement in subjective assessment (ESS) (p=0.04). No significant difference was found between CPAP treatment and fake-CPAP in the evaluation of -LVEF, exercise capacity and quality of life ($p>0.05$)	- CPAP treatment improved subjective daily sleepiness, but did not improve other quality of life measures or CHF markers. The symptomatic benefit in this patient group is the alleviation of OSA rather than the improvement in cardiac function
Randerath et al. (12) OSA CSA	- RCT, parallel group, double blind, single center clinical study. - CPAP (n=34) or ASV (n=36) + optimal medical treatment - Optimal medical treatment	- Mainly male - CHF (LVEF ≥20%) - NYHA class II and III-AHI ≥15/hr - Central rate 80% - Obstructive rate 20%-50%	1 year	- ECO at the baseline, 3rd, 12th months - CPET - proBNP - MLHFQ - After 6 and 9 months, quality of life data was received by telephone.	CPAP=67.4 ASV=65.3 (mean)	- Both methods have significantly improved total AHI. - Approximately 50% of patients with CPAP have decreased central respiratory disability, and with ASV treatment, there is a better reduction in AHI than CPAP. - Compared to CPAP treatment at 12th month follow-up, there was an improvement in periodic and different respiratory disorders and proBNP levels with ASV treatment	It has been proven that ASV (compared to CPAP in patients with mild to moderate HF during a 12-month period) is effective in suppressing central, periodic, different respiratory disorders more effectively and obstructive events in an equally effective manner. Patients showed improvement in BNP levels

Table 2 contiuned

Kasai et al. (15) CSA	- RCT, prospective, single-center, single-blind study. - CPAP mode or ASV mode	- Gender not specified. - Total 74 patients - NYHA ≥II - CHF (LVEF <50%) - AHI ≥15/h	3 months	- PSG - BMI - ABG - CV variables - 6MWT - ECHO - LVEF - SF-36 quality of life assessment	CPAP: 65.8 ASV=64.3 (mean)	- Significant reduction in plasma proBNP level in the ASV mode group. The decrease in UNE and increase in 6MWD are significantly higher in the ASV group. Significant reduction in LV end-systolic diameters in the LV group	ASV treatment has been shown to improve underlying dysfunction in non-CPAP-induced CSA Japanese male HF patients. Effective suppression of CSA has been shown to be useful in improving cardiac function. It is recommended to investigate the long-term effects of CSA treatment with ASV
Bradley et al. (9) CSA	RCT, open-label, multi-center (11-center) operation. - CPAP + optimal medical treatment (n=128) - Optimal medical treatment (n=130) at least 6 hours of CPAP use at home during the night	- Mainly male Total of 258 patients - NYHA class II-IV - At least one medical treatment - Stable CHF (LVEF <40%) - CSA	3 months	- Radionuclide angiography resting LVEF - 6MWT - Life Quality Survey Atrial natriuretic peptide and plasma norepinephrine levels were measured at -3 centers	18-79	In the CPAP group, 6MWD increased more at three-month follow-up (p=0.016). There is no significant difference between the two groups in the Chronic Heart Failure Questionnaire A significant increase in LVEF in the CPAP group (p=0.02). - Plasma norepinephrine level decreased significantly (p=0.009)	- CPAP improved central sleep apnea, nocturnal oxygenation, left ventricular function, sympathetic nerve activity, and submaximal exercise performance. - The CANPAP study did not show a beneficial effect of CPAP on morbidity or mortality in patients with central sleep apnea and heart failure. There was no significant difference in mortality rates between the two groups
Hetzenecker et al. (13) OSA CSA	- RCT, multi-center, parallel group - ASV (BIPAP-ASV) + medical treatment (n=32) - Optimal medical treatment (n=31) (1:1)	- Mainly male - Total 63 patients - Severe sleep apnea - CHF	12 weeks	- Actigraphy device (wrist) - BMI - Resting heart rate - NYHA - proBNP	- ASV=64 - Control=65 (mean)	- Significant greater reduction in sleep fragmentation index compared to the control group and significantly improved sleep efficiency and proBNP decrease in the ASV group (p=0.062)	The study showed that ASV treatment at home could reduce sleep disruption and improve sleep quality in CHF patients with severe CSA or OSA
O'Connor et al. (10) OSA	- RCT, multi-center clinical study - ASV - General care control group (1:1)	- Mostly male - Reduced or preserved EF - AHI ≥15/h - Hospitalized HF patients	6 months	- BMI - NYHA - LVEF - proBNP - ESS - SaO2 - 6MWT	62 (mean)	- There was a significant decrease in baseline in both groups in AHI (p=0.0001). - 6MWD was similar in both groups (p>0.05)	It was found that ASV treatment, which was added to the optimal medical treatment compared to those receiving only optimal medical treatment, did not improve CV outcomes over a 6-month period.

Table 2 contiuned

Cowie et al. (14) CSA	- RCT, Multi-center, parallel group, event-based study. - ASV + medical treatment (n=666) - Medical treatment (n=659)	- Mainly male - Symptomatic CHF (LVEF CHF 45%) - Hospitalized at least 1 time within 2 years, - NYHA II, III or IV - CSA (AHI ≥15/h, >50% of apnea or hypopnea event and central AHI ≥10/hr)	-Evaluation on first 2 weeks, 3 and 12 months - On the 6th and 12th months, phone contact. -Total 31 months follow-up	- NYHA classification - 6MWT - EQ-5D - MLHFQ - ESS	69 (mean)	- SRD was better controlled during ASV treatment. - AHI 6,6/h, ODD 8,6/h - Mortality and CV mortality for all causes were higher (29.3%, 24.0%) than in the control group, respectively (34.8%, 29.9%) in the ASV group ($p<0.05$)	- In addition to guideline-based medical therapy, the treatment of ASV was found not to improve results. - It was found that ASV increased the risk of CV death (34%) and had no beneficial effect on quality of life or HF symptoms. These results were seen despite effective control of central sleep apnea during treatment of ASV
Arzt et al. (11) OSA CSA	- RCT - ASV (BIPAP) + optimal medical treatment (n=37) - Optimal medical treatment (n=35) (1:1)	- Mostly male - Total 72 - Stable CHF (LVEF) 40%) (in the last 4 weeks) - NYHA class II-III - AHI≥20/hr	12 weeks	- SF-36 - MLHFQ - proBNP - Creatinine - GFR - Fatigue severity scale - ESS	- ASV=64 - Control=65 (mean)	- Moderate improvement in LVEF in both groups ($p>0.05$). - In the ASV group, AHI and central AHI significantly decreased ($p<0.001$). - Significant increase in mean arterial SaO_2 in the ASV group ($p=0.001$). - Further decline in BNP in the ASV group, and an increase in GFR ($p>0.05$). - Quality of life and symptom scores were similar in both groups ($p>0.05$)	The study showed that ASV is an effective treatment for both CSA and OSA in CHF patients. It has been shown that ASV treatment decreases BNP levels in CHF patients with SRD, thus improving cardiac functions
Lyons et al. (22) OSA CSA	- RCT, multi-center, multinational, parallel group, open label, single blind - ASV + standard medical treatment - Standard medical treatment - 430 OSA and 430 CSA patients	- Men and women - Stable HFrEF (LVEF 3 45) for at least 3 months - SRD (AHI≥15/h)	In a maximum period of 5 years; basal, 1st, 3rd and 6th months and every 6 months: PSG In 6 months: - ECHO - proBNP - 6MWT	- Physical examination - 6MWT - MLHFQ - ESS	18 years and over	- OSA in HFrEF patients is more common than CSA. - ASVmV improves the CSA, but there is no difference in the first evaluation between those who are not using ASV mode. - Secondary evaluation of the ASV mode for all causes and increased mortality and morbidity in CV	According to the results of the ADVENT-HF study, data are provided to improve the quality of life and decrease the morbidity and mortality in patients with OSA and HFrEF treated with ASV. The information obtained from the ADVENT-HF study will provide important information in the treatment of patients with HFREF and CSA in the SERVE-HF study

Table 2 contiuned

Priefert, et al. (16) OSA CSA	- RCT, multi-center, controlled, parallel, open label. - ASV (BIPAP-ASV) + optimal medical treatment at night (n=37) - Optimal medical treatment (n=35)	- Mostly male - A total of 72 patients - Stable HFrEF - SRD	12 weeks	- PSG - NYHA - Pulse - LVEF - BP - BMI - EEG - EOG - EMG - SaO_2 - Single channel ECG	- Control=67 - ASV=65 (mean)	- Significant improvement in AHI/hr. ($p<0.001$), obstructive AHI/hr. ($p=0.003$) and central AHI/hr. ($p<0.001$) in ASV group. - Further improvement in total sleep time (min.) ($p=0.259$) and mean SaO_2 (%) ($p=0.0031$) in the ASV group. - The number of single, multiple and double VEAs in ASV group was less ($p>0.05$). - Decreased heart rate (min) in the treatment of ASV, but no significant difference between the groups ($p>0.05$)	In the study, it was stated that ASR treatment could be applied in patients with HFrEF and SRD. It is recommended to repeat the study with larger patient groups
Nokao et al. (19) CSA	- RCT, open label, multi-center operation. - HOT (3 liters oxygen therapy per minute (with 92% density) with nasal cannula + optimal medical treatment - Optimal medical treatment	- Mostly male - Short term: 30 HOT, 33 controls in total 63 - Long term: 26 HOT, 25 controls total 51 - A total of 107 patients - CSA - Symptomatic, stable CHF (LVEF, 45%) - NYHA II-III - At least 5 episodes of apnea-hypopnea with ≥5/hr. reduction in ODI and 5 hours of sleep	Baseline and 12-week evaluation with two-channel real-time Holter device at night	- PSG - NYHA classification - Pulse - LVEF - proBNP - SaO_2 - Specific Activity Scale (Mets) - QoL scale	- HOT=65.3 - Control=66.5 (mean)	- Significant improvement in AHI ($p<0.01$), a significant decrease in CAI ($p<0.05$) in the HOT group. - Significant improvement in ODI ($p<0.01$), increase in functional capacity ($p<0.01$), further improvement in LVEF ($p>0.05$), greater reduction in VEAs ($p>0.05$), further improvement in NYHA ($p=0.02$) in the HOT group	- HOT has been shown to improve SRD, quality of life, and cardiac function in patients with CHF and CSA. The efficacy of HOT on ventricular arrhythmias has not been demonstrated. Further studies have been proposed
Kawechka-Jaszcz et al. (17) CSA	- RCT, cross design, open label - Slow Respiratory Exercise (SRE) with + RESPERATE + optimal medical treatment - The standard care group	- 86 male, 24 female with a total of 110 stable HF patients (LVEF <40%). - NYHA class I-III - A 24-hour Holter with sinus rhythm - Those who have the ability to apply breathing exercises after training	10-12 weeks	- PSG - Ambulatory cardiorespiratory device (Emblatta Gold) - ECHO - 6MWT - NYHA - BP - BMI - Laboratory tests	23-87 64.5 (mean)	- Significant decrease in global AHI in the SRE group ($p=0.043$), - Significant increase in LVEF ($p=0.03$) and 6MWD ($p<0.001$)	- In stable systolic CHF patients, SRE was found to reduce narrow central apnea and hypopnea in SRD, improving functional capacity and systolic LVEF. It is stated that the SRE device can be used successfully as a home-based rehabilitation tool in CHF patients

Table 2 contiuned

Sharafkhaneh et al. (21) OSA	- RCT - Atrial overdrive pacemaker - CPAP	- 15 men - Medium-severe OSA with pacemaker applied 46 months ago - Stable systolic HF (LVEF <55%)	Pacemaker implanted 46 months before the study	- ESS	74 (mean)	- Decrease in AHI (7±7.9) and total stimulation index (17±16.8) with CPAP treatment. - Improvement at nocturnal SaO_2	- Atrial overdrive pacemaker has been shown to reduce AHI safely. - Although atrial overdrive pacemaker is not as effective as CPAP in the treatment of OSA, it may play a therapeutic role in patients with systolic cardiac dysfunction with other treatment modalities
Suna et al. (20) OSA CSA	- RCT (sub-study) - Disease training program + structured physical exercise training (n=54) - Self-management support program (+52), which includes disease training program + standard exercise recommendations	- Mostly male - A total of 106 patients	12 weeks	- PSQI - 6MWT - GDS - BMI - Resting heart rate	- Control=62 - Intervention=61 (mean)	- Significant improvement in sleep disturbance ($p<0.01$), sleep duration, drowsiness during the day, sleep efficiency habit scores were not significantly different in the intervention group. - PSQI-Subjective sleep quality and global scores significantly improved in the intervention group ($p<0.01$)	In the second week of 12-week follow-up, heart failure patients visited by the exercise physiologist were found to have improved sleep quality

CAI: Central apnea index, ASVmV: ASV mode set in minute ventilation, BMI: body mass index, EEG: electroencephalography, EOG: electrooculography, EMG: electromyography, VEA: ventricular premature beats, proBNP: brain natriuretic peptide, GFR: glomerular filtration rate, UNE: norepinephrine amount in 24-hour urine, 6MWD: 6 minutes walking distance; CPET: cardiopulmonary exercise test, MLHFQ: minnesota living with heart failure questionnaire, EQ-5D: euroQol group 5-dimension self-report questionnaire, GDS: geriatric depression scale, SRD: sleep respiratory disorder

Effect of Adaptive Servo-ventilation Methods and Continuous Positive Airway Pressure on Mortality

Two studies published in 2015 showed that there was no significant difference between the ASV treatment group and the medical treatment group in terms of quality of life or changes in HF symptoms (14), and that ASV treatment increased the risk of death due to all reasons and CV death ($p<0.05$) (14). In contrast to these studies, the ADVENT-HF study showed that treatment with ASV in HFrEF patients improved health-related quality of life and reduced morbidity and mortality (22) (Tables 2, 3).

Discussion

One newly defined factor that is considered to contribute to morbidity and mortality in CHF is SRD. Sleep respiratory disorder is usually defined as OSA and CSA (23).

As a result of the polysomnographic examination, the presence of more than 5 AHIs indicates the presence of OSA. For the diagnosis of OSA with AHI, excessive daytime sleepiness and cardiac disorders are expected. It has been shown that the risk of morbidity and mortality increases especially when AHI is more than 20 (2).

Non-invasive mechanical ventilator devices used in the treatment of PAP include CPAP, Auto CPAP (APAP), BIPAP, Auto BIPAP, BIPAP-ST (/Auto), volume cycle ventilator (AVAPS/IVAPS), and Servo-Ventilator (/Auto). The first treatment option for the treatment of SRD is CPAP. The aim of the treatment of SRD is to ensure that the upper airway remains open during sleep and to regulate ventilation and sleep quality (2). This method has been shown to significantly improve symptoms such as snoring, morning headaches and daytime sleepiness in many studies. It is stated that BIPAP treatment should be considered for the treatment of CSA in CHF patients to normalize AHI when it does not respond to adequate CPAP, ASV and oxygen treatments. However, it is also emphasized that ASV treatment is indicated for the treatment of CSA (23).

As a result of the evaluations made in this study, treatment interventions for CHF patients with OSA and CSA included mostly CPAP (7-9,12,18) and ASV (10-16,22), as well as BIPAP (8), overdrive pacing (21), oxygen therapy with nasal cannula (6,19), slow breathing training (17) and exercise training (20).

In these studies, the CPAP treatment for the treatment of CHF patients with OSA was found to improve LVEF (7) and daytime sleepiness (7,8,18), and ASV treatment was also found to improve AHI (10,11,16), reduce obstructive events, improve respiratory distress (12) and quality of life (22), increase oxygen saturation (11,16) and sleep time, reduce ventricular premature stroke and mean heart rate (16) (Tables 2,3).

Table 3. Treatment interventions for the treatment of sleep respiratory disorders

Author and Type of Sleep Respiratory Disorder	CPAP	BIPAP	ASV	PM	Oxygen Treatment	Slow Respiratory Exercise	Physical Exercise
Egea et al. (7) (OSA)	- LVEF (+) - Sleepiness (+) - QOL (-) - Functional capacity (-)	-	-	-	-	-	-
Smith et al. (18) (OSA)	- Sleepiness (+) - QOL (-) - CV markers (-)	-	-	-	-	-	-
Khayat et al. (8) (OSA)	Sleepiness (+)	- LVEF (+) - QOL (+) - Functional capacity (+) - Blood pressure (+) - AHI/hour (-)	-	-	-	-	-
Bradley et al. (9) (CSA)	- LVEF (+) - Sympathetic nerve activity (+) - Nocturnal SaO_2 (+) - Mortality for all causes (-)	-	-	-	-	-	-
Hetzenecker et al. (13) (OSA, CSA)	-	Sleep quality (+)	-	-	-	-	-
Lyons et al. (22) (OSA)	-	-	QOL (+) Mortality for all causes (-) Morbidity (-)	-	-	-	-
O'Connor et al. (10) (OSA)	-	-	AHI (+) CV symptom (-) Functional capacity (-)	-	-	-	-
Cowie et al. (14) (OSA)	-	-	QOL (-) CV symptom (-) CV mortality (-)	-	-	-	-
Randerath et al. (12) (OSA, CSA)	-	-	OSA (+) CSA (+) NT-proBNP (+)	-	-	-	-
Kasai et al. (15) (CSA)	-	-	NT-proBNP (+) UNE (+) Functional capacity (-) LV end-systolic diameters (+)	-	-	-	-
Arzt et al. (11) (OSA, CSA)	-	-	NT-proBNP (+) AHI / hour (+) Mean SaO_2 (+) GFR (+) LVEF (-) QOL (-) Symptom scores (-)	-	-	-	-

Table 3 contiuned

Priefert et al. (16) (OSA, CSA)	-	-	AHI / hour (+) Obstructive AHI / hour (+) Central AHI / hour (+) Sleep time (+) Mean SaO_2 (+) VEA (+) Mean heart rate (+)	-	-	-	-
Sharafkhaneh et al. (21) (OSA)	-	-	-	AHI/hour (+)	-	-	-
Nokao et al. (19) (CSA)	-	-	-	-	CSA (+) QOL (+) Functional capacity (+) VEA (+) AHI / hour (+) LVEF (+)	-	-
Kawecha-Jaszcz et al. (17) (OSA, CSA)	-	-	-	-	-	OSA (+) CSA (+) Functional capacity (+) Systolic LVEF (+)	-
Suna et al. (20) (OSA, CSA)	-	-	-	-	-	-	Sleep quality (+)

Improvement (+), No improvement: (-), OSA: Obstructive sleep apnea, CSA: central sleep apnea, LVEF: left ventricular ejection fraction, QOL: quality of life, SaO2: oxygen saturation, AHI: Apnea-Hypopnea index, VPB: ventricular premature beats, UNE: norepinephrine in 24-hour urine, BNP: brain natriuretic peptide, PM: pacemaker

The American College of Cardiology/American Heart Association 2013 guide states that CPAP may be useful for improving functional status and increasing LVEF in HF patients with sleep apnea (Evidence B) (24). Similarly, HF Society of America (2010) guideline also recommends the use of CPAP therapy in HF patients with a diagnosis of PSG-documented OSA to improve daily functional capacity and quality of life (25). The treatment of OSA with CPAP showed decrease in sympathetic flow and BP during sleep. The results of studies describing the effect of long-term CPAP treatment on BP in patients with OSA are not very impressive. Most studies have reported a reduction in systolic or diastolic pressure between 2-10 mmHg after several weeks of CPAP treatment. These studies have shown that the effect of CPAP treatment on BP in patients with OSA is modest and variable (26).

In patients with HF, CSA appears as CSR, a periodic respiration resulting in a long apnea or hypopnea. CSA, which is quite common in HF, is seen in 30-50% of patients. CPAP treatment aimed at normalizing AHI is shown as the first treatment to be considered for CHF patients (23). CPAP treatment intervention for the treatment of HF patients with CSA has been found to improve nocturnal oxygenation, LVEF, sympathetic nerve activity and functional capacity (9), however, in the same patient group, ASV treatment has been found to decrease plasma proBNP (12,15), the amount of norepinephrine in 24-hour urine (UNE), left ventricular end systolic diameter (15), in central AHI and to increase functional capacity (16). Improvement in LVEF is associated with improvement in plasma BNP levels (Table 2,3) (27). For this reason, BNP levels were also examined in the studies in which ASV and CPAP treatments were used. In contrast, Hastings et al. (27) found no change in BNP levels in ASV-treated patients compared to the control group.

Adaptive servo-ventilators work primarily with the BIPAP principle. ASV is indicated in the presence of CSR on PSG in patients with predominant congestive HF (EF <40%) (2). However, it has been reported that ASV treatment is indicated for normalizing AHI and for the treatment of CSA syndrome associated with CHF (23). In a non-randomized study, 11 patients were treated with ASV in addition to medical treatment for 6 months, and only medical treatment was applied to the comparison group. At the end of 6 months, AHI hourly event decreased significantly compared to the baseline (p=0.001) and there was also a significant improvement in sleep efficiency (p=0.01), LVEF (p=0.04), daytime sleepiness (p=0.001) and quality of life (p=0.005) in the ASV group (28).

BIPAP is not the first treatment option in patients with OSA, but it is stated that it can be the first choice in non-invasive methods in patients with hypoxemia-hypoventilation syndromes who can not tolerate CPAP treatment and who are not able to exhale against high pressure (2). As a result of the evaluations, only one study has applied BIPAP therapy in CHF patients with OSA and improvement was observed in LVEF, quality of life and functional capacity (8).

American Academy of Sleep Medicine (2011) states that administered oxygen therapy at night is indicated for the treatment of CSA in patients with CHF (29). In patients with HF, additional nocturnal oxygen therapy is administered through nasal cannula for the treatment of CSA. Data from some small-sample, short-term studies suggest that oxygen therapy with nasal cannula improves AHI, exercise capacity and LVEF, and decreases BNP level and sympathetic nervous system activity (23). In a small sample study with CHF patients with CSA (LVEF <45%, mean age 65 years, AHI >5/hour), oxygen therapy at night was shown to improve exercise capacity, cardiac function, and cardiac sympathetic nerve activity (30). In the light of the findings of our study, two studies in the literature (6,19) reported that oxygen therapy for the treatment of CHF patients with CSA improved SRD (6,19), LVEF (19) and had a positive effect on ventricular arrhythmias (19). One of the studies showed that oxygen therapy improved quality of life and functional capacity (17), but the other study (6) did not achieve the same effect (Table 2). When the literature is examined, it has been shown that night oxygen therapy through nasal cannula have no positive effect on daytime sleepiness, sleep quality, quality of life or cognitive functions. Unlike CPAP and ASV, nighttime oxygen therapy was found not effective in eliminating upper airway obstruction, which may be accompanied by central apneas. In the light of these findings, it is stated that oxygen therapy can be used only if pressure-assisted treatments are ineffective or patients cannot tolerate these treatments (23,31-33).

In the literature, it has been hypothesized that atrial overdrive pacemaker therapy can increase cardiac filling and decrease pulmonary obstruction by increasing the heart rate, thus reduce or prevent CSA formation. In some small sample studies, atrial overdrive pacemaker therapy has been shown to reduce the number of CSA attacks, improve oxygen saturation, and reduce stimulation in HF patients (23,34,35). In another study, it was reported that atrial overdrive pacemaker treatment in CSA did not provide any improvement (36). In this study, it was determined that atrial overdrive pacemaker treatment in CHF patients with OSA provided significant reduction in AHI in a single RCT (Table 2) (21).

Conclusion

Sleep disorder is a common problem in HF patients. In the studies performed within the systematic review, the effectiveness of medical treatments and interventions for sleep disturbance in HF patients were evaluated. When the efficacy of the interventions was examined, it was observed that the addition of CPAP to medical therapy improved CSA and nocturnal oxygenation and increased 6MWD. The use of CPAP improved daytime sleepiness and LVEF with regular use in HF patients with OSA, but no effect on quality of life was observed. ASV treatment added to medical therapy also improved CSA and OSA with regular use. ASV alone was effective in reducing respiratory distress and sleep apnea, and it reduced AHI, improved LVEF, and reduced ventricular pulse. The use of ASV increased 6MWD compared to CPAP. When CPAP and BIPAP were evaluated, CPAP was effective in improving sleep quality and quality of life, while BIPAP was more effective in improving quality of life, functional capacity and BP. In addition to these interventions, the physical exercise program has been shown to be effective in improving sleep quality.

Ethics

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - H.U., H.B.O.; Design - H.U., H.B.O.; Supervision - H.U.; Resources - H.U., H.B.O.; Materials - H.U., H.B.O.; Data Collection and/or Processing - H.U., H.B.O.; Analysis and/or Interpretation - H.U., H.B.O.; Literature Search - H.U., H.B.O.; Writing Manuscript - H.U., H.B.O.; Critical Review - H.U.

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

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

References

1. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. Akut ve kronik kalp yetersizliği tanı ve tedavisine yönelik 2012 ESC kılavuzu. Türk Kardiyol Dern Arş 2012;(Özel Sayı 3): 1-128.
2. Fırat H. OSAS'ta PAP tedavisi ve cihaz seçimi. Güncel göğüs hastalıkları derisi 2014; 2: 184-91.
3. Demir A, Ursavaş A, Tana Aslan A, Gülbay B, Çiftçi B, Çuhadaroğlu Ç, et al. Türk Toraks Derneği Obstrüktif Uyku Apne Sendromu Tanı ve Tedavi Uzlaşı Raporu. Türk Toraks Dergisi 2012; 13(Suppl 1): 1-65.
4. Karaçam Z. Sistematik derleme metodolojisi: Sistematik derleme hazırlamak için bir rehber. DEUHYO ED 2013; 6: 26-33.
5. The joanna briggs institute critical appraisal tools for use in JBI. Checklist for randomized controlled Trials. Joanna Briggs Institute 2017: 1-9.
6. Staniforth AD, Kinnear WJ, Starling R, Hetmanski DJ, Cowley AJ. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J 1998; 19: 922-8.
7. Egea CJ, Aizpuru F, Pinto JA, Ayuela JM, Ballester E, Zamarro´n C, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: A multicenter study. Sleep Med 2008; 9: 660-6.
8. Khayat RN, Abraham WT, Patt B, Roy M, Hua K, Jarjoura D. Cardiac effects of continuous and bilevel positive airway pressure for patients with heart failure and obstructive sleep apnea: A Pilot Study. Chest 2008; 134: 1162-8.
9. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005; 353: 2025-33.
10. O'Connor CM, Whellan DJ, Fiuzat M, Punjobi NM, Tasissa G, Anstrom KJ, et al. Cardiovascular outcomes with minute ventilation-targeted adaptive servo-ventilation therapy in heart failure. The CAT-HF Trial. J Am Coll Cardiol 2017; 69: 1577-87.
11. Arzt M, Schroll S, Series F, Lewis K, Benjamin A, Escourrou P, et al. Auto-servoventilation in heart failure with sleep apnoea: a randomised controlled trial. Eur Respir J 2013; 42: 1244-54.
12. Randerath WJ, Nothofer G, Priegnitz C, Anduleit N, Treml M, Kehl V, et al. Long-term auto-servoventilation or constant positive pressure in heart failure and coexisting central with obstructive sleep apnea. CHEST 2012; 142: 440-7.
13. Hetzenecker A, Escourrou P, Kuna ST, Series F, Lewis K, Birner C, et al. Treatment of sleep apnea in chronic heart failure patients with auto-servo ventilation improves sleep fragmentation: a randomized controlled trial. Sleep Med 2016; 17: 25-31.
14. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015; 373: 1095-105.
15. Kasai T, Kasagi S, Maeno K, Dohi T, Kawana F, Kato M, et al. Adaptive servo-ventilation in cardiac function and neurohormonal status in patients with

heart failure and central sleep apnea non-responsive to continuous positive airway pressure. JACC Heart Fail 2013; 1: 58-63.

16. Priefert HJ, Hetzenecker A, Escourrou P, Luigart R, Series F, Lewis K, et al. Effects of adaptive servo-ventilation on ventricular arrhytmias in patients with stable congestive heart failure and sleep-disordered breathing. Subanalysis of a randomized controlled trail. Somnologie 2017; 21: 19-27.
17. Kawecka-Jaszcz K, Bilo G, Drozdz T, Debicka-Dabrowska D, Kiełbasa G, Malfatto G, et al. Effects of device guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure. Pol Arch Intern Med 2017; 127: 8-15.
18. Smith LA, Vennelle M, Gardner RS, McDonagh TA, Denvir MA, Douglas NJ, et al. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. Eur Heart J 2007; 28: 1221-7.
19. Nakao YM, Ueshima K, Yasuno S, Sasayama S. Effects of nocturnal oxygen therapy in patients with chronic heart failure and central sleep apnea: CHF-HOT study. Heart Vessels 2016; 31: 165-72.
20. Suna JM, Mudge A, Stewart I, Marquart L, O'Rourke P, Scott A. The effect of a supervised exercise training programme on aleep quality in recently discharged heart failure patients. Eur J Cardiovasc Nurs 2015; 14: 198-205.
21. Sharafkhaneh A, Sharafkhaneh H, Bredikus A, Guilleminault C, Bozkurt B, Hirshkowitz M. Effect of atrial overdrive pacing on obstructive sleep apnea in patients with systolic heart failure. Sleep Med 2007; 8: 31-6.
22. Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. Eur J Heart Fail 2017; 19: 579-87.
23. Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. J Am Coll Cardiol 2015; 65: 72-84.
24. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Associaion Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: 147-239.
25. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010; 16: 1-194.
26. Mohsenin V. Obstructive sleep apnea and hypertension: A Critical Review. Curr Hypertens Rep 2014; 16: 482-7.
27. Hastings PC, Vazir A, Meadows GE, Dayer M, Poole-Wilson PA, McIntyre HF, et al. Adaptive servo-ventilation in heart failure patients with sleep-apnea: A real world study. Int J Cardiol 2010; 139: 17-24.
28. Philippe C, Stoica-Hernan M, Drouot X, Raffestin B, Escourrou P, Hittinger L, et al. Compliance with and effectiveness of adaptiveservo ventilation versus continuous positive respiration in heart failure over a six month period. Heart 2006; 92: 337-42.
29. Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidencebased literature review and meta-analyses. Sleep 2012; 35: 17-40.
30. Toyama T, Seki R, Kasama S, Isobe N, Sakurai S, Adachi H, et al. Effectiveness of nocturnal home oxygen therapy to improve exercise capacity, cardiac function and cardiac sympatetic nerve activity in patients with chronic heart failure and central sleep apnea. Circ J 2009; 73: 299-304.
31. Krachman SL, D'Alonso GE, Berger TJ, Eisen HJ. Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne-Stokes respiration during sleep in congestive heart failure. Chest 1999; 116: 1550-7.
32. Campbell AJ, Ferrier K, Neill AM. Effect of oxygen versus adaptive pressure support servo-ventilation in patients with central sleep apnoea-Cheyne-Stokes respiration and congestive heart failure. Intern Med J 2012; 42: 1130-6.
33. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007; 115: 3173-80.
34. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002; 346: 404-12.
35. Weng CL, Chen Q, Ma YL, He QY. A meta analysis of the effects of atrial overdrive pacing on sleep apnea syndrome. Pacing Clin Electrophysiol 2009; 32: 1434-43.
36. Luthje L, Unterberg-Buchwald C, Dajani D, Vollmann D, Hassesfuss G, Andreas S. Atrial overdrive pacing in patients with sleep apnea with implanted pacemaker. Am J Respir Crit Care Med 2005; 172: 118-22.

İstanbul Med J 2019; 20(3): 188-92
DOI: 10.4274/imj.galenos.2018.85698

The Evaluation of External Dose Rate Measurements of Patients During and After F-18 FDG PET/CT Imaging and Appropriate Discharge Time from PET/CT Department

F-18 FDG PET/BT Görüntüleme Yönteminin Tetkik Sürecinde ve Sonrasında Çevresel Radyasyon Güvenliğinin Değerlendirilmesi

Burçak Yılmaz Güneş, Özlem Erez, Cihan Gündoğan, Nurhan Ergül
İstanbul Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, Turkey

ABSTRACT

Introduction: F-18 radioisotope has higher photon energy when compared with other radioisotopes that are preferred in conventional imaging procedures in nuclear medicine. The aim of this study was to measure external radiation dose rate from patients injected with F-18 fluorodeoxyglucose (FDG) and to determine appropriate discharge time after F-18 FDG positron emission tomography/computed tomography (PET/CT) procedure.

Methods: Our study included 29 (M/F=9/20) patients who were referred to nuclear medicine department for F-18 FDG PET/CT imaging. Dose rates were measured at a distance of 0, 0.5, 1, 1.5 and 2 m from patients via Geiger-Müller probe at 3 different time points: 1) Just after the intravenous injection of F-18 FDG, 2) before PET/CT imaging and 3) just before discharge of patients from PET/CT department. Statistical analysis was performed to evaluate the differences between measurements.

Results: Patients were injected 291±62 megabecquerel (MBq) (range: 226-440 MBq) F-18 FDG via IV route. The patients stayed in nuclear medicine department for 70.3±13.8 min (range: 53 min-100 min) after injection of F-18 FDG. Radiation dose velocity measurements taken at a distance of 1 meter were 39.7±11.9 μSv/h just after the injection, 21.1±4.5 μSv/h before PET/CT examination and 14.3±2.9 μSv/h just before discharge.

Conclusion: Although F-18 has high photon energy, its half-life is relatively short and this makes F-18 FDG an ideal radiopharmaceutical for PET/CT imaging. When the PET/CT scan is terminated, the dose rate measurements of the patients at a distance of 1 m are appropriate for discharge according to Turkish Atomic Energy Authority regulations. Therefore, patients can be safely discharged by explaining the necessary radiation safety measures after completing F-18 FDG PET/CT imaging.

Keywords: F-18 FDG, PET/CT, radiation safety, dose rate

ÖZ

Amaç: Nükleer tıpta pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) görüntüleme yönteminde kullanılan F-18 radyoizotopu konvansiyonel nükleer tıpta tanı amacıyla kullanılan diğer radyoizotoplara göre daha yüksek foton enerjisine sahiptir. Çalışmamızda rutin uygulamada yaygın olarak kullanılan F-18 fluorodeoksiglukoz (FDG), PET/BT çekimi için kullanılan F-18 FDG radyoizotopunun enjeksiyonundan sonra hastadan çevreye salınan radyasyonun doz hızının ölçülmesi ve çevresel radyasyon maruziyetinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmamıza, Nükleer Tıp PET/BT ünitesine başvuran toplam 29 (E/K=9/20) hasta dahil edilmiştir. Hastalara intravenöz (IV) olarak F-18 FDG enjekte edildikten hemen sonra, çekim öncesi ve taburcu edilmeden önce 0 m, 0,5 m, 1 m, 1,5 m ve 2 m mesafeden toraks düzeyinden Geiger-Müller sayacı kullanılarak doz hızı ölçümleri yapılmıştır. Her bir ölçümün ortalama ve standart sapma değerleri hesaplanmış, ayrıca ölçümler arasında istatistiksel olarak anlamlı farklılık olup olmadığı değerlendirilmiştir.

Bulgular: Hastalara IV yol ile 291±62 megabecquerel (MBq) (Aralık: 226-440 MBq) radyoaktif madde enjekte edilmiş ve nükleer tıp kliniğinde enjeksiyon sonrası 70,3±13,8 dk (Aralık: 53 dk-100 dk) beklemiştir. Bir m mesafeden alınan radyasyon doz hızı ölçümleri, radyoaktif madde enjeksiyonu sonrası 39,7±11,9 μSv/sa, çekim esnasında 21,1±4,5 μSv/sa, taburcu anında 14,3±2,9 μSv/sa olarak hesaplanmıştır.

Sonuç: F-18'in foton enerjisi 511 kilo elektron volt olmasına karşın nispeten kısa yarı ömürlü olmasından dolayı F-18 FDG tanı amacı ile kullanılabilen ideal bir radyofarmasötiktir. PET/BT çekimi sonlandığında hastaların 1 m mesafedeki doz hızı ölçümlerinin, Türkiye Atom Enerjisi Kurumu mevzuatları da göz önünde bulundurulduğunda, çevresel radyasyon güvenliği açısından bir tehlike arz etmediği gösterilmiştir. Bu nedenle hastalar F-18 FDG PET/BT görüntülemesi tamamlandıktan sonra gerekli radyasyon güvenlik önlemleri anlatılarak güvenli bir şekilde taburcu edilebilmektedir.

Anahtar Kelimeler: F-18 FDG, PET/BT, radyasyon güvenliği, doz hızı

Address for Correspondence/Yazışma Adresi: Burçak Yılmaz Güneş MD, İstanbul Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, Turkey
Phone: +90 212 459 60 00 **E-mail:** drburcak@gmail.com

Cite this article as/Atıf: Yılmaz Güneş B, Erez Ö, Gündoğan C, Ergül N. The Evaluation of External Dose Rate Measurements of Patients During and After F-18 FDG PET/CT Imaging and Appropriate Discharge Time from PET/CT Department. İstanbul Med J 2019; 20(3):188-92.

Received/Geliş Tarihi: 20.10.2018
Accepted/Kabul Tarihi: 20.11.2018

Introduction

18-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/ CT) is a non-invasive imaging method that has been widely used in nuclear medicine centers for many years with indications such as staging of various cancers, treatment response evaluation, re-staging, radiotherapy planning, investigating the cause of unknown fever, differential diagnosis of dementia, investigation of epileptic focus, and infection imaging (1-4).

F-18 is a cyclotron product radioisotope. It emits positron and has a short physical half-life [(109.7 minute (min.)] (5). Although it has a short half-life, it has a significantly higher photon energy compared to the most commonly used technetium-99m in conventional nuclear medicine (140 keV and 511 keV, respectively). The most commonly used F-18 labeled metabolic product in daily life is FDG. FDG is a glucose analogue, and is taken into the cell through glucose transporters and is added to the glycolytic pathway. FDG accumulation in the tissues is observed proportional to the glucose utilization of the cells. Since intravenously administered F-18 FDG is excreted through the urinary tract, patients' micturition before PET/CT scan in order to reduce bladder activity is of great importance (5).

The minimum F-18 FDG activity required for PET/CT scan depends on the patient's age, body mass index, PET/CT device used and the scanning protocol (5). In this process, it is necessary to keep in mind the principles of the lowest possible dose (As low as reasonably achievable) for both patients and health workers (6-8).

The effective dose exposure of patients and those around them during diagnostic tests in nuclear medicine has been reported in national and international studies (9). In our country, according to the Turkish Atomic Energy Authority (TAEK) Law (No 2690), TAEK department of radiation health and safety implements the tasks, given by this law, concerning the services related to licensing, determination of the regulations and principles, and safe use of ionizing radiation and radioactive substances (10). The exemption limits of various radioisotopes used by TAEK in nuclear medicine are listed in annex-1 of the radiation safety regulation and it is reported as 106 Bq for F-18 (11). However, in the radiation safety regulation-annex-4, maximum reference levels per test for radionuclides and adult patients do not include any reference value for F-18-bound radioisotopes in the list (12). In this case, it is obvious that the evaluation of the external dose rate during discharge is important in order to ensure the radiation safety of the employees, patients and caregivers.

The aim of this study was to measure external radiation dose rate from patients injected with F-18 FDG and to determine appropriate discharge time after PET/CT scan.

Methods

Patient Population

This prospective study was approved by the local ethics committee (İstanbul Şişli Hamidiye Etfal Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2017-1506). Patients over 18 years of age who were randomly selected among the patients who applied to the nuclear medicine clinic for whole-body F-18 FDG PET/CT scan with various indications for 5 days consecutively were included in the study. Patients under 18 years of age, patients with known renal insufficiency, patients with problems with urinary system (patients with urinary catheter, patients with urinary output problems, etc.) and patients with Eastern Cooperative Oncology Group performance score ≥3 were not included in the study. A total of 29 patients (20 female, 9 male; 59.4 years±12.4 years) who met the inclusion criteria and accepted to participate were included in the study and informed consent forms were obtained. Patients were trained for radiation safety prior to scanning in accordance with the TAEK radiation safety regulations and annex-6, and things to do during and after scanning were described verbally in detail and given as texts (13).

Study Design, Data Collection and External Dose Rate Measurement

For F-18 FDG PET/CT scan, blood glucose levels of patients were measured following 4-6 hours of fasting. Patients with fasting glucose levels <200 mg/dL were injected intravenously with 291±62 MBq (range: 226-440 MBq) F-18 FDG according to the European Nuclear Medicine Association FDG PET/CT guideline version 2 recommendations (5). After the injection, the patients consumed an average of 1 liters of water.

Dose rate measurements were performed by Geiger-Müller (GM) probe (Eberline ESP-2, NM, USA) calibrated by Secondary Standard Dosimeter Laboratory of İstanbul Çekmece Nuclear Research and Training Center. The accuracy of the GM probe has been reported to be within ±3% range (14). Using this detector, external dose rate measurements were made at three different times from 0, 0.5, 1, 1.5 and 2 m distance from the central part of the thorax for a total of 15 times for each patient. The first measurements were taken immediately after the F-18 FDG injection, the second measurements were taken just before the scan after micturition and the third measurements were taken after PET/CT scan just before leaving the nuclear medicine clinic after micturition.

Patients were kept in private rooms with bulletproof insulations in the department until discharge. Patients' height, weight, injection and scan hours, measurement hours and results were recorded.

Statistical Analysis

The mean and standard deviation values of age, body weight, height, length of stay in the nuclear medicine clinic after injection, and external dose rates were calculated. The statistical significance of the differences between dose rate measurements was evaluated by Student's t-test. $P<0.05$ was considered statistically significant.

Results

The age of the patients included in the study was 59.4±12.4 years (range: 41-81 years). Mean body weight was 72.8±18.5 kg (range: 50-120 kg) and height was 161.83±8.34 cm (range: 150-180 cm). The mean length of stay in the nuclear medicine department from the moment of F-18 FDG injection until discharge was 70.3±13.8 min (range: 53-100 min).

Mean dose rates calculated from measurements taken with GM counter at 0, 0.5, 1, 1.5 and 2 m distance from the thorax level immediately after the injection, immediately before scanning after micturition and before

Table 1. Dose rate measurements

Dose rate measuring distance (meters)	Immediately after the injection (µSv/h)	Immediately before scanning (µSv/h)	Before discharge (µSv/h)
0	718.31±186.33	222.03±59.47	148.61±43.73
0.5	117.97±44.02	49.31±14.49	33.68±9.14
1	39.66±11.91	21.07±4.49	14.28±2.94
1.5	18.45±4.95	11.10±2.23	8.04±1.79
2	12.10±2.95	6.62±1.89	4.25±1.65

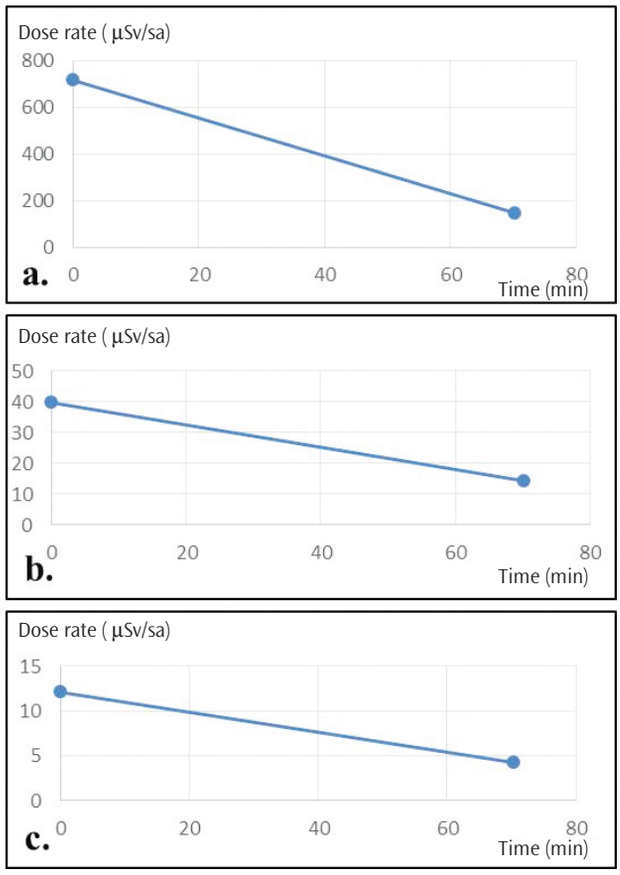


Figure 1. Dose rates versus time from 0 a), 1 b) and 2 m c)

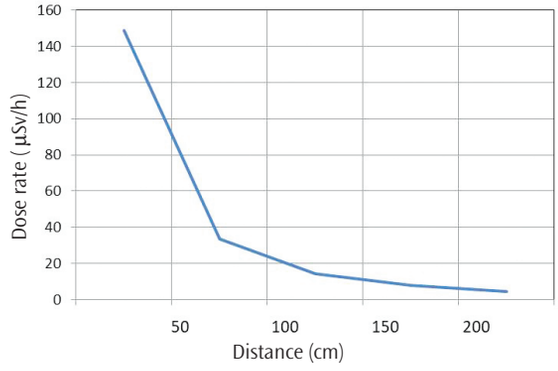


Figure 2. The relationship between mean dose rate (µSv/h) and distance (cm) during discharge

discharge after micturition were given in Table 1. Also, Figure 1 shows the dose rate measurements from 0 m, 1 m and 2 m distances versus time, and Figure 2 shows the relation between distance and mean dose rates during discharge.

A significant difference was found between the dose rates at 0, 1 and 2 m distance ($p<0.001$). A significant difference was found between the dose rates at different times in the measurements taken at the same distance ($p<0.001$). Although there is no data by TAEK regarding external dose rates of F-18-bound radiopharmaceuticals during discharge, the discharge limit for I-131 was determined as safety limit dose rate <30 µSv/h in annex-5 of the Radiation Safety Regulation (15). All patients included in our study were able to be discharged with safe dose rate with an external dose rate of 14.3±2.9 µSv/h (range: 8-21 µSv/h) at a distance of 1 meter at the end of scanning.

Discussion

In our country, patients receiving radionuclide treatment according to TAEK regulations are kept in private single rooms with isolation until the dose rate level is reduced to <30 µSv/h. The external dose rate limits during discharge are <50 µSv/h in the United States and <20 µSv/h in European Union countries (16,17). Although defined values have been determined for radionuclide treatments, it has been shown that discharge rate limits are rapidly achieved in our country and European Union countries in nuclear medicine during the time for PET-BT scanning regarding the short half-life of the F-18 isotope, relatively low level of radioactivity compared to treatment and biological elimination of F-18 isotope used for diagnosis in our study, but with a high photon energy.

International (International Commission on Radiological Protection) and national (TAEK) radiation protection institutions have reported an annual acceptable radiation (internal and/or external) exposure dose for individuals in the community as 1 mSv (18,19). In addition, in the manual published by TAEK, it has been described that dose limits above this level are acceptable in adults who are knowingly and intentionally near the patients who had radioactive substance for diagnostic or therapeutic purposes. The effective dose in caregivers or those who come for a patient visit has been reported not to exceed 5 mSv during diagnosis and treatment. In addition, it has also been explained that patient-induced dose exposure should not exceed 1 mSv for pregnant women and children (9).

In our study, although the external dose limits of patients during discharge are well below the criteria determined in accordance with the legal regulations, it is necessary to prevent unnecessary radiation exposure of the people and the society around the patient who underwent radioactive material and became a source of radiation for a certain period of time (9). This is also important for the hospital staff working in the services of the patients as well as staff working in the nuclear medicine clinics. It has been reported that if the patient transfers are performed with the same personnel, the personnel will be exposed to 0.1 mSv/month radiation because the distance between the staff in charge of transporting the inpatients to the relevant services and the patient is very low (9). In another study, it was suggested that the hospital staff accompanying the patient or the patient's relative should

accompany the patients by at least 0.5 m distance if possible, within 2 hours of F-18 FDG injection (20). In addition, the highest exposure dose of the nurse working in the intensive care unit was reported to be due to myocardial perfusion scintigraphy studies or positron emission imaging studies (21). The exposure dose of the personnel working outside the nuclear medicine clinic is related to the time taken for the patient to reach the relevant service after radionuclide injection. Although radionuclide agents and application doses vary with the doses administered, the time spent in delivering the patients from the nuclear medicine department to the service will decrease the external dose rates and decrease the exposure of the personnel (21-23). In a study by Cronin et al. (23), it was shown that there was no need for severe limitations for inpatients who had undergone F-18 FDG PET imaging and who remained in the nuclear medicine unit for 2 hours after injection. Care should be taken not to establish close contact only with children and pregnant women for at least 6 hours after injection (20).

In studies conducted, it was shown that the radiation technicians working in the nuclear medicine clinic were below the 20 mSv/year dose limits (24). It was claimed that approximately 60% of this exposures was due to contact with radioactive material and about 40% was due to close contact with the patients (24). In this case, the radiation safety personnel as we have shown in our study can reduce the radiation dose to a significant extent by paying attention to distance between the patient injected with a radioactive substance during his/her stay in the clinic and by keeping the contact with radioactive material as short as possible (20,25,26).

The minimum F-18 FDG activity required for PET-CT scan depends on the device used and the patient's body weight (27,28). On the other hand, the maximum dose that can be applied has been reported in some countries (5). However, maximum normal activity level for F-18 radioisotope are not specified in annex-4 of TAEK Radiation Safety Regulation, in which the maximum normal activity levels of radioisotopes used for diagnostic methods in nuclear medicine in our country. In our daily practice, as stated in our study, we inject F-18 FDG and discharge our patients according to European Association of Nuclear Medicine guideline and International Commission on Radiological Protection recommendations (5,18,29-31).

In addition, it is very important that patients are hydrated and micturition is achieved before and after F-18 FDG PET/CT. Bladder is the organ that receives the most radiation dose in the F-18 FDG PET procedure. Prompting patients to drink water during F-18 FDG injection until after scanning reduces bladder radiation dose and thus external dose rate levels (26).

Conclusion

According to the results of this study, despite having a physical half life of 109.8 min., it was determined that more than half of the F-18 radioactive material was discarded after about 60 minutes through biological elimination, hydration and micturition. Since external dose rate at a distance of 1 m from the patient does not pose a risk for environmental radiation safety after F-18 FDG PET/CT procedure, it is concluded that patients can be safely discharged by explaining the necessary radiation safety measures immediately after the examination.

Ethics Committee Approval: İstanbul Şişli Hamidiye Etfal Training and Research Hospital, Clinical Research Ethics Committee (decision no: 2017-1506).

Informed Consent: Informed consent forms were obtained.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - B.Y.G.; Design - B.Y.G.; Supervision - B.Y.G.; Resources - Ö.E.; Materials - Ö.E.; Data Collection and/or Processing - B.Y.G., Ö.E.; Analysis and/or Interpretation - B.Y.G., Ö.E., C.G., N.E.; Literature Search - C.G.; Writing Manuscript - B.Y.G.; Critical Review - Ö.E., C.G., N.E.

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

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

References

1. Gunes BY, Onsel C, Sonmezoglu K, Ozaras R, Halac M, Tabak F, et al. Diagnostic value of F-18 FDG PET/CT in patients with spondylodiscitis: Is dual time point imaging time worthy? Diagn Microbiol Infect Dis 2016; 85: 381-5.
2. Ergul N, Kadioglu H, Yildiz S, Yucel SB, Gucin Z, Erdogan EB, et al. Assessment of multifocality and axillary nodal involvement in early-stage breast cancer patients using 18F-FDG PET/CT compared to contrast-enhanced and diffusion-weighted magnetic resonance imaging and sentinel node biopsy. Acta Radiol 2015; 56: 917-23.
3. Ergül N, Cermik TF. FDG-PET or PET/CT in Fever of unknown origin: The diagnostic role of underlying primary disease. Int J Mol Imaging 2011; 2011: 318051.
4. Akaike G, Itani M, Shah H, Ahuja J, Yilmaz Gunes B, Assaker R, et al. PET/CT in the diagnosis and workup of sarcoidosis: Focus on atypical manifestations. Radiographics 2018; 38: 1536-49.
5. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42: 328-54.
6. Atci IB, Yilmaz H, Antar V, Ozdemir NG, Baran O, Sadillioglu S, et al. What do we know about ALARA? Is our knowledge sufficient about radiation safety? J Neurosurg Sci 2017; 61: 597-602.
7. Siegel JA, Sacks B, Pennington CW, Welsh JS. Dose optimization to minimize radiation risk for children undergoing CT and nuclear medicine imaging is misguided and detrimental. J Nucl Med 2017; 58: 865-8.
8. Chen MK, Menard DH 3rd, Cheng DW. Determining the minimal required radioactivity of 18F-FDG for reliable semiquantification in PET/CT imaging: A Phantom Study. J Nucl Med Technol 2016; 44: 26-30.
9. Aras F, Kıraç S, Ayan A, Değer M, Demir M, Dönmez S, et al. Radiation safety process for the patient and people around during diagnostic radionuclide studies. Nucl Med Semin 2016; 3: 172-175.
10. Türkiye Atom Enerjisi Kurumu Kanunu. Kanun No: 2690. R.G: 13.7.1982/17753.
11. TAEK (Türkiye Atom Enerjisi Kurumu), Radyasyon Güvenliği Yönetmeliği Ek-1
12. TAEK (Türkiye Atom Enerjisi Kurumu), Radyasyon Güvenliği Yönetmeliği Ek-4
13. TAEK (Türkiye Atom Enerjisi Kurumu), Radyasyon Güvenliği Yönetmeliği Ek-6
14. Yeyin N, Abuqbeitah M, Çavdar İ, Sönmezoğlu K, Demir M. The evaluation of dose rate measurements and discharge time after radionuclide therapy. J Ist Faculty Med 2017; 80: 1.
15. TAEK (Türkiye Atom Enerjisi Kurumu), Radyasyon Güvenliği Yönetmeliği Ek-5
16. European Commission Radiation Protection 97: Radiation Protection Following Iodine-131 Therapy (Exposure due to out-patients or discharged

inpatients). Luxembourg, Belgium: Office for Official Publications of the European Communities; 1998.

17. Yeyin N, Demir M. Hasta ve atıklarından çevreye salınan radyasyon miktarının belirlenmesi ve doz hızı ölçümleri. 1.Ulusal Sağlık Kuruluşları Çevre Yönetim Sempozyumu Yayınları, İstanbul, 29-30 Kasım 2012.
18. ICRP. Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007. Ann ICRP 2008; 38: 1-197.
19. Radyonüklit tedavisi gören hastaların taburcu edilmesine ilişkin kılavuz. RSGD-KLV-009. TAEK, Ankara, 14 Kasım 2016.
20. Demir M, Demir B, Sayman H, Sager S, Sabbir Ahmed A, Uslu I. Radiation protection for accompanying person and radiation workers in PET/CT. Radiat Prot Dosimetry 2011; 147: 528-32.
21. Bartlett ML. Estimated dose from diagnostic nuclear medicine patients to people outside the Nuclear Medicine department. Radiat Prot Dosimetry 2013; 157: 44-52.
22. Mountford PJ, O'Doherty MJ. Exposure of critical groups to nuclear medicine patients. Appl Radiat Isot 1999; 50: 89-111.
23. Cronin B, Marsden PK, O'Doherty MJ. Are restrictions to behaviour of patients required following fluorine-18 fluorodeoxyglucose positron emission tomographic studies? Eur J Nucl Med 1999; 26: 121-8.
24. Seierstad T, Stranden E, Bjering K, Evensen M, Holt A, Michalsen HM, Wetteland O. Doses to nuclear technicians in a dedicated PET/CT centre utilising 18F fluorodeoxyglucose (FDG). Radiat Prot Dosimetry 2007; 123: 246-9.
25. Demir M, Demir B, Yasar D, Sayman HB, Halaç M, Ahmed AS, et al. Radiation doses to technologists working with 18F-FDG in a PET center with high patient capacity. Nukleonika 2010; 55: 107-12.
26. Alenezi A, Soliman K. Trends in radiation protection of positron emission tomography/computed tomography imaging. Ann ICRP 2015; 44: 259-75.
27. de Groot EH, Post N, Boellaard R, Wagenaar NR, Willemsen AT, van Dalen JA. Optimized dose regimen for whole-body FDG-PET imaging. EJNMMI Res 2013; 3: 63.
28. Masuda Y, Kondo C, Matsuo Y, Uetani M, Kusakabe K. Comparison of imaging protocols for 18F-FDG PET/CT in overweight patients: optimizing scan duration versus administered dose. J Nucl Med 2009; 50: 844-8.
29. Radiation protection and safety of radiation sources: international basic safety standards. IAEA General Safety Requirements. GSR 2014; 3: 10-11.
30. Stabin MG. Radiopharmaceuticals for Nuclear Cardiology: Radiation Dosimetry, Uncertainties, and Risk. J Nucl Med 2008; 49: 1555-63.
31. Radiation Dose to Patients from Radiopharmaceuticals. ICRP 2007.

İstanbul Med J 2019; 20(3): 193-7
DOI: 10.4274/imj.galenos.2018.58826

The Evaluation of the Effect of Cranioplasty on Cerebral Metabolism Using F-18 FDG PET/CT

Dekompresyon Amacıyla Yapılan Kraniyektomi Sonrası Kemik Defektlerinin Kraniyoplasti ile Kapatılmasının Beyin Metabolizması Üzerine Etkisinin F-18 FDG PET/BT ile Değerlendirilmesi

Mehmet Yaman[1], Cihan Gündoğan[2], Mustafa Yavuz Samancı[1], Esra Arslan[2], Veysel Antar[1]

[1]University of Health Sciences, İstanbul Health Research and Application Center, Clinic of Neurosurgery, İstanbul, Turkey
[2]University of Health Sciences, İstanbul Health Research and Application Center, Clinic of Nuclear Medicine, İstanbul, Turkey

ABSTRACT

Introduction: Decompressive craniectomy (DC) is commonly used as the treatment for refractory intracranial hypertension. The indications for cranioplasty after DC are cosmetic repair and, mainly, restoration of cerebral protection. Unexpected improvement in patient's neurological status has been observed among patients that underwent cranioplasty. This study was conducted to determine the impact of cranioplasty on cerebral metabolism and its correlation with clinical outcome.

Methods: Twelve patients who underwent DC for various reasons underwent positron emission tomography/computed tomography (PET/CT) with F-18 labeled fluorodeoxyglucose (FDG) before and after cranioplasty.

Results: There were 11 (92%) male patients and 1 (8%) female patient in the study. The mean age was 46.8±14.1 years. The most common indication was trauma (58%), while the most frequently affected side was right (67%). The cerebral metabolism evaluated by FDG-PET/CT was found to be significantly decreased in the hemisphere ipsilateral to the trauma compared with the contralateral hemisphere (3.87 vs 2.72, p=0.012). All patients showed improvement in one or more anatomic areas with cranioplasty (median: 6, minimum: 3, maximum: 8). Cranioplasty did not cause a significant change in FDG uptake in both hemispheres (ipsilateral p=0.814, contralateral p=0.308). Nevertheless, a general improvement and decrease in symptoms were observed in all patients before and after cranioplasty.

Conclusion: Though we are unable to demonstrate a significant increase in the cerebral metabolism, cranioplasty was observed to have a therapeutic role in terms of clinical outcome improvement.

Keywords: Cerebral metabolism, cranioplasty, decompressive craniectomy

ÖZ

Amaç: Dekompresif kraniyektomi (DK), dirençli intrakraniyal hipertansiyon tedavisinde sıklıkla kullanılmaktadır. DK sonrası kraniyoplasti endikasyonları kozmetiktir ve temel olarak serebral dokunun korunması amaçlanır. Kraniyoplasti yapılan hastalarda, hastaların nörolojik durumunda beklenmedik iyileşmeler gözlenmiştir. Bu çalışma, kraniyoplastinin beyin metabolizmasına olan etkisini ve bunun klinik sonuç ile korelasyonunu belirlemek için yapıldı.

Yöntemler: Kliniğimizde çeşitli sebepler ile DK yapılan on iki hastaya kraniyoplasti öncesi ve sonrası 18-F işaretli florodeoksiglukoz (FDG) ile pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) çekimi yapıldı.

Bulgular: Çalışmada 11 (%92) erkek ve 1 (%8) kadın hasta vardı. Ortalama yaş 46,8±14,1 yıldı. En sık endikasyon travma (%58) iken, en sık etkilenen taraf sağ (%67) idi. FDG-PET/BT ile değerlendirilen serebral metabolizmanın, travma ile aynı taraftaki hemisferde karşı taraf hemisfer ile karşılaştırıldığında anlamlı olarak azalmış olduğu saptandı (3,87 vs 2,72, p=0,012). Tüm hastalarda kraniyoplasti ile 1 veya daha fazla anatomik bölgede düzelme gözlendi (medyan: 6, minimum: 3, maksimum: 8). Kraniyoplasti her iki hemisferde FDG alımında anlamlı bir değişikliğe sebep olmamıştır (ipsilateral p=0,814, kontralateral p=0,308). Buna rağmen, hastaların kraniyoplasti öncesi ve sonrası nörolojik durumları arasında tüm hastalarda genel bir iyileşme ve semptomlarda azalma tespit edildi.

Sonuç: Serebral metabolizmada belirgin bir artış gösteremesekte, kraniyoplastinin klinik sonuçlarda iyileşme açısından terapötik bir rolü olduğu gözlendi.

Anahtar Kelimeler: Serebral metabolizma, kraniyoplasti, dekompresif kraniyektomi

Address for Correspondence/Yazışma Adresi: Mustafa Yavuz Samancı MD, University of Health Sciences, İstanbul Health Research and Application Center, Clinic of Neurosurgery, İstanbul, Turkey
Phone: +90 530 886 87 27 **E-mail:** mysamanci@hotmail.com **ORCID ID:** orcid.org/0000-0001-8952-6866

Cite this article as/Atıf: Yaman M, Gündoğan C, Samancı MY, Arslan E, Antar V. The Evaluation of the Effect of Cranioplasty on Cerebral Metabolism Using F-18 FDG PET/CT. İstanbul Med J 2019; 20(3):193-7.

Received/Geliş Tarihi: 05.12.2018
Accepted/Kabul Tarihi: 26.12.2018

Introduction

Brain edema may develop after traumatic brain injury (TBI), ischemic stroke, and many other conditions affecting the brain (1,2). Increased brain edema leads to increased intracranial pressure, due to the fact that the skull is stiff and does not have the possibility of expansion, which leads to a decrease in cerebral perfusion pressure, cerebral blood flow and oxygenation. These effects can lead to brain herniation and death if not treated.

Decompressive craniectomy (DC), which is the removal of a part of the skull, is a treatment option to prevent tissue damage due to brain edema. It was described by Kocher in 1901 and Harvey Cushing reported a reduction in surgical mortality from 50% to 15% with DC in 1908 (3). Despite the reduced morbidity and mortality associated with this surgical technique, early and late onset complications can be seen in many patients (4-7). Patients with large skull defects are at risk for trephine syndrome (TS), characterized by headache, dizziness, behavior and mood changes, seizures, fatigue, motor deficits and language disorders (8,9).

Following DC, cranioplasty was previously considered to be useful in terms of protection and cosmetic. However, unexpected improvements were observed in the neurological status of patients in many centers (10-12). Although the mechanism of action of cranioplasty is not known, it is thought to neutralize the possible pathophysiological mechanisms (abnormal brain pulsatility, changes in cerebrospinal fluid (CSF) and venous drainage dynamics, changes in blood flow and metabolism) by normalizing atmospheric pressure (13). Good results are thought to be due to improved collateral circulation, decreased tissue edema, oxygenation in damaged tissues and improvement in energy metabolism (10,14,15).

This prospective study was designed to investigate the effect of cranioplasty on cerebral metabolism using positron emission tomography/computed tomography (PET/CT) with F-18 labeled fluorodeoxyglucose (FDG) as an indication of functional recovery.

Methods

This prospective observational study was performed by İstanbul Health Research and Application Center, University of Health Sciences, Department of Neurosurgery and Department of Nuclear Medicine. Following approval of the ethics committee of our hospital (decision number: 826, decision date: 02.09.2016), 13 patients who underwent DC and who were admitted to our clinic for cranioplasty between January 2016 and February 2017 were included in this study. Patients were included in the study after signing informed consent form. Of the 13 patients, one patient was excluded from the study due to missing follow-up. Routine CT scans were performed preoperatively and postoperatively in all patients.

Positron Emission Tomography/Computed Tomography Imaging Protocol

PET/CT imaging of the patients included in the study was performed by Biograph mCT 20 Excel LSO FDG-PET/CT scanner (Siemens Molecular Imaging, Hoffmann Estates, IL, USA). After at least six hours of fasting, 3.7-5.2 MBq/kg F-18 FDG was administered intravenously when the serum glucose level was below 140 mg/dL. The cranial region was visualized 50-70 minutes after injection.

CT imaging for PET/CT imaging was performed by a 20-slice multi-detector CT scanner with 80-140 kV, 20-666 mAs (It is determined automatically according to the patient and the region examined by the manufacturer's software (CareDose 4D) with personalized automatic exposure control system), 0.8 pitch and 512x512 matrix. CT scan was performed in a craniocaudal direction with a cross-sectional thickness of 5 mm and a rotation time of 0.5 sec, followed by a PET scan of 1.5-min acquisition time per bed position. PET parameters were as follows: PET crystal material: LSO, crystal size: 4x4x20 mm, crystal number: 24.336, crystal ring number: 39, ring diameter: 84.2 cm, resolution: 4.2 mm, gantry opening: 70 and 78 cm, detector pixelar transverse field of view (FOV): 70 cm, and axial FOV: 16.2 cm. Ultra HD images were obtained using the time of flight + True X algorithm for reconstruction.

Evaluation of Positron Emission Tomography/Computed Tomography Images

The images of all patients were evaluated together by two nuclear medicine experts who had 3 and 5 years experience in the field of PET/CT. The images were analyzed at Syngo.via Workstation (SyngoMI, Siemens). In addition to visual evaluation, PET axial section images were evaluated using a three-dimensional stereotactic surface projection software (3D-SSP; 3D Stereotactic Surface Projection) or NEUROSTAT (University of Utah, Department of Radiology and Imaging Sciences, Salt Lake City, UT, USA) software. This program resizes the brain images of the patient according to a standard template and makes a rotation correction, and compares voxel counts in each image unit placed according to Talairach coordinates with a normal database of suitable age (19-30, 31-54, 55-91 age ranges). It then provides the regional deviations in the patient (z-score) as standard deviation (SD) and reflects on the brain template in 8 different projections (right lateral, left lateral, superior, inferior, anterior, posterior, right medial, left medial) by converting values to numerical and color scale. FDG-PET/CT images before and after surgery were re-evaluated with the NEUROSTAT program, and SD (z-score) values were obtained by comparing the data of the patients with the normal means of their age group.

Statistical Analysis

Mean, SD, median, minimum, maximum, frequency and ratio values were used in descriptive statistics of the data. Kolmogorov-Smirnov test was used to analyze the normal distribution. ANOVA (Tukey test), independent sample t test, Kruskal-Wallis, Mann-Whitney-U test were used to analyze the quantitative independent data. Wilcoxon test was used to analyze the dependent quantitative data. SPSS 22.0 for Windows 10 (IBM Corporation Armonk, NY, USA) was used in the analysis.

Results

The differences between demographics, surgical characteristics and clinical symptoms of patients before and after cranioplasty are presented in Table 1. There were 11 (92%) male patients and one (8%) female patient. The mean age was 46.8±14.1 years. The most common

indication was trauma (58%), while the most frequently affected side was right (67%). The median time between craniectomy and cranioplasty was 16 weeks (range 6-936 weeks). Autologous bone graft was placed in 10 patients and synthetic bone graft was used in two patients. The differences between the neurological status of the patients before and after cranioplasty were done by routine clinical evaluation, not by specific tests, and overall functional and cognitive improvement was observed in all patients after cranioplasty.

The cerebral metabolism assessed by FDG-PET/CT was found to be significantly decreased in the hemisphere ipsilateral to trauma compared to the contralateral hemisphere (3.87 vs 2.72, p=0.012) (Figure 1). Improvement was observed in one or more regions with cranioplasty in all patients (median: 6, minimum: 3, maximum: 8). The most significant improvement was seen in the right parietal (n=8), right caudate (n=8) and left caudate (n=8) regions (Figure 2). Cranioplasty did not cause a significant change in FDG uptake in both hemispheres (ipsilateral p=0.814, contralateral p=0.308). There were no statistically significant differences between the values of other regions before and after cranioplasty. In spite of this, a general improvement and decrease in symptoms were observed in all patients.

Table 1. Demographic and surgical characteristics

Patient	Age (years)	Gender	Indications	Side	Timing	Cranioplasty material	Pre-op/Post-op neurological condition
1	61	Male	Hemorrhagic stroke	Left	20 wk.	Autograft	Improvement in headache, tinnitus, dizziness with head movements, speech difficulties
2	54	Male	Trauma	Right	16 wk.	Autograft	Significant improvement in left leg function
3	22	Male	Trauma	Left	18 yrs.	Synthetic	Progressive improvement in both cognitive and motor functions
4	65	Male	Hemorrhagic stroke	Right	8 wk.	Autograft	Improvement in headache and irritability
5	53	Male	Trauma	Right	60 wk.	Synthetic	A partial improvement in left hemiparesis
6	61	Male	Hemorrhagic stroke	Right	6 wk.	Autograft	Improvement in severe depressive mood with anhedonia, irritability and sleep changes
7	44	Male	Trauma	Left	28 wk.	Autograft	Improvement in functional use of right hand
8	46	Male	Trauma	Right	12 wk.	Autograft	Improvement in speech difficulties
9	35	Male	Hemorrhagic stroke	Right	48 wk.	Autograft	Spastic left hemiparesis, but can walk without help and simple movements in the left upper extremity
10	23	Male	Trauma	Right	12 wk.	Autograft	Significant improvement in balance, and place and time orientation, becoming independent in some daily activities
11	52	Female	Hemorrhagic stroke	Right	16 wk.	Autograft	Improvement of muscle strength in the left lower extremity
12	46	Male	Trauma	Left	16 wk.	Autograft	Better performance in memory tasks, improvement in hand skills in the right upper extremity

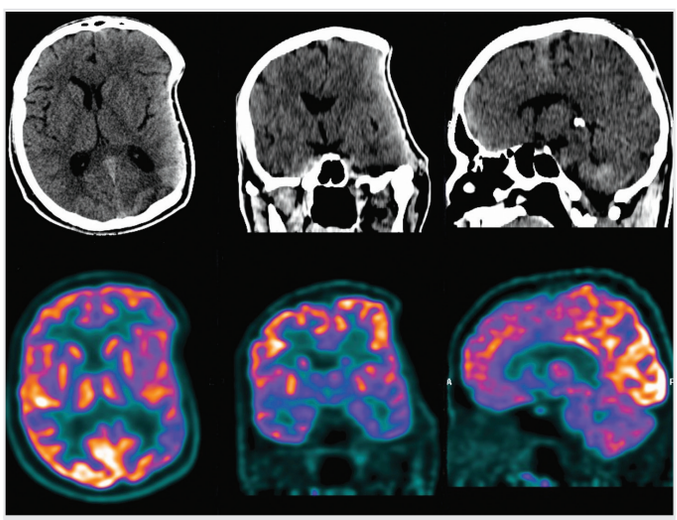


Figure 1. Axial, coronal and sagittal computed tomography and positron emission tomography images showing hypometabolism in the left parietotemporal cortex and basal ganglia compared to right in a 46-year-old male patient before cranioplasty

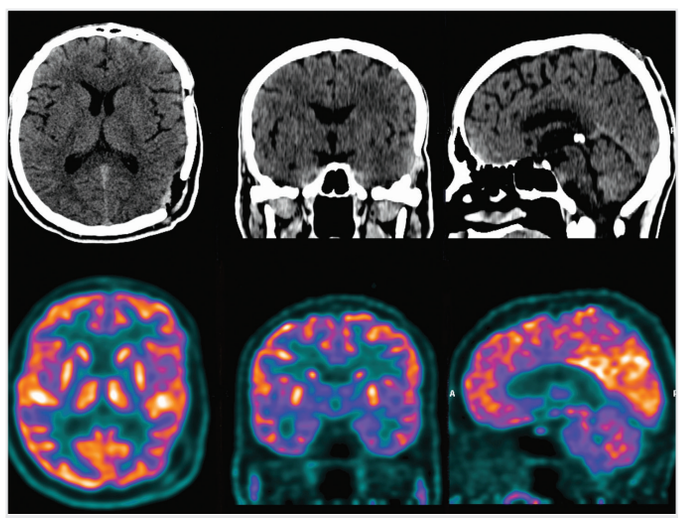


Figure 2. A significant improvement in the metabolism in the left parietotemporal cortex and basal ganglia observed in post-cranioplasty 3rd month computed tomography and positron emission tomography scan of the patient mentioned in Figure 1

Discussion

DC has been widely used for the treatment of intracranial hypertension resistant to drug therapy and has succeeded in effectively reducing intracranial hypertension in 85% of such patients. Good clinical results were obtained in 40% of patients in the long term (16). In the past, the majority of patients after DC underwent cranioplasty for cosmetic or protective reasons, and studies have shown that cranioplasty has a positive effect on normal CSF and blood flow dynamics. A number of studies, the oldest being in 1977, have been published reporting improved clinical status after cranioplasty (10,17,18). In our prospective study, we aimed to evaluate clinical outcome and cerebral metabolism after cranioplasty. Unlike other studies, hemorrhagic stroke patients were included in our study in addition to TBI and we aimed to show the positive effect of cranioplasty in these patients.

After DC, a sunken skin is observed above the bone defect and various neurological symptoms, such as neurological deficit, headache, dizziness, fatigue, and psychiatric changes, have been attributed to this condition, namely TS or Sinking Skin Flap Syndrome (8,19). The pathophysiology of this syndrome has been suggested to include many factors such as cerebral blood flow, CSF and atmospheric pressure (18,20). Among these factors, it has been reported that atmospheric pressure causes compression and cortical tissue damage on the unprotected brain tissue in the bone defect area as a main factor, leading neurological deficits, and that neurological improvement is achieved with the disappearance of this condition after cranioplasty (20). In a study by Segal et al. (11), it was claimed that atmospheric pressure changed cerebral hemodynamics and inhibited cerebral blood flow, and cerebral perfusion increase after cranioplasty was shown in subsequent studies (10,17,21-23).

Imaging with cranial F-18 FDG-PET/CT is useful in evaluating regional cerebral metabolism. Following brain damage, glucose metabolism is affected as a result of ionic alterations and neurochemical cascades. F-18-FDG-6-Phosphatase is a good marker for the *in vivo* distribution of glucose uptake by cells. FDG-PET/CT was evaluated in previous studies in both TBI (24,25) and stroke (26,27) patients, and correlations between cognitive and behavioral disorders and decreased cortical metabolism were demonstrated. In our patients, it was found that glucose metabolism was significantly decreased in the hemisphere ipsilateral to trauma compared to the contralateral hemisphere. An increase in glucose metabolism after cranioplasty was seen in one or more regions, but unlike other studies, no statistically significant differences were found between the values. However, similar to other studies, neurological improvement of varying degree was observed in all patients after cranioplasty. The discrepancy between the change in glucose metabolism over time and the neurological improvement in our study may be explained by the fact that our patient group is composed of patients of different ages, patients having different injury mechanisms and severities, different timing of cranioplasty, different cranioplasty materials and PET timing. The reason for this is the time and resource limitation of patient selection in our study. In addition, independent of our patient group, use of drugs that suppress brain metabolism and neurological recovery such as benzodiazepines and anticonvulsants (28,29) and transient hyperglycemia attacks (30) which can be seen in all patients with brain damage may have affected our results.

Conclusion

DC affects cortical perfusion and clinical outcome. In our study, F-18 FDG-PET/CT showed a decrease in glucose metabolism in hemisphere ipsilateral to brain damage. Considering the complex nature of brain injury, it should be considered that the improvement in cerebral metabolism and the degree of neurological recovery might be multifactorial. However, this preliminary study is the first metabolic imaging study. We believe that F-18 FDG-PET/CT may have a potential to contribute to a better understanding of metabolic changes that may occur in the brain after DC and in other regions with studies including larger patient series.

Ethics Committee Approval: This prospective observational study was performed by İstanbul Health Research and Application Center, University of Health Sciences, Department of Neurosurgery and Department of Nuclear Medicine. Following approval of the ethics committee of our hospital (decision number: 826, decision date: 02.09.2016).

Informed Consent: Patients were included in the study after signing informed consent form.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - M.Y., C.G., M.Y.S., E.A., V.A.; Design - M.Y., C.G., M.Y.S., E.A., V.A.; Supervision - A M.Y., C.G., M.Y.S.; Resources - M.Y., C.G., M.Y.S., E.A.; Materials - M.Y., M.Y.S., V.A.; Data Collection and/or Processing - M.Y., C.G., M.Y.S., E.A., V.A.; Analysis and/or Interpretation - M.Y., C.G., M.Y.S., E.A.; Literature Search - M.Y., C.G., M.Y.S.; Writing Manuscript - M.Y., C.G., M.Y.S., E.A.; Critical Review - M.Y., C.G., M.Y.S.

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

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

References

1. Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. Neuroscience 2004; 129: 1021-9.
2. Katzman R, Clasen R, Klatzo I, Meyer JS, Pappius HM, Waltz AG. Report of joint committee for stroke resources. IV. Brain edema in stroke. Stroke 1977; 8: 512-40.
3. Cushing H. I. Subtemporal decompressive operations for the intracranial complications associated with bursting fractures of the skull. Ann Surg 1908; 47: 641-4.
4. Honeybul S. Complications of decompressive craniectomy for head injury. J Clin Neurosci 2010; 17: 430-5.
5. Stiver SI. Complications of decompressive craniectomy for traumatic brain injury. Neurosurg Focus 2009; 26: 7.
6. Yang XJ, Hong GL, Su SB, Yang SY. Complications induced by decompressive craniectomies after traumatic brain injury. Chin J Traumatol 2003; 6: 99-103.
7. Flint AC, Manley GT, Gean AD, Hemphill JC 3rd, Rosenthal G. Post-operative expansion of hemorrhagic contusions after unilateral decompressive hemicraniectomy in severe traumatic brain injury. J Neurotrauma 2008; 25: 503-12.
8. Yamaura A, Makino H. Neurological deficits in the presence of the sinking skin flap following decompressive craniectomy. Neurol Med Chir (Tokyo) 1977; 17: 43-53.
9. Stiver SI, Wintermark M, Manley GT. Motor trephine syndrome: a mechanistic hypothesis. Acta neurochir Suppl 2008; 102: 273-7.

10. Suzuki N, Suzuki S, Iwabuchi T. Neurological improvement after cranioplasty. Analysis by dynamic CT scan. Acta Neurochir (Wien) 1993; 122: 49-53.

11. Segal DH, Oppenheim JS, Murovic JA. Neurological recovery after cranioplasty. Neurosurgery 1994; 34: 729-31. 7

12. Kuo JR, Wang CC, Chio CC, Cheng TJ. Neurological improvement after cranioplasty - analysis by transcranial doppler ultrasonography. J Clin Neurosci 2004; 11: 486-9.

13. Wee HY, Kuo JR. Never neglect the atmospheric pressure effect on a brain with a skull defect. Int Med Case Rep J 2014; 7: 67-9.

14. Winkler PA, Stummer W, Linke R, Krishnan KG, Tatsch K. Influence of cranioplasty on postural blood flow regulation, cerebrovascular reserve capacity, and cerebral glucose metabolism. J Neurosurg 2000; 93: 53-61.

15. Richaud J, Boetto S, Guell A, Lazorthes Y. Effects of cranioplasty on neurological function and cerebral blood flow. Neurochirurgie 1985; 31: 183-8.

16. Morgalla MH, Will BE, Roser F, Tatagiba M. Do long-term results justify decompressive craniectomy after severe traumatic brain injury? J Neurosurg 2008; 109: 685-90.

17. Chibbaro S, Vallee F, Beccaria K, Poczos P, Makiese O, Fricia M, et al. The impact of early cranioplasty on cerebral blood flow and its correlation with neurological and cognitive outcome. Prospective multi-centre study on 24 patients. Rev Neurol (Paris) 2013; 169: 240-8.

18. Yamaura A, Sato M, Meguro K, Nakamura T, Uemura K. Cranioplasty following decompressive craniectomy-analysis of 300 cases (author's transl). No Shinkei Geka 1977; 5: 345-53.

19. Dujovny M, Aviles A, Agner C, Fernandez P, Charbel FT. Cranioplasty: cosmetic or therapeutic? Surg Neurol 1997; 47: 238-41.

20. Stula D. The problem of the "sinking skin-flap syndrome" in cranioplasty. J Maxillofac Surg 1982; 10: 142-5.

21. Yoshida K, Furuse M, Izawa A, Iizima N, Kuchiwaki H, Inao S. Dynamics of cerebral blood flow and metabolism in patients with cranioplasty as evaluated by 133Xe CT and 31P magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 1996; 61: 166-71.

22. Sakamoto S, Eguchi K, Kiura Y, Arita K, Kurisu K. CT perfusion imaging in the syndrome of the sinking skin flap before and after cranioplasty. Clin Neurol Neurosurg 2006; 108: 583-5.

23. Mah JK, Kass RA. The impact of cranioplasty on cerebral blood flow and its correlation with clinical outcome in patients underwent decompressive craniectomy. Asian J Neurosurg 2016;11:15-21.

24. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. J Neurosurg 1997; 86: 241-51.

25. Langfitt TW, Obrist WD, Alavi A, Grossman RI, Zimmerman R, Jaggi J, et al. Computerized tomography, magnetic resonance imaging, and positron emission tomography in the study of brain trauma. Preliminary observations. J Neurosurg 1986; 64: 760-7.

26. Nasu S, Hata T, Nakajima T, Suzuki Y. Evaluation of 18F-FDG PET in acute ischemic stroke: assessment of hyper accumulation around the lesion. Kaku Igaku 2002; 39: 103-10.

27. Kuhl DE, Phelps ME, Kowell AP, Metter EJ, Selin C, Winter J. Effects of stroke on local cerebral metabolism and perfusion: mapping by emission computed tomography of 18FDG and 13NH3. Ann Neurol 1980; 8: 47-60.

28. Schallert T, Hernandez TD, Barth TM. Recovery of function after brain damage: severe and chronic disruption by diazepam. Brain Res 1986; 379: 104-11.

29. Hernandez TD, Holling LC. Disruption of behavioral recovery by the anti-convulsant phenobarbital. Brain Res 1994; 635: 300-6.

30. Melamed E. Reactive hyperglycaemia in patients with acute stroke. J Neurol Sci 1976; 29: 267-75.

İstanbul Med J 2019; 20(3): 198-201
DOI: 10.4274/imj.galenos.2018.36043

Prognosis in Patients with Melanosis Coli; A Prospective Study

Melanozis Kolili Hastalarda Prognoz; Prospektif Bir Çalışma

Aylin Hande Gökçe[1], Feridun Suat Gökçe[2]

[1]İstanbul Medicine Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]Istanbul Balıklı Rum Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: Melanosis coli is a benign lesion associated with the overuse of laxatives containing anthraquinone. The aim of this study is to determine whether melanosis recovers after the discontinuation of laxatives and whether this condition is associated with a higher incidence of colon polyps or cancer compared to the general population.

Methods: Patients with confirmed melanosis coli were performed a repeat colonoscopy and biopsy 2 years later and their histopathological examination results were compared. Data on age, sex, the use of any medicinal laxative or herbals, the presence of findings after the discontinuation of laxatives, constipation, colon polyp, and the relationship with colon cancer were examined. The similarity of segments and their relationships in the first and control colonoscopies were investigated in cases detected to have melanosis coli.

Results: All 104 patients included in the study were suffering from constipation. While the number of patients using laxatives or herbal tea was initially 96, it was 24 at the time of follow-up colonoscopy. Although the majority of subjects had discontinued laxatives, histological findings of melanosis coli persisted in 88 of 104 subjects. Mostly descending colon and rectum were involved.

Conclusion: It is thought that the findings of melanosis coli disappear in about 6 months following the discontinuation of laxative drugs and herbal teas. However, it was detected in our series that while the macroscopic findings were mostly healed even in the follow-up after two years, microscopic findings of melanosis coli continued to remain. No relationship was found between melanosis coli and the development of colon cancer and polyp. In the present study, it was aimed to emphasize that melanosis coli's becoming chronic and its creating a predisposition to colon cancer should be investigated with longer follow-ups and some herbal teas may cause a long-term change in the colon mucosa.

Keywords: Melanosis coli, constipation, colonoscopy, hyperpigmentation

ÖZ

Amaç: Melanozis koli antrakinon içeren laksatiflerin fazla kullanımına bağlı olarak ortaya çıkan benign bir lezyon olarak düşünülür. Çalışmanın amacı melanozis kolili hastaların laksatiflerle ilişkisi, laksatif bırakılınca iyileşip iyileşmediği, normal popülasyona göre kolon polibi ve kolon kanseri ile ilişkili olup olmadığını saptamaktır.

Yöntemler: Kolonoskopi ile melanozis koli saptanan olgulara 2 yıl sonra kontrol kolonoskopisi yapıldı ve histopatoloji sonuçları karşılaştırıldı. Olguların yaşları, cinsiyetleri, laksatif ilaç veya bitki çayı kullanıp kullanmadığı, laksatif kullananların bıraktıktan sonra bulgularının devam edip etmediği, konstipasyon, kolon polibi ve kolon kanseriyle ilişki olup olmadığı araştırıldı. Melanozis koli saptanan olguların ilk ve kontrol kolonoskopilerindeki segmentlerin benzerliği ve ilişkisi araştırıldı.

Bulgular: Çalışmaya alınan 104 olgunun hepsinde konstipasyon mevcuttu. Laksatif ilaç veya çay kullanan olgu sayısı ilk başta 96 idi, kontrolde ise 24 hasta laksatif ilaç veya çay kullanmaya devam ediyordu. Olguların büyük çoğunluğu laksatif kullanımını bıraktığı halde 104 olgunun 88'inde histopatolojik olarak melanozis koli bulguları devam etmekteydi. Çalışmamızda en sık sol kolon ve rektum tutulmuştu.

Sonuç: Melanosis coli bulgularının laksatif ilaç veya çayların kullanımı bırakıldıktan yaklaşık 6 ay sonra düzeldiği düşünülmektedir. Fakat bizim serimizde 2 yıl sonraki takipte bile büyük çoğunluğunda makroskopik bulgular düzeldiği halde mikroskobik olarak melanosis koli bulgularının devam ettiği saptandı. Çalışmada melanosis koliyle kolon kanseri ve kolon polibi arasında bir ilişki saptanmadı. Melanosis kolinin kronikleşmesinin ve kolon kanserine yatkınlık oluşturup oluşturmamasının daha uzun takiplerle araştırılması gerektiğini ve bazı bitki çaylarının kolon mukozasına uzun süreli değişikliğe yol açabileceğini vurgulamak istedik.

Anahtar Kelimeler: Melanozis koli, konstipasyon, kolonoskopi, hiperpigmentasyon

Address for Correspondence/Yazışma Adresi: Aylin Hande Gökçe MD, İstanbul Medicine Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 505 250 20 79 **E-mail:** ahgokce79@hotmail.com **ORCID ID:** orcid.org/0000-0003-1908-2889

Cite this article as/Atıf: Gökçe AH, Gökçe FS. Prognosis in Patients with Melanosis Coli; A Prospective Study. İstanbul Med J 2019; 20(3): 198-201.

Received/Geliş Tarihi: 26.11.2018
Accepted/Kabul Tarihi: 26.12.2018

Introduction

Melanosis coli is a condition characterized by the dark pigmentation of the mucosal lining of the large intestine, resulting from chronic use of laxatives containing anthraquinone. This condition may occur within a few months following the use of laxatives and may gradually disappear within a few months following the discontinuation of laxatives (1,2). Overuse of laxatives, notably the ones containing anthraquinone laxative, and overuse of herbal teas, including aloe vera, meadow saffron, cockspur-hawthorn, and buckthorn, have been implicated in the development of melanosis coli. The mechanism of action of this group of drugs and herbal teas is to increase the accumulation of fluid and electrolytes in the distal ileum. Herbal laxatives containing anthraquinone cause a damage in the epithelial cells and lead to changes in absorption, secretion and motility (3,4).

The pigment deposits in melanosis coli consist of hemosiderin, lipofuscin, lipofuscin-like pigment and ferrous sulfate rather than melanin (3,4). The diagnosis of melanosis coli is made based on the histological examination of biopsy specimens collected from suspicious segments during colonoscopy or biopsy specimens taken for any other reasons (Figure 1). Pigment deposits are observed in macrophages located in lamina propria of the large intestine while pigments are unequally distributed across different segments of the large intestine and melanosis affects more frequently the cecum and proximal colon (5,6).

Although melanosis coli has been considered as a benign condition, it remains unknown whether melanosis increases the risk for colorectal cancer. Melanosis begins 4 months after the initiation of anthraquinone laxatives. Melanosis has been usually reported to be a benign condition and resolves within one year after the discontinuation of laxatives (4,7). In this study, we aimed to assess follow-up clinical and colonoscopy findings in comparison with initial findings in patients diagnosed with melanosis coli.

Methods

This study was designed to prospectively assess patients diagnosed with melanosis coli following the histopathological examination of biopsy specimens taken from the areas of macroscopic hyperpigmentation which were detected during colonoscopy that was performed in our clinic. Ethics approval for this study was obtained from the İstanbul Training and Research Hospital Ethics Committee (KAEK-50-1267). All participants provided their informed consent. Patients who had bowel movements 3 times or less per week were considered as constipated. Data on the age and sex were collected and study subjects were asked if they were using any medicinal laxative or herbal teas and whether they had a history of constipation or colon polyps or colon cancer and they were screened for such lesions via colonoscopy. Colonoscopy findings of these patients were assessed to detect whether colon segments found to be involved in melanosis during the follow-up colonoscopy were similar or connected to those detected during the initial colonoscopy.

Statistical Analysis

Data were analyzed using w-2 test in SPSS version 16 software. Continuous variables were presented as mean ± standard deviation, whereas categorical variables were shown as percentages. A p value less than 0.05 indicated statistical significance.

Results

During the above-mentioned period, a total of 3416 colonoscopy procedures were performed and 112 patients were diagnosed with melanosis coli (Figures 1, 2). Eight of these patients died of unrelated causes during the follow-up, therefore, a follow-up colonoscopy procedure could not be performed. Seventy-two of these patients were female (64.3%), and 40 patients were male (35.7%). The age range of study patients varied from 29 to 82 years (the mean age 56.1±17.8 years). All patients were experiencing constipation. Benign colon polyps were removed in 16 subjects (14.3%) during the initial colonoscopy. The descending colon was affected by melanosis in 64 patients (57.1%) while ascending colon involvement was detected in 16 patients (14.3%) and melanosis affected the colon in whole in 32 patients (28.6%) (Table 1).

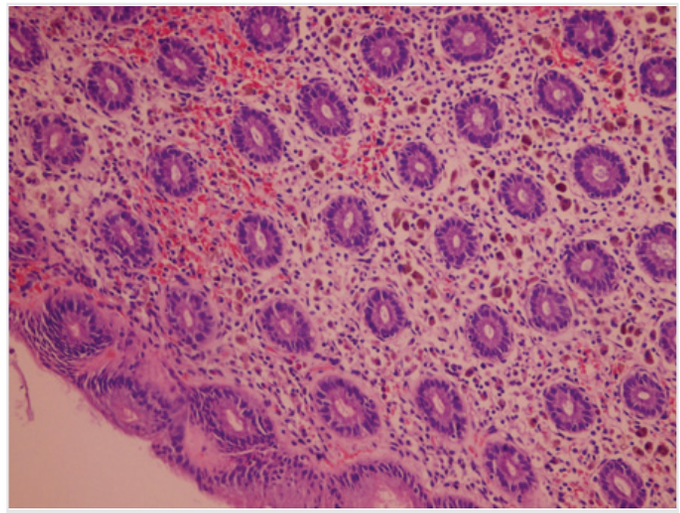


Figure 1. Microscopic appearance of melanosis coli with hematoxylin eosin enlargement of 100 dyes

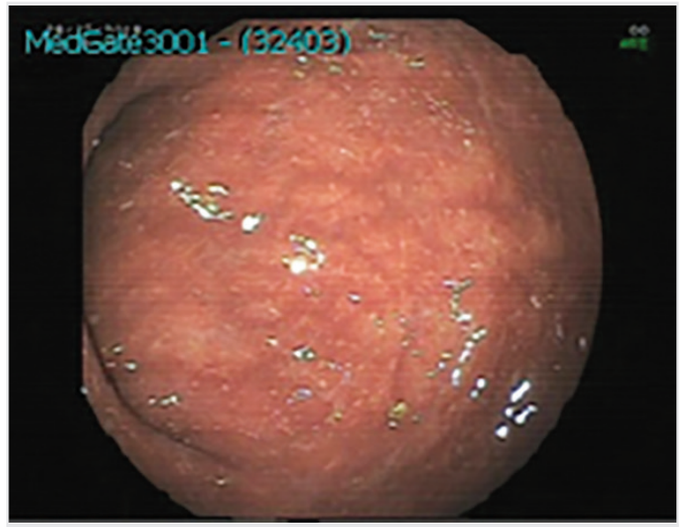


Figure 2. Macroscopic appearance of melanosis coli during colonoscopy

Table 1. Locations of melanosis coli in the initial colonoscopy and follow-up colonoscopy

	Location (at the diagnosis) n=112	Location (follow-up) n=104	p
None	0	16 (15.4%)	-
Ascending colon	16 (14.3%)	16 (15.4%)	$\chi2$=0.052, p=0.82
Descending colon	64 (57.1%)	48 (46.1%)	$\chi2$=1.107, p=0.293
Entire colon	32 (28.6%)	24 (23.1%)	$\chi2$=0.848, p=0.357

Table 2. The use of laxatives and herbal teas at the diagnosis and during the follow-up

	At the diagnosis, n=112	During the follow-up, n=104
None	8 (7.1%)	80 (76.9%)
Use of laxatives	24 (21.4%)	16 (15.4%)
Herbal tea consumption	80 (71.4%)	8 (7.7%)

Eighty of the patients diagnosed with melanosis coli were drinking herbal teas (71.4%) and 24 patients were receiving laxatives (21.4%). Only eight patients (7.1%) had received neither laxatives nor herbal tea (Table 2).

Patients with melanosis coli were advised not to receive laxatives or herbal teas. These 104 patients underwent a follow-up colonoscopy within two years after the initial colonoscopy. Follow-up colonoscopy procedures did not reveal any polyps or malignancy in these patients. At the time of follow-up colonoscopy, the age of study subjects varied from 30 to 83 years (the mean age: 56.1±17.1 years). All study subjects except eight (7.7%) were experiencing constipation at the time of follow-up colonoscopy. Eighty study subjects (76.9%) had stopped using laxatives and herbal teas while 16 study subjects (15.4%) were still using laxatives and eight subject (7.7%) had not stopped drinking herbal tea. Follow-up colonoscopy revealed melanosis in the descending colon in 48 patients (46.1%), in the entire colon in 24 subjects (23.1%) and in the ascending colon in 16 subjects (15.4%) while melanosis coli disappeared only in 16 subjects (15.4%). The last 16 study subjects were the ones who had discontinued laxatives and herbal teas and had ascending colon involvement at the time of the initial colonoscopy. No statistically significant differences were found between the initial colonoscopy and follow-up colonoscopy in terms of the location of melanosis.

Discussion

Melanosis coli was first defined by Andral and Cruveilhier in 1830 as black discoloration of the mucosal lining of the colon detected during the autopsy of a patient with chronic diarrhea. In 1858, Virchow used the term “melanosis” to describe this finding.

The association between melanosis coli and constipation and the use of laxatives was first reported by Freeman (8) in 1829. Our study provided further evidence for the presence of such association as all subjects were constipated and 104 of 112 subjects were receiving laxatives or herbal teas. The cecum and ascending colon have been reported as the most common locations of melanosis in several publications (9,10). In our study, the descending colon and rectum were predominantly involved in melanosis.

In a study conducted by Liu et al. (11), any association was not found between colon polyps and melanosis coli. In our study, benign colon polyps were detected only in 16 patients (14.3%) with melanosis coli during the initial colonoscopy. Melanosis persisted in most of the subjects (84.6%) in this study, as detected by follow-up colonoscopy procedures performed 2 years later, while none of the subjects developed colon polyps during the follow-up period. The prevalence of colon polyps in our study patients was found to be similar to the prevalence in age-matched general population.

In a prospective study, Siegers et al. (12) found associations between colon cancer and melanosis coli in patients who were suffering from constipation and using anthraquinone laxatives. In another study, a retrospective analysis revealed preexisting melanosis coli in 11.9% of those with colon cancer (13). That study reported an association between melanosis coli and colon cancer. In another study presented by Speare, no association was found between melanosis coli and colon cancer and the author declared that melanosis coli might be reversible upon the discontinuation of laxatives (14). In line with this study, neither initial nor follow-up colonoscopy procedures revealed any evidence of colon cancer.

There are several publications reporting that the incidence of melanosis coli increases with age and this condition has been detected only in constipated patients over the age of 50 years and using anthraquinone laxatives (12,15). Although the mean age of study subjects was 56.1 years, the youngest study subject was a 29-year-old patient in our study. We would like to emphasize that melanosis coli may also be seen in young people although it is usually diagnosed in the elderly.

Higher incidence rates have been reported among women in the study conducted by Siegers (12) as well as in studies conducted in Mayo Clinic (15). This difference has been explained by higher prevalence of constipation among women, which is associated with an increased use of anthraquinone laxatives compared to a male population. However, any significant gender difference was not detected in the incidence of melanosis coli in the studies conducted by Speare (16). A female dominance (64.3%) was observed in this study.

Conclusion

While melanosis coli has been reported to be a reversible condition by several studies, clinical and histological findings have persisted in our study subjects. Considering studies reporting a potential association between colon cancer and melanosis coli, the presence of melanosis coli may be underestimated, and we believe that these patients should be monitored. Although constipation underlies melanosis coli and anthraquinone laxatives used in the treatment of constipation have been implicated in the development of melanosis coli, one should keep in mind that herbal tea consumption is another etiological factor. Many publications reported anthraquinone-related melanosis while our literature search did not reveal any studies on a possible association between melanosis coli and herbal teas containing anthraquinone. We would like to emphasize that increased herbal tea consumption

in the society may increase the prevalence of melanosis coli and even macroscopic evidence of melanosis coli may disappear and histopathological findings may persist after stopping drinking herbal teas. Considering reports on potential associations between melanosis coli and colon cancer, we believe that consideration should be given on the consumption of herbal teas and drugs containing anthraquinone hence public awareness and even awareness among healthcare professionals about melanosis coli should be raised.

Ethics Committee Approval: Ethics approval for this study was obtained from the İstanbul Training and Research Hospital Ethics Committee (KAEK-50-1267).

Informed Consent: All participants provided their informed consent.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - A.H.G., F.S.G.; Design - A.H.G., F.S.G.; Supervision - A.H.G., F.S.G.; Resources - A.H.G., F.S.G.; Data Collection and/or Processing - A.H.G., F.S.G.; Analysis and/or Interpretation - A.H.G., F.S.G.; Literature Search - A.H.G., F.S.G.; Writing Manuscript - A.H.G., F.S.G.; Critical Review - A.H.G., F.S.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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

References

1. Ahmed S, Gunaratnam NT. Images in clinical medicine. Melanosis Coli. N Engl J Med 2003; 349: 1349.
2. Li D, Browne LW, Ladabaum U. Melanosis coli. Clin Gastroenterol Hepatol 2009; 7: 20.
3. Batistatou A, Panelos J, Agnantis NJ. Melanosis intestine: case report. Diagn Pathol 2006; 31: 1-3.
4. Freeman HJ. "Melanosis" in the small and large intestine. World J Gastroenterol 2008; 14: 4296-9.
5. Mengs U, Rudolph RL. Light and electron-microscopic changes in the colon of the guinea pig after treatment with anthranoid and nonanthranoid laxatives. Pharmacology 1993; 47(Suppl 1): 172-7.
6. Van Gorkom BA, de Vries EG, Karrenbeld A, Kleibeulier JH. Rewiew article: Anthranoid laxatives and their potential carcinogenic effects. Aliment Pharmacol Ther 1999; 13: 443-52.
7. Badiali D, Marcheggiano A, Pallone F, Paoluzi P, Bausano G, Iannoni C, et al. Melanosis of the rectum in patients with chronic constipation. Dis Colon Rectum 1985; 28: 241-5.
8. Freeman HJ. "Melanosis" in the small and large intestine. World J Gastroenterol 2008; 14: 4296-9.
9. Park HJ, Kamm MA, Abbasi AM, Talbot IC. Immunohistochemical study of the colonic muscle and innervation in idiopathic chronic constipation. Dis Colon Rectum 1995; 38: 509-13.
10. López-Vicente J, Lumbreras M. Melanosis coli secondary to chronic ingest of chitticum bark. Med Clin (Barc) 2011; 137: 430.
11. Liu ZH, Foo DCC, Law WL, Chan FSY, Fan JKM, Peng JS. Melanosis coli: Harmless pigmentation? A case-control retrospective study of 657 cases. Plos One 2017; 12: e0186668.
12. Siegers CP, von Hertzberg-Lottin E, Otte M, Schneider B. Anthranoid laxative abuse: A risk for colorectal cancer? Gut 1993; 34: 1099-101.
13. Biernacka-Wawrzonek D, Stepka M, Tomaszewska A, Ehrmann-Jósko A, Chojnowska N, Zemlak M, et al. Melanosis coli in patients with colon cancer. Prz Gastroenterol 2017; 12: 22-7.
14. Speare GS. Melanosis coli. Experimental observations on its production and elimination in twenty-three cases. Am J Surg 1951; 82: 631-6.
15. Koskela E, Kulju T, Collan Y. Melanosis coli. Prevalence, distribution, and histologic features in 200 consecutive autopsies at Kuopio University Central Hospital. Dis Colon Rectum 1989; 32: 235-9.
16. Li XA, Zhou Y, Zhou SX, Liu HR, Xu JM, Gao L, et al. Histopathology of melanosis coli and determination of its associated genes by comparative analysis of expression microarrays. Mol Med Rep 2015; 12: 5807-15.

İstanbul Med J 2019; 20(3): 202–7
DOI: 10.4274/imj.galenos.2018.82195

Impact of the Functional VNTR Variants of the Interleukin-1 Receptor Antagonist and Interleukin-4 Genes on Oral Squamous Cell Carcinoma

Interlökin-1 Reseptörü Antagonisti ve Interlökin-4 Gen Fonksiyonel VNTR Varyantlarının Oral Skuamöz Hücreli Karsinoma Etkisi

Özge Gümüşay[1], Ayşe Feyda Nursal[2], Serbülent Yiğit[3], Akın Tekcan[4], Tuba Öz[3]

[1]Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Medical Oncology, Tokat, Turkey
[2]T.C. Hitit University, Faculty of Medicine, Department of Medical Genetics, Çorum, Turkey
[3]Tokat Gaziosmanpaşa University, Faculty of Medicine, Department of Medical Biology, Tokat, Turkey
[4]Kırşehir Ahi Evran University, Faculty of Medicine, Department of Medical Biology, Kırşehir, Turkey

ABSTRACT

Introduction: It has been shown that the host immune response and chronic inflammation could play a role as important risk factors for cancer. Oral squamous cell carcinoma (OSCC) is a common cancer worldwide. In this study, we aimed to evaluate the impact of interleukin-1 receptor antagonist (IL-1RA) and IL-4 variable number tandem repeat (VNTR) polymorphisms on OSCC susceptibility in a Turkish population.

Methods: Study subjects comprised of 36 OSCC patients and 100 healthy controls. Genotyping of the IL-1RA VNTR (rs2234663) and IL-4 VNTR (rs79071878) polymorphisms were analyzed by polymerase chain reaction.

Results: The frequency of IL-1RA VNTR 1/2+2/2 genotypes increased in the patients than healthy controls while IL-1RA VNTR 1/1 genotype was higher in the control group than in the patients (p=0.002). The subjects carrying IL-1RA VNTR 1/2+2/2 genotypes showed a 12.011-fold increased risk of susceptibility to OSCC. IL-1RA VNTR allele 1 was higher in the control group than the patient group while IL-1RA VNTR allele 2 was higher in the patient group than the control group (respectively, p=0.000, p=0.000). The subjects carrying IL-1RA VNTR allele 2 showed a 2.609-fold increased risk of susceptibility to OSCC. The IL-4 VNTR P1/P1 and P1/P2 genotype frequencies were higher in the patient group compared to the control group (p=0.039). IL-4 VNTR P1 allele was higher in the patients compared to the controls (p=0.030).

Conclusion: The significant association between the functional VNTR polymorphisms of IL-1RA/IL-4 genes and OSCC suspectibility in a Turkish population confirmed a role of altered inflammatory process in OSCC pathogenesis.

Keywords: Oral squamous cell carcinoma, IL-1RA, IL-4, VNTR, polymorphism

ÖZ

Amaç: Konakçı immün cevabının ve kronik enflamasyonun kanser için önemli risk faktörleri olarak rol oynadığı gösterilmiştir. Oral skuamöz hücreli kanser (OSHK) tüm dünyada yaygın bir kanser türüdür. Bu çalışmada Türk toplumunda interlökin-1 reseptörü antagonisti (IL-1RA) ve IL-4 değişken sayılı ardışık tekrar (VNTR) polimorfizminin OSHK yatkınlığına olan etkisini incelemeyi amaçladık.

Yöntemler: Çalışma grubu 36 OSHK hastası ve 100 sağlıklı kontrolden oluşmaktadır. IL-1RA VNTR (rs2234663) ve IL-4 VNTR (rs79071878) polimorfizmlerinin genotiplemesi polimeraz zincirleme tepkimesi ile analiz edildi.

Bulgular: IL-1RA VNTR 1/1 genotipi kontrol grubunda hastalardan daha fazla iken IL-1RA VNTR 1/2+2/2 genotipleri hastalarda sağlıklı kontrollere göre artmıştı (p=0,002). IL-1RA VNTR 1/2+2/2 genotiplerini taşıyan kişiler OSHK'ye yatkınlık yönünden 12,011 kat fazla risk gösterdiler. IL-1RA VNTR allel 2 hasta grubunda kontrol grubundan daha fazla iken IL-1RA VNTR allel 1 kontrol grubunda hasta grubundan daha fazlaydı (sırasıyla, p=0,000, p=0,000). IL-1RA VNTR allel 2 taşıyan kişiler OSHK'ye yatkınlık yönünden 2,609 kat fazla risk gösterdiler. IL-4 VNTR P1/P1 ve P1/P2 genotip sıklığı hasta grubunda kontrol grubuna göre daha fazlaydı (p=0,039). IL-4 VNTR P1 alleli hastalarda kontrollere göre daha yüksekti (p=0,030).

Sonuç: Türk popülasyonundaki IL-1RA/IL-4 VNTR polimorfizmleri ve OSHK yatkınlığı arasındaki önemli ilişki OSHK etiyopatogenezinde değişen enflamatuvar işlevlerin rolü olduğunu doğrulamıştır.

Anahtar Kelimeler: Oral skuamöz hücreli karsinom, IL-1RA, IL-4, VNTR, polimorfizm

Address for Correspondence/Yazışma Adresi: Ayşe Feyda Nursal MD, T.C. Hitit University, Faculty of Medicine, Department of Medical Genetics, Çorum, Turkey
Phone: +90 364 222 11 00 **E-mail:** feyda.nursal@gmail.com **ORCID ID:** orcid.org/0000-0001-7639-1122

Cite this article as/Atıf: Gümüşay Ö, Nursal AF, Yiğit S, Tekcan A, Öz T. Impact of the Functional VNTR Variants of the IL-1RA and IL-4 Genes on Oral Squamous Cell Carcinoma. İstanbul Med J 2019; 20(3): 202-7.

Received/Geliş Tarihi: 20.09.2018
Accepted/Kabul Tarihi: 31.12.2018

Introduction

Oral cancer is among the most frequent cancers in the world. Its pathogenesis remains unclear. Oral squamous cell carcinoma (OSCC) originates from the squamous cells that cover the mouth mucosa and is a common type of oral cancer, responsible for more than 90% of cases (1). Risk factors for OSCC include smoking, alcohol use, and human papilloma virus infections (2), however, molecular mechanisms associated with OSCC are still being under research, and genetic predisposition is gaining interest of the scientists.

In recent years, the role of leucocytes and their relevant cytokines in inflammatory mechanisms and malignant transformation has been well investigated and documented by many studies. The interleukin-1 receptor antagonist (IL-1RA) is a significant innate cytokine that hinders IL-1 activity by binding to the IL-1 receptors without causing any signal transmission (3). The gene encoding IL-1RA (IL-1RA, also called IL-1RN) is found in the chromosome 2q14 and there is an identified variant occurring as a result of variable numbers of an 86-bp tandem repeat (VNTR) (rs2234663) in intron 2 (4). This variant causes the presence of five alleles, each linked with a distinct to a distinct number of repeats. The allele 2 of IL-1RA VNTR variant was found to be related to elevated production of the IL-1β *in vitro* (5).

The human IL-4 is a cytokine synthesized in CD4+Th2 cells, basophils and mast cells, which has a role in the modulation of the humoral immune response (6). IL-4 also interferes with the secretion of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), IL-6 and IL-1. It can also stimulate the production and secretion of anti-inflammatory factors including IL-1RA (7). The gene encoding IL-4 is found in the chromosome 5q31.1 and there is a 70 bp VNTR (rs79071878) variant in its third intron that might alter the expression of *IL-4* gene; with the P1 allele increasing IL-4 expression compared to the P2 allele (7). Numerous genetic susceptibility research has been done to examine the relations between the IL1-RA and IL-4 VNTR variants and different types of cancers, but results were inconsistent. Considering the importance of IL-1RA and IL-4 cytokines in inflammatory disorders, in this study, our purpose was to evaluate the possible association between IL-1RA/IL-4 VNTR variants and an increased risk of potential OSCC in a Turkish population.

Methods

Study population

The study included 36 Turkish patients with histologic diagnosed OSCC, who were recruited at the Department of Medical Oncology, Gaziosmanpasa University, Faculty of Medicine, Turkey. One hundred healthy participants with no medical history of cancer were enrolled in the control group. Patients who had oral precancerous diseases including oral submucous fibrosis, leukoplakia, erythroplakia, and verrucous hyperplasia were excluded from the control group. All subjects had come from the same geographic area. Tumor degree was assessed by a pathologist using the AJCC classification. Informed consent was obtained from all participants before they were enrolled in this study. The study was carried out in compliance with the Declaration of Helsinki and was approved by the Hitit University Faculty of Medicine Regional Ethical Committee (2017/200).

Genotyping

For all participants, peripheral blood was collected into tubes with EDTA as an anticoagulant. Genomic DNA was extracted from the samples by the DNA extraction kit (Sigma-Aldrich, St. Louis, MI, USA) and was kept at -20 °C until investigation. The VNTR polymorphisms in *IL-1RA* and *IL-4* genes were examined by the polymerase chain reaction (PCR) method described previously, respectively (4,8). The identification of IL-1RA VNTR polymorphism was done by the PCR technique using the forward 5′-CTC AGC AAC ACT CCT AT-3′ and reverse 5′-TTC CAC CAC ATG GAA C-3′ primers following these conditions: first, an initial denaturalization at 94 °C for 4 minutes; second, 30 cycles at 94 °C, 51 °C for 30 seconds, and 72 °C for 45 seconds at each temperature; and third, final extension at 72 °C for 5 minutes. PCR products were separated by electrophoresis within a 3% agarose gel and visualized by ethidium bromide staining. Five different alleles of IL-1RA were identified as follows: allele 1, four repeats (410 bp); allele 2, two repeats (240 bp); allele 3, five repeats (500 bp); allele 4, three repeats (325 bp), and allele 5, six repeats (595 bp).

For **IL-4**, amplification was done using the forward 5′AGG CTG AAA GGG GGA AAG C-3′ and reverse 5′-CTG TTC ACC TCA ACT GCT CC-3′ primers, with initial denaturation at 95 °C for 5 minutes, 30 cycles of denaturation at 94 °C for 30 seconds, annealing at 58 °C for 45 seconds, extension at 72 °C for 1 minutes and final extension at 72 °C for 10 minutes. PCR was done in a 25 µl reaction mixture containing 50 ng DNA, 0.8 µM of each primer, 200 µM of each dNTP, 2.5 mM MgCl, 1.5 units Taq polymerase, 2.5 µl 10×KCl buffer. The resultant PCR products were examined by gel electrophoresis. The PCR products were of 183 bp for the P1 allele and 253 bp for the P2 allele.

Statistical Analysis

The SPSS software version 20.0 (Chicago, IL, USA) and OpenEpi ver. 3.01 was used for all statistical analyses. Continuous data were presented as mean ± standard deviation (SD) and minmax. Chi-square test was used to determine the significance of differences in allele frequency and genotype distributions between the groups. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated. A p value of less than 0.05 was considered statistically significant.

Results

This study included 36 OSCC patients (22 males and 14 females; mean age ± SD, 63.94±13.96 years) and 100 healthy unrelated subjects as the control group (65 males and 35 females; mean age ± SD, 57.31±11.85 years). The baseline demographic and clinical features of the studied cases were summarized in Table 1.

IL-1RA genotyping

The allelic and genotype frequencies of the IL-1RA VNTR polymorphism among the patients with OSCC and the healthy control subjects are summarized in Table 2. The significant difference between patients and controls was observed for both genotype and allele frequencies of IL-1RA VNTR polymorphism. In our population, we did not found individuals carrying the following genotypes: 1/4, 1/5, 2/3, 2/4, 2/5, 3/4, 3/5, 4/4, 4/5 and 5/5. The genotypic frequencies of the IL-1RA VNTR polymorphism

Table 1. Baseline clinical and demographics features of the patients with OSCC		
Characteristics	**Controls (n=100)**	**Patients (n=36)**
Gender, male/female, n (%)	65/35 (65.0/35.0)	22/14 (61.1/38.9)
Age, mean ± SD, years	57.31±11.85	63.94±13.96
Smoking	**-**	**-**
Yes, n (%)	-	5 (13.9)
No, n (%)	-	26 (72.2)
Ex-smoking, n (%)	-	5 (13.9)
Smoking onset age, Yes/No, n (%)	**-**	**-**
Smoking duration	**-**	**-**
10-20 years, n (%)	-	2 (5.6)
20-30 years, n (%)	-	5 (13.9)
>30 years, n (%)	-	3 (8.3)
Daily cigarette consumption		**-**
One package, n (%)	-	3 (8.3)
> One package, n (%)		6 (16.7)
Alcohol consumption, Yes/No, n (%)	-	6/30 (16.7/83.3)
Frequency of alcohol consumption		
Daily, n (%)	-	4 (11.1)
Social drinker, n (%)	-	2 (5.6)
Family history, Yes/No, n (%)	-	29/7 (80.6/19.4)
Response to treatment, Yes/No, n (%)	-	27/9 (75.0/25.0)
Patients status		
Alive, n (%)	-	29 (80.6)
Exitus, n (%)	-	7 (19.4)
Disease State		
Complete response, n (%)	-	26 (72.2)
Stable disease, n (%)	-	1 (2.8)
Metastatic disease, n (%)	-	9 (25.0)
Disease area		
Intra-oral, n (%)	-	3 (8.3)
Floor of the mouth, n (%)	-	2 (5.5)
Buccal, n (%)	-	1 (2.8)
Roof of the mouth, n (%)	-	2 (5.5)
Tongue, n (%)	-	9 (25)
Lip, n (%)	**-**	**16 (44.4)**
Oral mucosa, n (%)	-	1 (2.8)
Tonsil, n (%)	**-**	**1 (2.8)**
Cheek mucosa, n (%)	-	1 (2.8)

SD: Standard Deviation, OSCC: oral squamous cell carcinoma

in patients were as follows: 8 individuals (22.22%) had 1/1 genotype, 26 (72.22%) had 1/2+2/2 genotype, and 2 (5.56%) had 1/3+3/3 genotype. In the control group, the genotypic frequencies of the VNTR IL-1RA polymorphism were as follows: 54 individuals (54%) had 1/1 genotype, 40 (40%) had 1/2+2/2 genotype, and 6 (6%) had 1/3+1/3 genotype. The frequencies of IL-1RA 1/2+2/2 genotypes were more common in the patients than healthy controls while IL-1RA VNTR 1/1 genotype was higher in the control group than in the patients (p=0.002, X^2=12.011).

The allele frequencies of IL-1RA VNTR showed a significant difference between the patient and the control groups. IL-1RA VNTR allele 1 was higher in the control group than the patient group while IL-1RA VNTR allele 2 was higher in the patient group than the control group (p=0.000, OR: 0.369, 95% CI: 0.204-0.656; p=0.000, OR: 2.609, 95% CI: 1.503-4.580, respectively). The subjects carrying allele 2 showed a 2.609-fold increased risk of susceptibility to OSCC.

Table 2. Genotype and allele frequencies of IL-1RA VNTR variant in OSCC patients and controls					
Genotypes				**X^2**	**p**
IL-1RA	**1/1 n (%)**	**1/2+2/2 n (%)**	**1/3+3/3 n (%)**		
Patients (n=36)	8 (22.22)	26 (72.22)	2 (5.56)	**12.011**	**0.002**
Controls (n=100)	54 (54.00)	40 (40.00)	6 (6.00)		
Alleles					
	IL-1RA 1 (+/-)	**IL-1RA 2 (+/-)**	**IL-1RA 3 (+/-)**		
Patients	24/48 (33.33/66.67)	44/28 (61.11/38.89)	2/70 (2.78/97.22)		
Controls	113/87 (56.50/43.50)	75/125 (37.50/62.50)	12/188 (6.00/94.00)	-	
OR (CI 95%)	**0.369 (0.204-0.656)**	**2.609 (1.503-4.580)**	0.448 (0.066-1.833)		
p	**0.000**	**0.000**	>0.05		
The results that are statistically significant are typed in bold IL-1RA: OSCC: oral squamous cell carcinoma					

Table 3. Genotype and allele frequencies of IL-4 VNTR variant in OSCC patients and controls					
Gene	**OSCC patients, n=36 (%)**	**Controls, n=100 (%)**	**X^2**	**p**	**OR (CI 95%)**
IL-4 VNTR					
Genotypes					
P1/P1	1 (2.78)	0 (0.00)	**6.514**	**0.039**	**2.646 (1.13-6.10)**
P1/P2	10 (27.78)	14 (14.00)			
P2/P2	25 (69.44)	86 (86.00)			
Alleles					
P1	12 (16.67)	14 (7.00)		**0.030**	
P2	60 (83.33)	186 (93.00)			
The results that are statistically significant are typed in bold IL-4: OSCC: oral squamous cell carcinoma					

IL-4 genotyping

The allelic and genotype frequencies of the IL-4 VNTR polymorphism among the patients with OSCC and the healthy controls are shown in Table 3. The frequencies of P1/P1, P1/P2, and P2/P2 genotypes of IL-4 VNTR polymorphism in the control group were 0%, 14%, and 86%, respectively; and 2.78%, 27.78%, and 69.44% in OSCC patients, respectively. There was a significant difference in the distribution of both genotypic and allelic frequencies between OSCC patients and the control group. The IL-4 VNTR P1/P1 and P1/P2 genotype frequencies were higher in the patient group compared to the control group while the P2/P2 genotype frequency was higher in the controls compared to the patients (p=0.039, X^2=6.514) (Table 3). IL-4 VNTR P1 allele was higher in the patients compared to the controls while IL-4 VNTR P2 allele was higher in the control group than the patients (p=0.030; OR: 2.646, 95% Cl: 1.13-6.10).

Discussion

In the present study, we scrutinized whether functional VNTR polymorphisms of the IL-1RA and IL-4 were associated with OSCC in a Turkish population. OSCC is an aggressive epithelial cancer. Despite early diagnosis and several treatments, the overall survival rate of patients with OSCC is still low (9). The immune response to inflammation is commonly involved in the cancer pathogenesis. Genetic changes also take place in the inflammatory response that could be linked with the risk of several cancers, including the OSCC. Functional DNA polymorphisms affecting gene expression of inflammatory molecules were reported to predispose the individual to disease and worsen the prognosis. Studies suggest that serum levels of inflammatory cytokines (including TNF-α and TNF-β (TNF-α and TNF-β), IL-6, IL-8) and anti-inflammatory cytokines (such as IL-10) are likely to be associated with carcinogenesis via multiple and usually controversial pathways, thus they may have a prognostic importance in OSCC and other cancer types (10-12).

IL-1RA is a crucial immunologic modulator and its expression inhibits pro-inflammatory signals from cellular damages during wide immunologic responses (3). In intron 2 of the *IL-1RA* gene, a variant due to the presence of variable numbers of an 86-bp VNTR was described. Although this IL-1RA VNTR-polymorphism is found in intron 2, it is probably responsible for a change in IL-1RA synthesis (13). The number of repeats, present in intron 2 of the *IL-1RA* gene, may manifest a functional role as it is thought that each repeat has considerable number of binding sites for transcription factors. Thus, a higher amount number of repeats would result in a higher transcriptional activity. IL-1RA alleles 1-5 contain 4 repeats, 2 repeats, 5 repeats, 3 repeats, and 6 repeats, respectively. The role of IL-1RA VNTR polymorphism has been investigated for years in the development of inflammatory diseases. Actually, some studies reported different relations of IL-1RA VNTR alleles with the occurrence of some cancers, including gastric (14),

esophageal (15), bladder (16), breast (17), colorectal (18), lung (19), brain (20), and nasopharyngeal (21). In a meta-analysis evaluating the relationship between IL-1RA VNTR variant and cancer, Zhang et al. (22) suggested that the IL1-RA VNTR variant might play a role in the genetic susceptibility to gastric cancer. Shiiba et al. (23) reported that expression of IL-1RA mRNA was significantly downregulated in OSCCs compared to normal tissues. Also, they demonstrated that IL-1RA expression level was lower in the oral premalignant lesion cases with severe dysplasia compared to those with mild/moderate dysplasia. Gupta et al. (24) reported that the percentage of IL-1RA I/2 individuals was higher in patients with OSCC than controls. Additionally, in carriage rate analysis, they reported that 2 allele of IL-1RA was to be significantly associated with OSCC. In the present study, statistical analysis of the IL-1RA allele and genotype frequencies in the OSCC patient group affirms the significance of the IL-1RA VNTR variant in OSCC in comparison to the control population. Despite the small sample size in our study, we found a significant association with OSCC and IL-1RA VNTR variant. IL-1RA VNTR 1/2+2/2 genotypes were more common in patients than healthy controls. The subjects carrying IL-1RA VNTR 1/2+2/2 genotypes showed a 12.011-fold increased risk of susceptibility to OSCC. (Table 2). IL-1RA VNTR allele 1, associated with high IL-1RA levels, was lower in patients. Conversely, IL-1RA allele 2, leading to an inadequate synthesis of IL-1RA protein or to an overproduction of IL-1β in response, was higher in the patient group (p=0.00). The subjects carrying allele 2 showed a 2.609-fold increased risk of susceptibility to OSCC. This condition could explain why carriage of IL-1RA allele 2 could influence an individual's susceptibility to OSCC. Our results were consistent with those reported by Gupta et al. (24).

IL-4 is a fundamental differentiation cytokine that stimulates development of Th2 subset of lymphocytes. This group of lymphocytes activates granulocytes and eosinophils and inhibits angiogenesis, making it crucial in surveillance and clearance of tumor cells (25). IL-4 is a strong modulator of anti-tumor immune responses with both tumor-promoting and tumor-inhibiting features because it acts as both immunosuppressive and anti-angiogenic factor (26). More and more epidemiologic studies have been performed to examine the impact of some IL-4 variants on human cancer risk. The IL-4 VNTR variant could change messenger ribonucleic acid splicing, which leads to different splice variants (27). There is strong evidence that the IL-4 intron 3 VNTR polymorphism might affect the synthesis of IL-4, with the P1 (two 70-bp repeats) allele enhancing IL-4 expression compared to P2 (three 70-bp repeats) allele (8). In a study, Duan et al. (25) evaluated eight eligible case-control studies including 1583 cases and 1638 controls with respect to the relationship of IL-4 VNTR variant and cancer. They indicated that the IL-4 VNTR RP2 allele was related to a reduced cancer risk compared to the RP1 allele. In subgroup analyses, they stratified by ethnicity and they found that there was evidence in the Asian population for an association between this variant and cancer risk. In a meta-analysis performed on 1896 patients and 2526 controls for IL-4 VNTR variant, Jia et al. (28) reported that IL-4 VNTR variant was associated with a higher risk of bladder cancer risk. Also, they showed that IL-4-33CT (rs2070874) variant was correlated with leukemia and oral carcinoma. Yang et al. (29) demonstrated that IL-4 VNTR P1/P1 geno type was associated with an increased risk of OSCC, particularly early-stage OSCC.

In the present study, IL-4 VNTR P1/P1 genotype and P1 allele, a higher IL-4 production allele and genotype, were more common in the patient group (p=0.039, p=0.030, respectively). The subjects carrying IL-4 VNTR P1/P1 genotype showed a 6.514-fold increased risk of susceptibility to OSCC (Table 3). Our findings are compatible with the potentially growth-promoting effect of IL-4 on OSCC.

Conclusion

The results of this study revealed an association of both IL-1RA and IL-4 VNTR polymorphisms with the occurrence of OSCC. To the best of our knowledge, this is the first research study to evaluate an association between IL-1RA and IL-4 VNTR polymorphisms and the risk of OSCC in a Turkish population. In conclusion, within the limitations of ethnicity, sample size and sample selection, the IL-1RA and IL-4 VNTR polymorphisms seem to be associated with developing OSCC.

Ethics Committee Approval: The study was carried out in compliance with the Declaration of Helsinki and was approved by the Hitit University Faculty of Medicine Regional Ethical Committee (decision no: 2017/200)

Informed Consent: Informed consent was obtained from all participants before they were enrolled in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Y., A.T.; Design - A.F.N., S.Y., T.Ö.; Supervision - A.F.N., S.Y., A.T.; Resources - Ö.G. S.Y., A.T.; Data Collection and/or Processing - Ö.G., A.T., T.Ö.; Analysis and/or Interpretation - S.Y., A.T., T.Ö.; Literature Search - A.F.N., A.T.; Writing Manuscript - Ö.G., A.F.N., S.Y.; Critical Review - A.F.N., S.Y., A.T.

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

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

References

1. Xie S, Luo C, Shan X, Zhao S, He J, Cai Z. CYP1A MspI polymorphism and the risk of oral squamous cell carcinoma: Evidence from a meta-analysis. Mol Clin Oncol 2016; 4: 660-6.
2. Gaur P, Mittal M, Mohanti B, Das S. Functional variants of IL-4 and IL-6 genes and risk of tobacco-related oral carcinoma in high-risk Asian Indians. Oral Dis 2011; 17: 720-6.
3. Arend WP. Interleukin 1 receptor antagonist. A new member of the interleukin 1 family. J Clin Invest 1991; 88: 1445-51.
4. Tarlow JK, Blakemore AI, Lennard A, Solari R, Hughes HN, Steinkasserer A, et al. Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. Hum Genet 1993; 91: 403-4.
5. Qian N, Chen X, Han S, Qiang F, Jin G, Zhou X, et al. Circulating IL-1β levels, polymorphisms of IL-1B, and risk of cervical cancer in Chinese women. J Cancer Res Clin Oncol 2010; 136: 709-16.
6. Jha AN, Singh VK, Kumari N, Singh A, Antony J, van Tong H, et al. IL-4 haplotype-590T, -34T and intron-3 VNTR R2 is associated with reduced malaria risk among ancestral indian tribal populations. PloS One 2012; 7: e48136.
7. Pérez-Suárez TG, Gutiérrez-Robledo LM, Ávila-Funes JA, Acosta JL, Escamilla-Tilch M, Padilla-Gutiérrez JR, et al. VNTR polymorphisms of the IL-4 and IL-1RN genes and their relationship with frailty syndrome in Mexican community-dwelling elderly. Aging Clin Exp Res 2016; 28: 823-32.

8. Mout R, Willemze R, Landegent JE. Repeat polymorphisms in the interleukin-4 gene (IL-4). Nucleic Acids Res 1991; 19: 3763.

9. Blatt S, Krüger M, Ziebart T, Sagheb K, Schiegnitz E, Goetze E, et al. Biomarkers in diagnosis and therapy of oral squamous cell carcinoma: A review of the literature. J Craniomaxillofac Surg 2017; 45: 722-30.

10. Jablonska E, Piotrowski L, Grabowska Z. Serum Levels of IL-1b, IL-6, TNFa, a, sTNF-RI and CRP in patients with oral cavity cancer. Pathol Oncol Res 1997; 3: 126-9.

11. Fujieda S, Sunaga H, Tsuzuki H, Fan GK, Saito H. IL-10 expression is associated with the expression of platelet-derived endothelial cell growth factor and prognosis in oral and oropharyngeal carcinoma. Cancer Lett 1999; 136: 1-9.

12. St John MA, Li Y, Zhou X, Denny P, Ho CM, Montemagno C, et al. Interleukin-6 and interleukin-8 as potential biomarkers for oral cavity and oropharyngeal squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2004; 130: 929-35.

13. Vijgen L, Van Gysel M, Rector A, Thoelen I, Esters N, Ceelen T, et al. Interleukin-1 receptor antagonist VNTR-polymorphism in inflammatory bowel disease. Genes Immun 2002; 3: 400-6.

14. Persson C, Canedo P, Machado JC, El-Omar E.M, Forman D. Polymorphisms in inflammatory response genes and their association with gastric cancer: a HuGE systematic review and meta-analyses. Am J Epidemiol 2011; 173: 259-70.

15. Upadhyay R, Jain M, Kumar S, Ghoshal UC, Mittal B. Potential influence of interleukin-1 haplotype IL-1 beta-511 *T-IL-1RN*1 in conferring low risk to middle third location of esophageal cancer: a case-control study. Hum Immunol 2008; 69: 179-86.

16. Vishnoi M, Pandey SN, Choudhuri G, Mittal B. IL-1 gene polymorphisms and genetic susceptibility of gallbladder cancer in a north Indian population. Cancer Genet Cytogenet 2008; 186: 63-8.

17. Lee KM, Park SK, Hamajima N, Tajima K, Choi JY, Noh DY, et al. Genetic polymorphisms of interleukin-1 beta (IL-1B) and IL-1 receptor antagonist (IL-1RN) and breast cancer risk in Korean women. Breast Cancer Res Treat 2006; 96: 197-202.

18. Viet HT, Wågsäter D, Hugander A, Dimberg J. Interleukin-1 receptor antagonist gene polymorphism in human colorectal cancer. Oncol Rep 2005; 14: 915-8.

19. Lind H, Zienolddiny S, Ryberg D, Skaug V, Phillips DH, Haugen A. Interleukin 1 receptor antagonist gene polymorphism and risk of lung cancer: a possible interaction with polymorphisms in the interleukin 1 beta gene. Lung Cancer 2005; 50: 285-90.

20. Badr El-Din NK, Settin A, Ali N, Abdel-Hady el-SK, Salem FK. Cytokine gene polymorphisms in Egyptian cases with brain tumors. J Egypt Natl Cancer Inst 2009; 21: 101-6.

21. Yang ZH, Dai Q, Zhong L, Zhang X, Guo QX, Li SN. Association of IL-1 polymorphisms and IL-1 serum levels with susceptibility to nasopharyngeal carcinoma. Mol Carcinog 2011; 50: 208-14.

22. Zhang Y, Liu C, Peng H, Zhang J, Feng Q. IL1 receptor antagonist gene IL1-RN variable number of tandem repeats polymorphism and cancer risk: a literature review and meta-analysis. PLoS One 2012; 7: e46017.

23. Shiiba M, Saito K, Yamagami H, Nakashima D, Higo M, Kasamatsu A, et al. Interleukin-1 receptor antagonist (IL1RN) is associated with suppression of early carcinogenic events in human oral malignancies. Int J Oncol 2015; 46: 1978-84.

24. Gupta MK, Sagar N, Pant R, Banerjee M. Cytokıne gene polymorphısms and their association with oral squamous cell carcinoma (OSCC): A North Indian Study. EJPMR 2016; 550-8.

25. Duan Y, Pan C, Shi J, Chen H, Zhang S. Association between interleukin-4 gene intron 3 VNTR polymorphism and cancer risk. Cancer Cell Int 2014; 14: 131.

26. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 2009; 15: 425-30.

27. Inanir A, Tural S, Yigit S, Kalkan G, Pancar GS, Demir HD, et al. Association of IL-4 gene VNTR variant with deep venous thrombosis in Behçet's disease and its effect on ocular involvement. Mol Vis 2013; 19: 675-83.

28. Jia Y, Xie X, Shi X, Li S. Associations of common IL-4 gene polymorphisms with cancer risk: A meta-analysis. Mol Med Rep 2017; 16: 1927-45.

29. Yang CM, Chen HC, Hou YY, Lee MC, Liou HH, Huang SJ, et al. A high IL-4 production diplotype is associated with an increased risk but better prognosis of oral and pharyngeal carcinomas. Arch Oral Biol 2014; 59: 35-46.

İstanbul Med J 2019; 20(3): 208-13
DOI: 10.4274/imj.galenos.2018.80557

Knowledge, Attitude and Practice Regarding Type 2 Diabetes Mellitus Among Outpatients in a Health Center in East-Coast of Peninsular Malaysia

Malezya Yarımadası'nın Doğu Kıyısındaki Bir Sağlık Merkezindeki Ayaktan Hastalar Arasında Tip 2 Diabetes Mellitus ile ilgili Bilgi, Tutum ve Uygulama

Rawaida Mat Salleh[1], Nor Azlina A Rahman[2], Mainul Haque[3]

[1]Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Department of Biomedical Science, Pahang, Malaysia
[2]Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, Jalan Sultan Ahmad Shah Bander Indera Mahkota, Department of Physical Rehabilitation Sciences, Pahang, Malaysia
[3]University Pertahanan Nasional Malaysia (National Defence University Of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is becoming a global epidemic and a threat to the world population.

Methods: This cross-sectional study was carried out to assess the knowledge, attitude, and practice (KAP) regarding T2DM among outpatients of a health center in East-Cost of Peninsular Malaysia. A total of 104 participants aged above 18 years were selected using purposive sampling by the researcher to answer an interviewer-guided questionnaire. The total scores for each KAP were computed to find the associations using SPSS.

Results: There were significant correlations between knowledge and practice ($r=0.481$, $p<0.001$) and between age of participants with knowledge ($r=0.562$, $p<0.001$) and practice regarding T2DM ($r=0.607$, $p<0.001$). Besides, there was also a significant difference in terms of knowledge and practice regarding T2DM between different sexes and education levels. However, while making a comparison between Malays and other races, the significant difference was only found for practice regarding T2DM. The attitude was found to be similar in all groups. T2DM can be prevented by having accurate knowledge, adopting a positive attitude and practicing a healthy lifestyle.

Conclusion: Therefore, policies and campaigns which may change people's knowledge, attitudes, and practices for preventing T2DM should be properly formulated and implemented to tackle this health issue.

Keywords: Knowledge, attitude, practice, type 2 diabetes mellitus, outpatients, health center, East-Coast, Peninsular Malaysia

ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM) küresel bir salgın ve dünya nüfusu için bir tehdit haline gelimiştir.

Yöntemler: Bu kesitsel çalışma, Doğu Malezya Yarımadası'ndaki bir sağlık merkezinin ayaktan başvuru yapan hastalarında T2DM ile ilgili bilgi, tutum ve uygulamaları arasındaki ilişkiyi (BTU) değerlendirmek amacıyla yapıldı. On sekiz yaşından büyük toplam 104 katılımcı araştırmacı tarafından rehberlik edilen ankete cevap vermek amacıyla örneklemeye seçilmiştir. Her bir BTU için toplam puanlar arasındaki ilişki SPSS kullanılarak hesaplandı.

Bulgular: Bilgi ve uygulama arasında ($r=0,481$, $p<0,001$), katılımcıların yaşı ve bilgi düzeyi ($r=0,562$, $p<0,001$) ve T2DM ile ilgili uygulama arasında ($r=0,607$, $p<0,001$) anlamlı korelasyon bulundu. Ayrıca, farklı cinsiyetler ve eğitim düzeyleri arasında T2DM ile ilgili bilgi ve uygulama açısından da anlamlı bir farklılık vardı. Ancak, Malaylar ve diğer ırklar arasında karşılaştırma yaparken, önemli fark sadece T2DM ile ilgili uygulama için bulundu. Tutum tüm gruplar arasında benzer bulunmuştur. T2DM doğru bilgiye sahip olarak, olumlu bir tutum benimseyerek ve sağlıklı bir yaşam tarzı uygulayarak önlenebilir.

Sonuç: Bu nedenle, T2DM'yi önlemeye yönelik insanların bilgi, tutum ve pratiğini değiştirebilecek politika ve kampanyalar bu sağlık sorununu çözmek için uygun şekilde formüle edilmeli ve uygulanmalıdır.

Anahtar Kelimeler: Bilgi, tutum, uygulama, tip 2 diabetes mellitus, ayakta tedavi, sağlık merkezi, doğu sahili, Yarımada Malezya

Address for Correspondence/Yazışma Adresi: Mainul Haque MD, University Pertahanan Nasional Malaysia (National Defence University Of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia
Phone: +60 10 926 55 43 **E-mail:** runurono@gmail.com **ORCID ID:** orcid.org/0000-0002-6124-7993

Cite this article as/Atıf: Salleh R. M., Rahman N.A., Haque M. Knowledge, Attitude and Practice Regarding Type 2 Diabetes Mellitus Among Outpatients in a Health Center in East-Coast of Peninsular Malaysia. İstanbul Med J 2019; 20(3): 208-13.

Received/Geliş Tarihi: 20.09.2018
Accepted/Kabul Tarihi: 04.12.2018

Introduction

There are approximately 371-415 million people with diabetes mellitus (DM) across the world and around 50% of them are not diagnosed (1,2). The WHO estimates that diabetes will be the seventh main cause of death by 2030 (3). DM is still known as the most common chronic disease worldwide despite many interventions and research (3). The major factors for DM are obesity, unbalanced diet, and unhealthy lifestyles. Moreover, poor awareness and practices are other most important factors that lead to DM. The prevalence of DM is increasing globally, which is not only limited to affluent countries. Middle-income countries are also among the most markedly affected ones (1,2). Diabetes Research and Clinical Practice has reported that ¾ of diabetic patients at the age range of 18-99 years currently live in low- and middle-income countries and it has forecasted that the number of these patients would rise to 673 and 693 million by 2040 and 2045, respectively (2,4). Despite this shocking number of DM patients, it has been recognized that type 2 (T2) DM can be prevented (5). Therefore, suitable preventive approaches need to be designed clearly based on the factors causing diabetes. The adaption of a healthy lifestyle is greatly influenced by knowledge (6). The prevalence of DM reported from a National Health and Morbidity Survey done in Malaysia in 2006 was 11.6%, where the highest prevalence was in Indian (19.9%), followed by Malays (11.9%) and Chinese (11.4%) (7). Another study revealed that the prevalence was increased practically double that of the figure in 2006 to reach 22.6% in about twenty years' time. They also found hemoglobin A1c as a better predictive cut-off point in detecting new cases of DM in the multi-ethnic population in that study (8). The alarming increase in the prevalence of DM in Malaysia becomes a burden to the country. The occurrence of DM is thought to be influenced by knowledge, attitude, and practice (KAP) of the population (9). However, it was observed that patients might possess a reasonable level of knowledge regarding DM, but their attitudes towards diabetes care were insignificant (10).

Thus, this study was done generally for focusing on KAP regarding T2DM among patients attending a health center in the East-Coast of Peninsular Malaysia. The participants of this study were the outpatients who did not have any history of DM because the diabetic patients or anyone with the history of DM usually tend to have high knowledge about the disease due to the consultation with the physicians who can be a good source of health information regarding the disease itself (11). The results and findings of this study may assist the healthcare practitioners in tailoring their educational programs and appropriate preventive measures depending on the needs of the population to improve diabetes control.

Methods

Study Area: This study was carried out in a health center in the East-Cost of Peninsular Malaysia.

Source of Population: The participants were selected among outpatients in the selected health center.

Study Design: This was a cross-sectional study.

Study Period: The survey included cases from January 27, 2014 until January 31, 2014.

Sample Size Calculation: Using the Power and Sample Size Software version 3.0.43, the calculated sample size was 110, with the assumption of α=0.05, power of study=0.8, m=1, δ=0.32 and σ=0.81. The standard deviation (SD) (σ=0.81) was taken from a previous study (11).

Sampling Method: One hundred and four (104) study participants were selected by convenience sampling from the Outpatient Department of the selected health center considering inclusion and exclusion criteria.

Inclusion Criteria: This study included participants from both genders and with all education levels, regardless of their income status.

Exclusion Criteria: Diabetic patients and participants below 18 years old were excluded from the survey.

Research Tool and Data Collection: Data were collected by a set of interviewer-guided questionnaire which was distributed among the participants. The questionnaires were prepared in two languages, English and Malay languages. The questions had been constructed to be relevant according to the category of KAP regarding T2DM. The content validity of the questionnaires was checked by experts, and a pilot study had been done for face validity to improve the understandability of the questionnaire. A few corrections and amendments had been made to improve the questionnaires after the pilot study. The permission was obtained from the health center authority to do the survey. There were four sections which consisted of the socio-demographic variables (age, sex, education level, race and citizenship), the knowledge ("yes" or "no" answers), attitude (level of agreement or disagreement) and practices ("often", "seldom" or "never" answers) about T2DM and its prevention.

Ethical Approval: The study obtained ethical approval from both Medical Research and Ethics Committee, Ministry of Health Malaysia [KKM/NIHSEC/P14-374, Dated May-21-2014] and IIUM Research Ethics Committee [IIUM/310/G/20/4/14-42. Dated December-26-2013]. The written informed consent was obtained from the patients after full explanation of the nature and purpose of the study and all procedures used for the study.

Statistical Analysis

Data were analyzed using SPSS 21 (IBM, Armonk, NY, United States of America). Frequencies and percentages were used to describe the socio-demographic characteristics of the participants while Pearson correlation test was used to assess the association between KAP practice scores regarding T2DM, and their association with age of the participants. Independent t-test was employed to compare the KAP scores between different sexes and education levels, but in the comparison between Malays and other races, Mann-Whitney test was used because of the skewed distribution of the very small sample size of the other races group.

Results

Socio-Demographic Characteristics of Respondents

The total of 104 respondents involved in this study were outpatients attending the selected health center. The respondents' socio-demographic characteristics were obtained through the first part of the questionnaire. The range of respondents' age was between 18 and

70 years. The mean age of respondents was 32.1 (SD=13.46) years. The distribution of their sexes, educational levels, and races are shown in Table 1. More than half [52.9% (55)] of the respondents were males and had a secondary level of education [56.7% (59)] while the majority of them were Malays [91.3% (95)] and all were Malaysians.

Knowledge of Respondents Regarding T2DM

Most respondents knew that diabetes was a chronic health problem [82.7% (86)], it was worldwide [92.3% (96)], and it could be prevented [84.6% (88)]. Respondents identified the risk factors for diabetes as genetics [62.5% (65)], obesity [83.7% (87)], physical inactivity [96.2% (100)], poor dietary habit [84.6% (88)] and race [8.7% (9)]. The early symptoms of T2DM, which were correctly answered by the respondents, were extreme hunger [43.3% (45)], unusual thirst [72.15% (75)], frequent urination especially at night [75.0% (78)], numbness in hands or feet [76.0% (79)], blurred vision [35.6% (37)], increased fatigue [84.6% (88)], frequent infections [55.8% (58)], slow wound healing [85.6% (89)], and diarrhea [46.2% (48)]. Nevertheless, some wrongly answered prolonged cough [77.9% (81)] as an early symptom. The respondents identified the complications of T2DM as blindness [57.7% (60)], amputation [71.2% (74)], cardiovascular diseases [53.8% (56)], kidney disease [69.2% (72)], and difficulty in breathing [25.0% (26)]. Regarding the preventions of T2DM, the respondents correctly answered as losing weight [94.2% (98)], regular physical activity [97.1% (101)], low-fat diet [90.4% (94)], avoiding high calorie diet [64.4% (67)], low-sugar intake [94.2% (98)], and avoiding high-salt diet [74.0% (77)].

Table 1. Socio-demographic characteristics of the respondents (n=104)

	Frequency	Percentage
Sex		
Male	55	52.9
Female	49	47.1
Education level		
No formal education	1	1.0
Primary education	6	5.8
Secondary education	59	56.7
Tertiary education	38	36.5
Race		
Malay	95	91.3
Chinese	4	3.8
Indian	4	3.8
Others	1	1.0

The Attitude of Respondents Regarding T2DM

The majority [99.05% (103)] of the respondents agreed that doing regular exercise had a lot of benefits. Nonetheless, a big portion [93.3% (97)] of respondents wrongly believed that food containing more sugar improved health. All the respondents stated that the prevention of T2DM was important. Besides, only one of the respondents did not agree that loss of weight and diet control were the preventive measures for T2DM. One hundred percent of them believed that screening for T2DM was important and advantageous. All agreed that it was essential to control diet intake to keep their blood sugar in the normal range.

Practice of Respondents Regarding T2DM

Only 26.0% (27) and 32.8% (34) of the respondents read about DM and the overall health, respectively. Forty-three (41.3%), 24 (23.1%), and 6 (5.8%) of the respondents did physical activities regularly, tried to lose weight, and never took sweetened food or drinks, respectively. Only 26.0% (27), and 19.2% (20) of the respondents were concerned about reducing fat and calories in their diet and had the blood test done for T2DM, respectively. Furthermore, 17.3% (18) of them always consumed sweet food and drinks, which is not a healthy practice.

Association between Knowledge, Attitude, and Practice scores Regarding T2DM

The Pearson correlation test showed no significant association between knowledge and attitude scores regarding T2DM (r=0.178; p=0.070), nor between attitude and practice scores (r=0.074, p=0.455). However, there was little positive significant correlation between knowledge and practice scores regarding T2DM (r=0.481, p<0.001), which meant that higher knowledge scores were associated with better practice regarding T2DM.

Association between Ages with KAP scores Regarding T2DM

The Pearson correlation test showed no significant correlation between age and attitude scores regarding T2DM (r=0.067, p=0.500). However,

Table 2. Comparison of knowledge, attitude and practice scores regarding type 2 diabetes mellitus among sex, educational level and race (n=104) using independent t-test

		Knowledge		Attitude		Practice	
Characteristic	**n**	**Mean (SD)**	**p**	**Mean (SD)**	**p**	**Mean (SD)**	**p**
Sex							
Male	55	73.7 (6.31)	**0.001**	20.8 (0.62)	0.226	16.4 (2.72)	**0.028**
Female	49	77.9 (5.70)		20.9 (0.34)		17.6 (2.98)	
Education							
Lower level	66	74.4 (5.95)	**0.004**	20.9 (0.40)	0.381	16.5 (2.77)	**0.020**
Upper level	38	78.1 (6.46)		20.8 (0.66)		17.8 (2.94)	
Race							
Malay	95	77.0 (8.0)[a]	**0.871**[b]	21.0 (0)[a]	0.337[b]	17.0 (3.0)[a]	**0.047**[b]
Others	9	77.0 (9.0)[a]		21.0 (0)[a]		19.0 (5.0)[a]	

aMedian (IQR). bMann-Whitney test

the Spearman correlation test showed a moderate-to-good positive significant correlation between age and knowledge scores regarding T2DM ($r=0.562$, $p<0.001$), also between age and practice scores ($r=0.607$, $p<0.001$), meaning that older participants had better knowledge and practice regarding T2DM.

Comparison of KAP scores Regarding T2DM among Different Sexes, Education Levels, Races and Occupations

Table 2 shows the comparison of KAP scores regarding T2DM among different sexes, education levels and races. For this purpose, the levels of education were re-categorized into lower education which included informal, primary and secondary education and higher education level that also included tertiary education. All the races besides Malay were combined into "others" type of race. The findings showed that the knowledge and practice scores regarding T2DM were significantly higher in females compared to males ($p=0.001$ and 0.028, respectively) and significantly higher in those with higher education compared to those with lower education level ($p=0.004$ and 0.020, respectively). Practice scores were also found to be significantly lower in Malays compared to other races ($p=0.047$) while no significant difference was found for attitude scores among all the groups, nor for knowledge between Malays and other races.

Discussion

DM is becoming a global public health threat with an alarmingly increasing rate, making DM as an epidemic disease and an estimated 693 million people are projected to suffer from the disease by 2045 (4). Additionally, it is estimated that about 193 million patients with DM will continue to be unidentified because of the minimum initial symptoms, particularly in T2DM (12).

All respondents who participated in this study were Malaysian, possibly because the study was performed in a public health clinic in Malaysia. Most of them were Malay, which could be due to the high number of Malays in the nearby communities. Majority of the respondents attained a secondary and tertiary education level, which is consistent with the Malaysian education policy (13).

Most of the respondents knew that DM was a chronic health problem and could be prevented. This might be due to the phenomenon of DM that happens throughout the world. Previously, T2DM was only known to happen in Western countries. However, DM has now spread to almost every country throughout the world (14). Majority of respondents knew about the risk factors of T2DM including genetic factor, obesity, physical inactivity and poor dietary habits, which is good because they can take the important preventive measures indicated to reduce their risk of getting the disease. However, most of the respondents did not know that race was one of the risk factors of T2DM. Race is a risk factor for T2DM as it is known that certain ethnic group suffers from DM more than others (15).

Most of the respondents knew the correct early symptoms of T2DM, and therefore, they should be able to get early treatment for the disease. The low level of knowledge regarding DM in a community portrays the extent of health promotion for most chronic non-communicable diseases (16). One study covering five different sub-Saharan countries reported that there were still no effective primary care programs for DM (17). Malaysian public health system is much more effectively operated in comparison to sub-Saharan countries; therefore, people are commonly quite aware regarding the early symptoms of DM. Respondents were mostly aware of the complications of T2DM. However, most of them did not know about breathing difficulty as one of its cpmplications, which could be due to the late cardiovascular complications. Awareness level was quite consistent with another study report which reported that cognizance and responsiveness was a principal determinant for control and prevention of DM (18).

All respondents agreed that prevention of T2DM was important, and most of them also agreed that physical exercise benefited a lot. If this awareness is taken into action, it can prevent them from getting not only the disease, but also a few other chronic diseases such as cardiovascular diseases. People's daily diet intake is influenced by their habits acquired since childhood (19). Schools and other education settings have long been considered a primary target to deliver nutrition education (20). Proper nutrition is essential for the physical and mental development of children and adolescents, which means school children are at the phase of life when they are adapting habits that will last a lifetime; and children are an important link among school, home, and community (21). The current study findings were in the same line of healthy lifestyle and DM prevention strategies.

Weight loss and diet control could help in the prevention of T2DM. Multiple studies have reported that healthy lifestyle such as proper diet and regular exercise can prevent and improve T2DM (5,22). Besides, losing 5-10% of body weight can reduce the risk of getting DM (23). Subsequently, the current study respondents' opinion was quite scientifically valid and up to date. Most of the respondents believed that screening for T2DM was important and advantageous. Other study reported similarly regarding the importance of regular screening (24).

All respondents in the current study knew that it was essential for diabetic patients to control their diet to keep their blood sugar level in the normal range. Higher dietary glycemic load and trans-fat are associated with increased diabetes risk, whereas greater consumption of cereal fiber and polyunsaturated fat is associated with decreased risk (14). Overseas studies similarly recommended diet and glycemic control (25). Thus, it is very important to educate the public on proper and healthy nutrition intake to maintain a normal range of blood sugar level.

From the results on practice regarding T2DM in the current study, it can be deduced that practice regarding T2DM among respondents was not at a satisfactory level. Therefore, there is a need to improve knowledge and awareness about diabetes in or order to improve their practice accordingly. Community level awareness programs need to be launched to increase awareness (26).

The current study shows no significant correlation between knowledge and the attitude of the respondents regarding T2DM. Thereafter, it can be concluded that the knowledge of respondents did not contribute to their attitudinal change regarding T2DM. Similarly, good attitude alone did not contribute to having a healthy practice and is insufficient to

prevent T2DM. Other factors, such as motivation and awareness are also important (27). Psychological determinants of health behavior such as reasons, goals, expectations, values, beliefs, or self-perceptions will enhance the individual getting more motivation in managing their health, especially in preventing T2DM (28).

T2DM is a disease of people in older age-group, which might explain the reason for that most of the respondents at an older age could be more keen on ensuring their health, which might contribute to the betterment of their knowledge and practice regarding T2DM. Women could also be more aware of health issues and therefore, more likely to consult doctors compared to men. Therefore, women appear to have higher health problem rates than men, but this may reveal the fact that more men health problems are under-reported (29).

Even though the current study found no association between level of education and KAP regarding T2DM, it was found that people having a longer period of schooling tend to have better health due to their healthier lifestyles (30). This is supported by the results of the current study where those with higher education levels showed higher knowledge and practice scores. "Education improves health because it increases effective agency, enhancing a sense of personal control that encourages and enables a healthy lifestyle. Education's beneficial effects are pervasive, cumulative, and self-amplifying, growing across the life course" (31). Another study describes education as an important instrument for improving the overall physical and mental health of persons and folks because education promotes "healthy lifestyles and positive choices, supporting and nurturing human development, human relationships and personal, family and community well-being" (32). Thereafter, it cuts down health care costs at an individual and community level (32). The race of the respondents was not found to be significantly associated with their knowledge and attitude regarding T2DM. However, there was a significant association between races and practice regarding T2DM. This shows that race affects health (33).

Study Limitations

The nature of the current study does not allow for the conclusion of a causal-effect relationship because the temporal sequence of relationship cannot be ensured using a cross-sectional design as applied in this study. The complete generalization to the population needs to be done with caution because of the convenience sampling that was used. Therefore, it is recommended that further studies should be conducted by using a cohort or experimental design to ensure that the variables investigated are in a causal-relationship with the outcomes studied.

Conclusion

The knowledge regarding T2DM among the respondents in the current study was quite satisfactory as most questions was correctly answered by most or at least more than half of the participants. Although many of them showed a positive attitude towards T2DM, there were still many needs to be targeted to improve their awareness about the importance of screening for diabetes and healthy lifestyle in preventing T2DM. Knowledge was also found to be significantly correlated with practice regarding T2DM, as were age with knowledge and practice. Knowledge and practice regarding T2DM were all found to be significantly different between different sexes and levels of education, also for practice among different races.

Acknowledgement

Authors are much grateful to those patients who participated in this study.

Ethics Committee Approval: The study obtained ethical approval from both Medical Research and Ethics Committee, Ministry of Health Malaysia (KKM/NIHSEC/P14-374, Dated May-21-2014) and IIUM Research Ethics Committee (IIUM/310/G/20/4/14-42. Dated December-26-2013).

Informed Consent: The written informed consent was obtained from the patients after full explanation of the nature and purpose of the study and all procedures used for the study.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - R.M.S., N.A.A.R.; Design - R.M.S., N.A.A.R.; Supervision - N.A.A.R., M.H.; Materials - R.M.S., N.A.A.R.; Data Collection and/or Processing - R.M.S., N.A.A.R., M.H.; Analysis and/or Interpretation - R.M.S., N.A.A.R., M.H.; Literature Search - R.M.S., N.A.A.R., M.H.; Writing Manuscript - R.M.S., N.A.A.R., M.H.; Critical Review - A N.A.A.R., M.H.

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

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

References

1. Castillo M. 371 million people have diabetes globally, about half undiagnosed. CBS News. 2012. Available at https://www.cbsnews.com/news/371-million-people-have-diabetes-globally-about-half-undiagnosed/(Accessed August 24, 2018)
2. World Health Organization (WHO). Diabetes. Key Facts. 2017. Available at http://www.who.int/news-room/fact-sheets/detail/diabetes (Accessed August 24, 2018).
3. Sahoo K, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. J Family Med Prim Care 2015; 4: 187-92.
4. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271-81.
5. Asif M. The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. J Educ Health Promot 2014; 3: 1.
6. Tiedje K, Wieland ML, Meiers SJ, Mohamed AA, Formea CM, Ridgeway JL, et al. A focus group study of healthy eating knowledge, practices, and barriers among adult and adolescent immigrants and refugees in the United States. Int J Behav Nutr Phys Act 2014; 11: 63.
7. Letchuman GR, Wan Nazaimoon WM, Wan Mohamad WB, Chandran LR, Tee GH, Jamaiyah H. et al. Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. Med J Malaysia 2010; 65: 180-6.
8. Wan Nazaimoon WM, Md Isa SH, Wan Mohamad WB, Khir AS, Kamaruddin NA, Kamarul IM, et al. Prevalence of diabetes in Malaysia and usefulness of HbA1c as a diagnostic criterion. Diabet Med 2013; 30: 825-8.
9. Fatema K, Hossain S, Natasha K, Chowdhury HA, Akter J, Khan T, et al. Knowledge attitude and practice regarding diabetes mellitus among nondiabetic and diabetic study participants in Bangladesh. BMC Public Health 2017; 17: 364.

10. Herath HMM, Weerasinghe NP, Dias H, Weerarathna TP. Knowledge, attitude and practice related to diabetes mellitus among the general public in Galle district in Southern Sri Lanka: a pilot study. BMC Public Health 2017; 17: 535.

11. Shrestha L, Nagra JS. Knowledge, Attitude, and Practice (KAP) Study on diabetes mellitus among nepalese diabetic patients. Nepal Med Coll J 2005; 7: 51-3.

12. International diabetes federation. IDF Diabetes Atlas, 7th Edition. Available at http://www.diabetesatlas.org/(Accessed August 25, 2018).

13. Student Info & Guide. A Glance at the malaysian education system. 2015. Available at https://www.studymalaysia.com/education/higher-education-in-malaysia/a-glance-at-the-malaysian-education-system (Accessed August 25, 2018).

14. Hu BF. Globalization of Diabetes: The role of diet, lifestyle, and genes. Diabetes Care 2011; 34: 1249-57.

15. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. JAMA 2017; 318: 2457-65.

16. Ichiho HM, Demei Y, Kuartei S, Aitaoto N. An assessment of non-communicable diseases, diabetes, and related risk factors in the republic of palau: A systems perspective. Hawai J Med Public Health 2013; 72(5 Suppl 1): 98-105.

17. Azevedo M, Alla S. Diabetes in Sub-Saharan Africa: Kenya, Mali, Mozambique, Nigeria, South Africa and Zambia. Int J Diabetes Dev Ctries 2008; 28: 101-8.

18. Mumu SJ, Saleh F, Ara F, Haque MR, Ali L. Awareness regarding risk factors of type 2 diabetes among individuals attending a tertiary-care hospital in Bangladesh: a cross-sectional study. BMC Res Notes 2014; 7: 599.

19. Birch L, Savage JS, Ventura A. Influences on the development of children's eating behaviors: from infancy to adolescence. Can J Diet Pract Res 2007; 68: 1-56.

20. Sadegholvad S, Yeatman H, Parrish AM, Worsley A. what should be taught in secondary schools' nutrition and food systems education? Views from prominent food-related professionals in Australia. Nutrients. 2017; 9: 1207.

21. Hawkes C. Promoting health diets through nutrition education and changes in the food environment: an ınterventional review of actions and their effectiveness. International Conference on Nutrition. 2013. Available at http://www.fao.org/docrep/017/i3235e/i3235e.pdf (Accessed August 25, 2018).

22. Amuta AO, Mkuu R, Jacobs W, Barry AE. Number and severity of type 2 diabetes among family members are associated with nutrition and physical activity behaviors. Front Public Health 2017; 5: 157.

23. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in ımproving cardiovascular risk factors in overweight and obese ındividuals with type 2 diabetes. Diabetes Care 2011; 34: 1481-6.

24. Gilmer TP, O'Connor PJ. The growing ımportance of diabetes screening. Diabetes Care 2010; 33: 1695-7.

25. Shrivastava SR, Shrivastava PS, Ramasamy J. Role of self-care in management of diabetes mellitus. J Diabetes Metab Disord 2013; 12: 14.

26. Muninarayana C, Balachandra G, Hiremath SG, Iyengar K, Anil NS. Prevalence and awareness regarding diabetes mellitus in Rural Tamaka, Kolar. Int J Diabetes Dev Ctries 2010; 30: 18-21.

27. Saleh F, Mumu SJ, Ara F, Ali L, Hossain S, Ahmad KR. Knowledge, attitude, and practice of type 2 diabetic patients regarding obesity: study in a tertiary care Hospital In Bangladesh. J Public Health Afr 2012; 3: 8.

28. Teixeira PJ, Mata J, Williams GC, Gorin AA, Lemieux S. Self-regulation, motivation and psychosocial factors in weight management. J Obes 2012; 2012: 582348.

29. von Bothmer MI, Fridlund B. Gender differences in health habits and ın motivation for a healthy lifestyle among swedish university students. Nurs Health Sci 2005; 7: 107-18.

30. Kaplan R, Spittel M, David D (Eds). Population health: behavioral and social science insights. AHRQ Publication No. 15-0002. Rockville, MD: Agency for healthcare research and quality and office of behavioral and social sciences research, National Institutes of Health; July 2015. Available at https://www.ahrq.gov/sites/default/files/publications/files/population-health.pdf (Accessed August 25, 2018).

31. Feinstein L, Sabates R, Anderson TM, Sorhaindo A, Hammond C. What are the effects of education on health? Measuring the effects of education on health and civic engagement. Proceedings of the Copenhagen Symposium; 2006. Available at http://www.oecd.org/education/innovation-education/37437718.pdf (Accessed August 25, 2018).

32. Mirowsky J, Ross CE. Education, learned effectiveness and health. London Rev Educ 2005; 3: 205-20.

33. Nicklett EJ. Socio-economic status and race/ethnicity independently predict health decline among older diabetics. BMC Public Health. 2011; 11: 684.

İstanbul Med J 2019; 20(3): 214–7
DOI: 10.4274/imj.galenos.2019.37974

Evaluation of Lipid Parameters in Patients Receiving Vitamin B12 Therapy

Vitamin B12 Tedavisi Alanlarda Lipit Parametrelerinin Değerlendirilmesi

Yılmaz Sezgin[1], Sinan Becel[2]

[1]İstanbul Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey
[2]İstanbul Bahçelievler State Hospital, Clinic of Emergency Medicine, İstanbul, Turkey

ABSTRACT

Introduction: We believe that vitamin B12 supplementation may affect serum lipid levels because of its role in fatty acid catabolism and its relationship with serum lipids. In this study, it was investigated whether serum lipid and glucose values were affected in patients receiving vitamin B12 treatment.

Methods: This is a retrospective observational study. In this study, the medical records of patients who applied to the family medicine outpatient clinic were analyzed retrospectively, and serum parameters such as glucose, lipid and vitamin B12 levels and demographic data such as age and gender were evaluated. Twenty-one patients who received treatment due to vitamin B12 deficiency and who had control lipid profile within 6 months, and who did not use any antihiperlipidemics were included in the study.

Results: The mean serum cholesterol level was 209.6±30.1 before treatment and 195.6±31.7 after treatment (p=0.002). The mean serum triglyceride level was 196.2±117.8 before treatment and 142.1±81.4 after treatment (p=0.001).

Conclusion: We can conclude that there is a relationship between vitamin B12 and serum lipid parameters, and that serum triglyceride levels are especially affected by vitamin B12 treatment.

Keywords: Fatty acids, lipid parameters, vitamin B12 deficiency

ÖZ

Amaç: Yağ asit katabolizmasında rol alması ve serum lipitleri ile ilişkisinin gösterilmiş olması sebebiyle vitamin B12 takviyesinin serum lipit seviyelerini etkileyebileceğini düşünüyoruz. Bu çalışmada, vitamin B12 tedavisi alan hastalarda serum lipit ve glikoz değerlerinin etkilenip etkilenmediği araştırılmıştır.

Yöntemler: Bu çalışma retrospektif gözlemsel bir araştırmadır. Bu çalışmada, aile hekimliği polikliniğine başvurmuş hastaların kayıtları geriye dönük incelenmiş, glikoz, lipit ve vitamin B12 gibi serum parametreleri ile yaş ve cinsiyet gibi demografik veriler değerlendirilmiştir. Vitamin B12 eksikliği sebebiyle tedavi alan, altı ay içinde tekrar lipit profili baktırmış olan ve herhangi bir antihiperlipidemik kullanmayan 21 hasta çalışmaya dahil edilmiştir.

Bulgular: Serum kolesterol değerlerinin ortalaması tedavi öncesi 209,6±30,1 mg/dL, tedavi sonrası 195,6±31,7 mg/dL bulundu (p=0,002). Serum trigliserit değerlerinin ortalaması tedavi öncesi 196,2±117,8 mg/dL, tedavi sonrası 142,1±81,4 mg/dL bulundu (p=0,001).

Sonuç: Sonuç olarak vitamin B12 ile serum lipit parametreleri arasında bir ilişkinin olduğunu ve özellikle serum trigliserit seviyelerinin vitamin B12 tedavisinden etkilendiğini söyleyebiliriz.

Anahtar Kelimeler: Yağ asitleri, lipit parametreleri, vitamin B12 eksikliği

Introduction

Vitamin B12 acts as the cofactor of two major enzyme systems in the body. One of these enzyme systems, the methylmalonyl coenzyme A mutase, converts methylmalonyl coenzyme A to succinyl coenzyme A. Methylmalonyl coenzyme A is formed by propionyl coenzyme A carboxylation or valine catabolism, which is formed by isolocine, cholesterol and fatty acid catabolism (1).

Plasma lipids consist of 16% triacylglycerol (TG), 30% phospholipid, 14% cholesterol, 36% cholesterol esters and 4% free fatty acids (2). Lipids, such as TG and cholesterol, which are not free in plasma under normal conditions, are found in the form of macromolecules called lipoproteins. According to their electrophoretic activity in ultracentrifuge, lipoproteins are divided into chylomicrons, very low-density (pre-beta) lipoproteins (VLDL), LDL (beta) and high-density (alpha) lipoproteins (HDL) (3). Dyslipidemias, known as lipoprotein metabolism disorders, are classified

Address for Correspondence/Yazışma Adresi: Yılmaz Sezgin MD, İstanbul Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey
Phone: +90 538 342 56 44 **E-mail:** drysezgin@gmail.com **ORCID ID:** orcid.org/0000-0002-3626-0264

Cite this article as/Atıf: Sezgin Y, Becel S. Evaluation of Lipid Parameters in Patients Receiving Vitamin B12 Therapy. İstanbul Med J 2019; 20(3): 214-7.

Received/Geliş Tarihi: 24.11.2018
Accepted/Kabul Tarihi: 26.01.2019

Table 1. Causes of secondary dyslipidemia

Obesity	TG increases, HDL decreases
Sedentary life	HDL decreases
Diabetes mellitus	TG increases, TC increases
Alcohol	TG increases, HDL increases
Hypothyroidism	TC increases
Hyperthyroidism	TC decreases
Nephrotic syndrome	TC increases
Chronic renal failure	TG increases, TC increases
Cirrhosis	TC decreases
Obstructive hepatic impairment	TC increases
Malignancy	TC decreases
Cushing's disease/Corticosteroid use	TC increases
Oral contraceptives	TG increases, TC increases
Diuretics	TG increases, TC increases
Beta-blockers	TC increases, HDL decreases

TG: triacylglycerol; HDL: high-density lipoprotein; TC: total cholesterol.

as primary and secondary dyslipidemias according to their etiology. Primary dyslipidemias are characterized more by genetic disorders. The causes of secondary dyslipidemias and related serum lipid changes are shown in Table 1. Fatty acids, cholesterol and cholesterol esters, which are eliminated by the macrophages in the processes following the pathologies occurring in catabolism pathways, cause atherosclerotic plaque formation as a result of accumulation in intimal layers of arteries and lead to cerebral, coronary and peripheral arterial diseases. Dyslipidemia treatment includes lifestyle change, diet, treatment of secondary causes and medical treatment (4).

Vitamin B12 deficiency also increases the risk of developing high-mortality clinical conditions such as myocardial infarction and cardiac shock (5). There are studies suggesting that the prevalence of obesity is increased in patients with vitamin B12 deficiency (6,7). It is claimed that vitamin B12 may play a role in the synthesis of an antiprotease, alpha-1-antitrypsin (A1AT), and A1AT may be associated with obesity (8). It was suggested that there is a negative correlation between vitamin B12 and serum triglyceride levels and a positive correlation between HDL levels (9,10).

Vitamin B12 being a cofactor of the enzyme involved in fatty acid catabolism, increased risk of obesity and myocardial infarction in vitamin B12 deficiency, and negative correlation between vitamin B12 and triglycerides and positive correlation between HDL suggest that vitamin B12 supplementation may affect serum lipid levels. In this study, it was investigated whether serum lipid and glucose levels were affected in patients receiving vitamin B12 treatment.

Methods

Study Design

This is a retrospective observational study. In this study, the medical records of patients who applied to the family medicine outpatient clinic were analyzed retrospectively, and serum parameters such as glucose, lipid and vitamin B12 levels and demographic data such as age and gender were evaluated. Demographic data such as height, weight, marital status, smoking and alcohol use were not taken into account since they were not included in the patient records. As the study was retrospective, no ethics committee approval was obtained. Vitamin B12 and lipid analyzes were performed to 228 patients who applied to the family medicine outpatient clinic between 28 September 2012 and 17 May 2013. Twenty-one patients who received treatment due to vitamin B12 deficiency and who had control lipid profile within 6 months, and who did not use any antihiperlipidemics were included in the study.

The authors declare that the study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical principles for medical research involving human subjects". Ethical approval was not needed because it was a retrospective study. Consent was not taken from the patients because it was a retrospective study.

Exclusion Criteria

Patients who received medication due to hyperlipidemia, diabetes, obesity and thyroid disease and who received iron and folate treatment were not included in the study. In addition, since vitamin B12 is stored in the liver and kidney and excreted from the kidney, patients with liver and renal failure were not included in the study. While the exclusion criteria were determined, hospital information system and medulla physician program were used.

Treatment Protocol

Intramuscular vitamin B12 treatment was 1000 microgram/mL/day for 5 days, 1000 microgram/mL/week for the following 5 weeks and 1000 microgram/mL once a month.

Statistical Analysis

Statistical Package for the Social Sciences for Windows version 16.0 (SPSS, Chicago, IL, USA) was used to analyze the data. Categorical data were expressed as numbers and percentages. Numerical data were expressed as means and were evaluated by Wilcoxon signed ranks test. The normality of data was evaluated by skewness analysis. In addition, triglyceride values were evaluated by dividing into three subgroups as ≤150 mg/dL, 151-250 mg/dL and ≥251 mg/dL.

Results

Twenty-one patients aged 35 to 79 years were included in the study. Fifteen of the patients were female (71%) and six were male (29%). The distribution of serum glucose, lipid and vitamin B12 parameters of the patients is shown in Table 2.

Serum cholesterol and triglyceride levels were significantly lower in patients receiving vitamin B12 deficiency treatment than before treatment. The mean serum cholesterol level was 209.6±30.1 mg/dL before treatment and 195.6±31.7 mg/dL after treatment (p=0.002). The mean serum triglyceride level was 196.2±117.8 mg/dL before treatment and 142.1±81.4 mg/dL after treatment (p=0.001). All of the patients who received vitamin B12 treatment had a decrease in triglyceride

levels. There was no statistically significant difference between serum glucose, HDL and LDL levels before and after treatment (Table 3).

Serum total cholesterol levels after vitamin B12 treatment were significantly lower in patients with triglyceride levels ≥151 mg/dL before vitamin B12 treatment. There was no statistically significant difference between serum total cholesterol levels before and after vitamin B12 treatment in patients with triglyceride levels ≤150 mg/dL (Table 4). Serum triglyceride levels after vitamin B12 treatment were significantly lower in patients with triglyceride levels ≥151 mg/dL and ≤150 mg/dL before vitamin B12 treatment (Table 5).

Table 2. Distribution of serum vitamin B12, glucose, lipid parameters

	n	Mean ± SD*	Minimum	Maximum
Age (years)	21	55.38±14.22	35	79
Vitamin B12 (pg/mL)	21	214.14±73.16	82	300
Glucose (mg/dL)	21	89.95±17.18	61	137
Cholesterol (mg/dL)	21	209.57±30.09	119	256
Triglycerides (mg/dL)	21	196.19±117.79	55	476
HDL (mg/dL)	21	47.81±11.68	32	70
LDL (mg/dL)	21	122.10±25.53	69	173

*SD: standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 3. Comparison of serum glucose and lipid parameters before and after treatment

	Treatment	n	Mean ± SD*	↓	↑	→	p
Glucose (mg/dL)	Before	21	89.95±17.18	11	7	3	0.430
	After	21	88.71±12.51				
Cholesterol (mg/dL)	Before	21	209.57±30.09	17	3	1	0.002***
	After	21	195.57±31.70				
Triglycerides (mg/dL)	Before	21	196.19±117.79	21	0	0	0.001***
	After	21	142.14±81.38				
HDL (mg/dL)	Before	21	47.81±11.68	12	6	3	0.458
	After	21	54.14±21.79				
LDL (mg/dL)	Before	21	122.10±25.53	8	11	2	0.615
	After	21	120.38±29.21				

*SD: standard deviation; ↓: negative ranks; ↑: positive ranks; →: ties; HDL: high-density lipoprotein, LDL: low-density lipoprotein. **Wilcoxon signed ranks test is significant at the 0.05 level (2-tailed); ***Wilcoxon signed ranks test is significant at the 0.01 level (2-tailed)

Discussion

In our study, serum cholesterol and triglyceride values were lower in patients receiving vitamin B12 deficiency treatment than before treatment. This result suggests that serum lipid parameters, especially triglycerides, are affected by vitamin B12 treatment. There are studies in the literature that support our findings. It has been suggested that hypertriglyceridemia can be effectively reduced by fenofibrate and gemfibrozil treatment, as well as vitamin B6 and vitamin B12 supplement (11). Khaire et al. (12) showed that vitamin B12 and omega-3 supplementation normalize triglyceride levels in rats. In our study, there was no significant difference in serum total cholesterol levels before and after vitamin B12 treatment in patients with triglyceride levels ≤150 mg/dL. This result shows that vitamin B12 treatment does not affect serum total cholesterol levels in patients with low triglyceride levels. The decrease in serum total cholesterol levels after vitamin B12 treatment in groups with high triglyceride levels suggests that this situation is due to the change in serum triglyceride levels. This finding shows that the relationship between vitamin B12 and lipid parameters can only be related to serum triglyceride levels. Studies in the literature suggest that the relationship between vitamin B12 and serum lipid parameters is more pronounced in obese individuals (13) and in diseases related to increased triglyceride levels such as diabetes (14,15).

Table 4. Comparison of serum total cholesterol levels before and after treatment in subgroups categorized according to triglyceride parameters

Triglycerides	Treatment	n	Mean ± SD*	↓	↑	→	p
≤150 mg/dL	Before	8	193.75±32.03	5	3	0	0.400
	After	8	190.62±37.15				
151-250 mg/dL	Before	8	215.12±24.32	7	0	1	0.018**
	After	8	197.75±30.88				
≥251 mg/dL	Before	5	226.00±28.24	5	0	0	0.043**
	After	5	200.00±29.32				

*SD: standard deviation; ↓: negative ranks; ↑: positive ranks; →: Ties; **wilcoxon signed ranks test is significant at the 0.05 level (2-tailed)

Table 5. Comparison of serum triglyceride levels before and after treatment in subgroups categorized according to triglyceride parameters

Triglycerides	Treatment	n	Mean ± SD*	Minimum	Maximum	p
≤150 mg/dL	Before	8	92.12±25.61	55	126	0.012**
	After	8	74.50±20.73	46	116	
151-250 mg/dL	Before	8	190.50±24.03	160	238	0.012**
	After	8	157.00±31.58	106	216	
≥251 mg/dL	Before	5	371.80±83.35	265	476	0,043**
	After	5	226.60±110.04	112	358	

*SD: standard deviation; **Wilcoxon signed ranks test is significant at the 0.05 level (2-tailed)

In our study, triglyceride levels were significantly decreased after vitamin B12 treatment in patients with higher triglyceride levels before vitamin B12 treatment. Since our study was retrospective, we do not know whether this decrease was affected by other factors, such as lifestyle changes, which would affect triglyceride levels during vitamin B12 treatment. However, a significant reduction in triglyceride levels was found in patients with triglyceride levels below normal, indicating that vitamin B12 treatment was associated with a decrease in serum triglyceride levels independent of other factors.

The limitations of this study are as follows: retrospective nature of the study, lack of control group, lack of vitamin B12 measurements after treatment, lack of assessment of other factors affecting serum lipid parameters in the treatment process, and post-treatment duration including a long interval of 6 months.

Conclusion

We can say that there is a relationship between vitamin B12 and serum lipid parameters and that especially serum triglyceride levels are affected by vitamin B12 treatment. However, we think that more comprehensive studies should be done on this subject.

Ethics Committee Approval: The authors declare that the study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical principles for medical research involving human subjects". Ethical approval was not needed because it was a retrospective study.

Informed Consent: Consent was not taken from the patients because it was a retrospective study.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - Y.S.; Design - Y.S.; Supervision - Y.S., S.B.; Resources - Y.S.; Data Collection and/or Processing - Y.S.; Analysis and/or Interpretation - Y.S.; Literature Search - Y.S.; Writing Manuscript - Y.S.; Critical Review - S.B.

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

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

References

1. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. Micronutrients: Vitamins & Minerals. In Harper's Illustrated Biochemistry, 28th ed. The McGraw-Hill Companies; 2009. pp. 467-81.
2. Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. Lipid Transport & Storage. In Harper's illustrated biochemistry, 28th ed. The McGraw-Hill Companies; 2009. pp. 212-23.
3. Beers MH, Berkow R. Hyperlipidemia. In the merck manual of diagnosis and therapy, 17th ed. Merck and Co. Inc; 1999: 200-11.
4. Sezgin Y, Özçakar N. Management of dyslipidemia. Turkish Family Physician 2011; 2: 30-5.
5. Oh RC, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003; 67: 993-4.
6. Pinhas-Hamiel O, Doron-Panush N, Reichman B, Nitzan-Kaluski D, Shalitin S, Geva-Lerner L. Obese children and adolescents, a risk group for low vitamin B12 concentration. Arch Pediatr Adolesc Med 2006; 160: 933-6.
7. Karatela RA, Sainani GS. Plasma homocysteine in obese, overweight and normal weight hypertensives and normotensives. Indian Heart J 2009; 61: 156-9.
8. Sezgin Y. Kartal M, Güldal AD. A comparison of serum alpha-1-antitrypsin and vitamin B12 levels in patients with vitamin B12 deficiency. J Clin Anal Med 2018; 9: 192-4.
9. Sezgin Y, Becel S. Comparison of serum lipid parameters and serum vitamin B12 levels. J Clin Anal Med 2018.
10. Saraswathy KN, Joshi S, Yadav S, Garg PR. Metabolic distress in lipid & one carbon metabolic pathway through low vitamin B-12: a population based study from North India. Lipids Health Dis 2018; 17: 96.
11. Dierkes J, Westphal S, Luley C. The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels. Expert Opin Drug Saf 2004; 3: 101-11.
12. Khaire A, Rathod R, Kale A, Joshi S. Vitamin B12 and omega-3 fatty acids together regulate lipid metabolism in Wistar rats. Prostaglandins Leukot Essent Fatty Acids 2015; 99: 7-17.
13. Abacı A, Akelma AZ, Özdemir O, Hızlı Ş, Razi CH, Akın KO. Relation of total homocysteine level with metabolic and anthropometric variables in obese children and adolescents. Turk J Med Sci 2012; 42: 69-76.
14. Adaikalakoteswari A, Jayashri R, Sukumar N, Venkataraman H, Pradeepa R, Gokulakrishnan K, et al. Vitamin B12 deficiency is associated with adverse lipid profile in Europeans and Indians with type 2 diabetes. Cardiovasc Diabetol 2014; 13: 129.
15. Ahmed S, Rohman SM. Study of serum Vitamin B12 and its correlation with Lipid profile in type 2 diabetes mellitus. Indian Journal of Basic and Applied Medical Research 2016; 5: 92-103.

İstanbul Med J 2019; 20(3): 218-23

DOI: 10.4274/imj.galenos.2018.04796

High-Risk Carotid Imaging Predicts ST-Segment Elevated Myocardial Infarction in Young Patients: A Cross-Sectional Study

Genç Hastalarda Karotis Görüntülemesinin ST-Elevasyonlu Miyokard Enfarktüsü Kestirebilirliği: Kesitsel Bir Çalışma

Mustafa Umut Somuncu[1], Huseyin Karakurt[2]

[1]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Cardiology, Zonguldak, Turkey
[2]University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: Myocardial infarction remains a major cause of morbidity and mortality in the young population. The relationship between carotid intima-media thickness (CIMT) and atherosclerosis has been shown in many studies, however, there is no study investigating the association between carotid imaging and cardiovascular events in young patients. In our study, we evaluated the carotid imaging of young patients who experienced ST-elevated myocardial infarction (STEMI) and individuals at the same age and with normal coronary arteries.

Methods: A total of 160 young patients were enrolled in the study. Of them, 115 patients were under the age of 45 years with STEMI and 45 were under the age of 45 years with normal coronary arteries shown in the coronary angiography. Carotid ultrasound was performed for all patients and they were divided into high-risk and low-risk carotid image groups according to CIMT and the presence of carotid plaque. Both groups were compared according to the traditional risk factors and the predictors of STEMI were investigated.

Results: Both CIMT (0.87±0.28, vs 0.70±0.16, p<0.001) and the presence of carotid plaque (14.8% vs 2.2%, p=0.024) were found to be significantly higher in young patients with STEMI compared to the control group. Independently from other traditional risk factors, 0.1 mm increase in CIMT was associated with a 42% increase in odds for STEMI. Similarly, being in the high-risk carotid image group had 9.2 times increased odds for STEMI than being in the low-risk carotid image group.

Conclusion: CIMT and the presence of carotid plaque have a predictive value for cardiovascular events in young age independently from traditional risk factors.

Keywords: Myocardial infarction, carotid intima-media thickness, young age, carotid plaque, subclinical atherosclerosis

ÖZ

Amaç: Miyokard enfarktüsü günümüzde en önemli mortalite ve morbidite sebebi olmaya devam etmektedir. Karotis intima media kalınlığının (KIMK) aterosklerozla ilişkisi, birçok çalışmada gösterilmiştir, fakat genç populasyonda karotis görüntüleme ile kardiyovasküler olayları araştıran bir çalışma mevcut değildir. Çalışmamızda, genç yaşta ST-elevasyonlu miyokard enfarktüsü (STEME) geçirmiş olan hastalar ile, aynı yaş grubunda normal koroner arterlere sahip olan bireylerin karotis görüntülemeleri değerlendirildi.

Yöntemler: Çalışmamıza dahil edilen 160 hasta, 45 yaş altı, STEME geçirmiş 115 hasta ve kontrol grubu olarak koroner anjiyografi ile koroner arterleri normal olarak saptanan 45 hastadan oluşuyordu. Tüm bireylere karotis ultrasonografisi yapıldı ve hastalar KIMK ve plak varlığına göre yüksek riskli ve düşük riskli karotis görüntüleme olacak şekilde 2 gruba ayrıldı. İki grup da geleneksel risk faktörleri ve STEME'nin bağımsız prediktörleri açısından incelendi.

Bulgular: STEME geçirmiş genç hastalarda hem KIMK (0,87±0,28, vs 0,70±0,16, p<0,001) hem de karotis plak varlığı (14,8% vs 2,2%, p=0,024) kontrol grubuna göre anlamlı olarak yüksek tespit edildi. Diğer geleneksel risk fak- törlerinden bağımsız olarak, KIMK'de 0.1 mm artış, STEME için %42 oranında artışla ilişkili bulundu. Benzer olarak, yüksek riskli karotis görüntüleme grubunda olmanın, düşük riskli gruba göre STEME açısından 9,2 kat artmış riskle ilişkili olduğu gösterildi.

Sonuç: Genç yaşta, geleneksel risk faktörlerinden bağımsız olarak, KIMK ve karotis plak varlığı, kardiyovasküler olaylar açısından prediktif değere sahiptir.

Anahtar Kelimeler: Miyokard enfarktüs, karotis intima-media kalınlığı, genç yaş, karotis plak, subklinik ateroskleroz

Address for Correspondence/Yazışma Adresi: Mustafa Umut Somuncu MD, Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Cardiology, Zonguldak, Turkey
Phone: +90 532 340 15 25 **E-mail:** umutsomuncu@hotmail.com **ORCID ID:** orcid.org/0000-0002-4615-5206

Cite this article as/Atıf: Somuncu MU, Karakurt H. High-Risk Carotid Imaging Predicts ST-Segment Elevated Myocardial Infarction in Young Patients: A Cross-Sectional Study. İstanbul Med J 2019; 20(3): 218-23.

Received/Geliş Tarihi: 30.09.2018
Accepted/Kabul Tarihi: 12.12.2018

Introduction

Coronary heart disease (CHD) remains one of the most important causes of mortality despite advances in diagnosis and treatment (1). Although CHD generally occurs in patients over the age of 45 years, it can also cause serious morbidity and mortality in younger individuals.

The Framingham risk score system, which is used mostly, is composed of traditional risk factors and has a modest predictive level at best (2). In addition, it has been reported that most of the patients having cardiovascular problems are classified as low- or moderate risk groups by conventional score systems (3,4). Regarding this, non-invasive tests are needed to be used to establish high-risk groups for subclinical atherosclerosis, which are classified as moderate risk group by traditional risk score systems.

Many studies have shown that carotid doppler ultrasonography (USG), ankle-brachial index, and coronary calcium score are all useful in predicting cardiovascular risk beside traditional risk factors (5-7). Those methods, especially carotid intima-media thickness (CIMT) and the presence of carotid plaque, can be widely used to determine early atherosclerotic lesions.

CIMT may be a predictor of cardiac related ischemic events (8). In addition, previous studies have shown that carotid imaging and CIMT are related to the severity of atherosclerosis and the increase in CIMT correlates with the prevalence of cardiovascular diseases (9,10).

To the best of our knowledge, there are a few studies which review the relation between young myocardial infarction (MI) patients and CIMT. Besides, in these studies, control group has not been selected from patients who have completely normal coronary arteries proven by conventional coronary angiography and none of them has been evaluated in terms of the presence of carotid plaque (11-14). For this reason, the clear separation of patient and control groups and the detailed examination of the carotid image make our study unique and valuable. Consequently, we aimed to compare the CIMT and the presence of carotid plaques in young patients who experienced ST-elevated myocardial infarction (STEMI) and in the same aged patients whose coronary angiography results were totally normal. In order to reach this study design, 115 patients that had STEMI and 45 patients with normal coronary angiography were compared considering their carotid scans.

Methods

Study Groups

Totally 160 patients under the age of 45 years, who were admitted to the hospital between the dates of January 1, 2012 and January 1, 2015, were included in the study. One hundred and fifteen patients, who were performed primary percutaneous coronary intervention because of STEMI (mean age: 39.4±4.3 years), and 45 control group patients, who were performed coronary angiography with the suspect of the acute coronary syndrome but resulted with normal coronary angiography (mean age: 39.3±4.2 years), were the subgroups of the study. The decision of angiography for the control group was made according to the patients' symptoms and risk factors. Stress tests (effort test and scintigraphy) were not performed because of suspected unstable angina pectoris. Routine provocation test is not performed in our catheter laboratory. Two of the patients that were clinically suspected of having vasospasm in the control group underwent a provocation test. No coronary vasospasm was detected in these patients. Although the limit values for young age MI vary in various studies, most studies have used an age cut-off of 40 to 45 years to identify young patients with MI. In our study, we used the upper limit to achieve an adequate number of patients and patients below the age of 45 years were accepted to be at young age. Framingham risk score was calculated for all patients. Patients' demographic properties, past medical histories, and cholesterol-hemogram levels were collected. The evaluation of blood lipid levels and other measurements were performed as the standard procedures. Risk factors were categorized as those having or not having the illness. Smoking habits were recorded according to the patients' statements. Hypertension was defined as a systolic blood pressure above 140 and diastolic blood pressure above 90 mmHg, daytime ABP of 135/85 mmHg or use of antihypertensive medications for longer than 2 weeks. Low density lipoprotein level above 130 or using antilipidemic medications was called hypercholesterolemia. A fasting glucose level above 126 or receiving insulin therapy or oral antidiabetic therapy for more than 2 weeks was evaluated as diabetes mellitus (DM). Ambulatory blood pressure monitorization and carotid USG were performed after the coronary angiography. This study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital under the (decision no: 03.07.2014/6). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Ambulatory Blood Pressure Monitorization

All patients underwent ABPM to rule out the effect of blood pressure on CIMT. A portable compact digital recorder (Tonoport V, Milwaukee, GE Healthcare) was used to perform 24-h ABMP measurement. This device was programmed to measure daytime and nighttime blood pressures. Daytime was defined as the time from 07.00 to 23.00 and the device measured blood pressure at 30-min intervals. Nighttime was defined as the time from 23.00 to 07.00 and the device measured blood pressure at 60-min intervals. The patients were told to do their daily activities, but only to remain stable during the device measurement. If more than 80% of the measurements were valid, the test was considered appropriate.

Evaluation of Carotid Images

Carotid USG was performed on all patients for CIMT measurement and carotid plaque evaluation after the coronary angiography. The recommendation of the American Society of Echocardiography and The Society of Vascular Medicine for the calculation was considered (15). Carotid USG was performed by a vascular radiologist who was certificated for the procedures of duplex scan. The LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) was used to measure the carotid arteries. All calculations were made from the common carotid arteries on both sides, approximately 15 mm proximal of the carotid

bifurcation. CIMT was calculated between the medial-adventitial surface and luminal-intimal surface. Three different places of the thickest ones were measured, and the maximum values were taken to reach valid CIMT without including the plaques. The mean values of the right and left carotid arteries were accepted as the ultimate CIMT. Carotid plaque was accepted and described as the increase of intima- media thickness focally for more than 50% or CIMT >1.5mm. Finally, the study population was divided into two groups as the high-risk carotid profile group and the low-risk carotid profile group. Having plaques or CIMT >0.9 mm was defined as the high-risk carotid profile and not having plaques or CIMT ≤0.9 mm was defined as the low risk carotid profile considering the previous studies (16,17).

Statistical Analysis

Continuous variables are presented as means and standard deviations. The categorical variables are expressed as numbers and percentages. Study groups were compared using the unpaired Student's t-test for continuous variables that displayed normal distribution and using the Mann-Whitney U test for continuous variables that did not display normal distribution. Categorical data were compared with the chi-square test. For predicting potential risk factors for MI, logistic regression analysis was used. A p value below than 0.10 was employed for potential variable selection in multivariate analysis. The Nagelkerke r-squared values for logistic regression were recorded. Receiver operating characteristics (ROC) curves for potential risk factors were drawn to distinguish MI. The Youden's index was used to derive the best cut-offs. The area under the ROC curves (AUC) was recorded. P values under 0.05 were considered to be statistically significant. Statistical analyses were performed using the SPSS software version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

There was no statistically significant difference between the groups in terms of traditional risk factors and Framingham risk score. As expected, only white blood cell level was significantly higher in the MI group (Table 1).

Carotid USG scans and ambulatory blood pressure monitorization results of the patients having MI and the patients with normal coronary arteries can be seen in Table 2. There was no difference between the two groups in terms of daytime, nighttime, and mean systolic and diastolic blood pressures. Thus, blood pressure effect, which is one of the most important determinants of CIMT, was ruled out. There was a statistically significant difference in CIMT ($p<0.001$) and carotid plaque presence ($p=0.024$) between the groups. In addition, high-risk carotid profile was significantly higher in the MI group. (40.0% vs 6.7%, $p<0.001$).

In logistic regression analysis, it was determined that Framingham risk score and traditional risk factors were not independent predictors of MI. Only high density lipoprotein was detected as a predictor ($p=0.019$). Nevertheless, independent from traditional risk factors and Framingham risk score, 0.1 mm increase in CIMT was associated with a 42% increase in odds for STEMI. Similarly, independent from traditional risk factors and Framingham risk score, being in the high-risk carotid image group had 9.2 times higher odds for MI than being in the low-risk carotid image group (Table 3). A CIMT cut-off >0.8 mm had AUC of 0.686 for distinguishing MI patients from patients with normal coronary angiography, with a 48.7% sensitivity and 80.0% specificity (Figure 1).

Table 1. Baseline characteristics of study population, mean ± standard deviation, or n (%)

Variable	MI patients, (n=115)	Control group, (n=45)	p
Age, years	39.4±4.3	39.3±4.2	0.856
Male, n (%)	103 (89.6%)	38 (84.4%)	0.368
BMI (kg/m^2)	29.1±3.9	29.1±4.1	0.949
Smoking, n (%)	58 (50.4%)	16 (35.6%)	0.090
DM, n (%)	16 (13.9%)	5 (11.1%)	0.637
HT, n (%)	33 (28.7%)	8 (17.8%)	0.155
HL, n (%)	48 (41.7%)	14 (31.1%)	0.215
Family H, n (%)	37 (32.2%)	9 (20.0%)	0.126
Framingham risk score, %	7.3±5.6	5.8±7.1	0.159
Creatinine (mg/dL)	0.81±0.17	0.78±0.14	0.165
Total cholesterol (mg/dL)	200.8±42.6	213.3±59.1	0.138
LDL (mg/dL)	132.7±34.1	129.3±42.5	0.601
HDL (mg/dL)	36.9±10.2	39.9±10.4	0.102
Triglycerides (mg/dL)	190.7±157.5	213.8±123.4	0.376
Glucose (mg/dL)	132.2±57.2	142.2±91.4	0.420
WBC count (10^3/L)	11.8±3.3	8.0±2.7	<0.001
Platelet (10^3/L)	270.1±61.4	266.2±69.2	0.727
Hematocrit (g/dL)	42.9±4.4	41.7±2.6	0.080

MI: myocardial Infarction, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, HL: hyperlipidemia, H: history, LDL: low density lipoprotein, HDL: high density lipoprotein, WBC: white blood cell

Table 2. Ambulatory blood pressure monitorization and carotid imaging results of study population mean ± standard deviation, or n (%)

	MI patients, (n=115)	Control group, (n=45)	p
Mean SBP, mmHg	125.3±16.4	126.5±10.9	0.651
Mean DBP, mmHg	80.7±12.9	79.4±13.8	0.584
Daytime SBP, mmHg	128.2±17.0	128.6±11.1	0.870
Daytime DBP, mmHg	83.6±13.3	83.1±9.0	0.816
Nighttime SBP, mmHg	116.8±18.1	117.2±20.2	0.911
Nighttime DBP, mmHg	72.3±13.5	74.6±10.8	0.311
CIMT, mm	0.87±0.28	0.70±0.16	<0.001
Carotid plaque presence, n (%)	17 (14.8%)	1 (2.2%)	0.024
High-Risk Carotid Profile, n (%)**	46 (40.0%)	3 (6.7%)	<0.001

**High risk carotid profiled defined as having plaques or CIMT >0.9 mm.

SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness

Table 3. Multivariate logistic regression analysis for potential predictors of myocardial infarction

	Univariate analysis		Multivariate analysis¶	
	OR (CI 95%)	p	OR (CI 95%)	p
Age, years	1.015 (0.935-1.103)	0.716	-	-
Male, yes	0.606 (0.215-1.708)	0.343	-	-
BMI, kg/m^2	0.997 (0.914-1.057)	0.940	-	-
Hyperlipidemia, yes	1.678 (0.796-3.677)	0.173	-	-
DM, yes	1.363 (0.454-4.090)	0.581	-	-
Smoking, yes	1.844 (0.907-3.757)	0.092	1.634 (0.759-3.520)	0.210
Hypertension, yes	1.861 (1.084-4.418)	0.159	-	-
Family history, yes	1.897 (0.829-4.345)	0.130	-	-
Framingham score	1.037 (0.970-1.105)	0.254	-	-
HDL, mg/dL	0.963 (0.931-0.997)	0.032	0.958 (0.923-0.993)	0.019
LDL, mg/dL	1.003 (0.993-1.012)	0.598	-	-
Mean SBP, mmHg	0.967 (0.924-1.012)	0.150	-	-
Mean DBP, mmHg	1.041 (0.984-1.100)	0.161	-	-
CIMT, mm x 10	27.162 (4.151-177.744)	0.001	1.420 (1.168-1.725)	0.001
Carotid plaque presence	7.633 (0.985-59.166)	0.052	5.138 (0.642-41.117)	0.123
High risk carotid image†	9.333 (2.730-31.909)	<0.001	9.241 (2.682-31.841)	<0.001

†These groups were included in a second model instead of carotid intima-media thickness and carotid plaque presence

¶Nagelkerke R square of the full model was 23.6%.

OR: odds ratio, CI: confidence interval, BMI: body mass index, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure, CIMT: carotid intima-media thickness

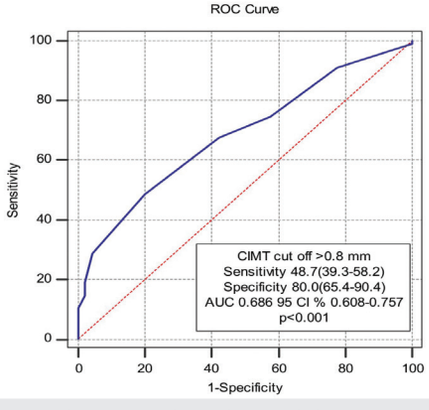


Figure 1. Receiver operating characteristics curve showing the distinguishing ability of Carotid Intima-Media Thickness for ST Segment Elevated Myocardial Infarction.

ROC: receiver operating characteristics, CIMT: carotid intima-media thickness, AUC: area under the ROC curve, CI: confidence interval

Discussion

In this study, we found an effect of CIMT on cardiovascular events in young patients. Besides, high-risk carotid image that was defined as CIMT >0.9 mm or the presence of carotid plaque was related with increased risk of cardiovascular events. Our findings have suggested that beyond traditional risk factors, the carotid imaging plays an important role in determining the risk of MI in young patients. The demonstration of the usefulness of carotid imaging as a predictor of MI in young age-matchedindividuals with similar Framingham scores makes our study unique and valuable.

It has been shown that more than half of the cardiovascular heart diseases are seen in low- and moderate-risk groups when patients are assembled into groups according to the traditional risk scores (3,4). Furthermore, there are insufficient data on the predictability of the Framingham risk score, which is used most commonly, in younger patients. Therefore, alternative scanning tests, which can be used to evaluate subclinical atherosclerosis in those patients, may become more important in revising the risk score systems.

CIMT measurement by carotid USG and plaque definition can be found in the guidelines. CIMT >0.9 mm or having a carotid plaque is defined as the target organ damage for hypertension according to the Europe Society of Cardiology (18). The American Heart Association (AHA) recommends CIMT measurement for cardiovascular risk evaluation but not in the form of population screening (19,20). Furthermore, under the guidance of a meta-analysis, which shows that detecting plaques in carotid arteries is more important than CIMT measurement, AHA also recommends carotid scan for plaques (21). Considering these guidelines, we arranged the risk groups according to both CIMT measurement and presence of carotid plaques in our study.

Many epidemiologic studies such as the atherosclerosis risk in communities (9) and the cardiovascular health study (10) detected a direct relationship between MI and CIMT even in the absence of cardiac illness. The study of Paroi Arterielle et Risque Cardiovasculare in Asia Africa/ Middle East and Latin America (parc-aala) is another study that found a relationship between CIMT and carotid plaques with Framingham risk score, free from geographic differences (22). In the Rotterdam study, Bots et al. followed 7893 patients and found 194 MI cases during that period. At the end of the study, MI group had higher CIMT values than the other group (23). The Kuppio ischemic heart disease study found that if the CIMT value had increased 0.1 mm, 11% increase of MI cases could happen regarding this (24). In another study, Salonen and Salonen (25) showed that plaque formation was related to increased MI risk by 4.15 times and accordingly, they speculated that early carotid USG and risk classification could have advantages to decrease acute coronary syndromes. Irie et al. (26) had shown that maximum CIMT measurement in addition to traditional risk factors could improve risk classification. Baldassare found that CIMT measurement in addition to Framingham risk score was a rational approach to prevent cardiovascular diseases (27). In our study, unlike above-mentioned studies, we focused only on young patients and we combined CIMT and plaque formation. Consequently, we investigated that being in the high-risk carotid image group had 9.2 times increased odds for MI. These results indicate the additional effect of CIMT and plaque presence. Besides, MI patients and

the patients with normal coronary arteries had no statistically significant difference in terms of traditional risk factors and Framingham risk score, however, there were significant differences in terms of CIMT and carotid plaque, which means that carotid scanning is a valuable test apart from traditional risk scores to determine the risk of coronary artery disease in the young population.

We established our study on young population. When choosing this population, our goal was to determine the function of the carotid imaging to determine the risk group in this population. Since both traditional risk scoring and scoring such as coronary calcium are not high predictive values, a primary precaution cannot be taken in young age groups. CIMT measurement is a reliable marker for the plaque formation for the atherosclerotic process in young patients (28). Similarly, studies showed that carotid USG was more confidential than coronary calcium score to detect atherosclerosis in young adults since the calcification period could take years (29,30). Carotid scanning becomes more valuable to detect subclinical atherosclerosis in young MI patients as Fournier et al. (31) have shown that atherosclerosis can be seen relatively less in young MI. Also, Linhart et al. (11) revealed that young MI patients had an increased CIMT thickness, which is consistent with our study data (p=0.001). So, we can speculate that atherosclerosis is a diffuse disease and may affect many vascular beds at the same time in young population.

Especially in patients with a moderate risk according to traditional risk factors for cardiovascular disease, carotid imaging appears to be valuable for detecting increased latent cardiovascular risk. However, there are not enough data to prescribe acetylsalicylic acid or statin in patients who have high-risk carotid images. Regarding this, more prospective randomized trials should be carried out.

There was no difference between the MI group and the control group in terms of traditional risk factors. Since risk factors were taken into account in the process of angiographic decision-making in the control group, it is not surprising that this group had as many risk factors as MI patients. Moreover, the scores on gender, DM, hyperlipidemia, smoking, family history, and hypertension were higher in the MI group, but the difference was not statistically significant. The statistically significant difference of carotid imaging between the groups may be considered to be additional effects of these risk factors. In addition, increased CIMT and the presence of carotid plaque may occur as a result of indirect mechanisms independently of traditional risk factors.

This study provided novel evidence enlightening the importance of carotid imaging in young patients. However, it has some limitations. First, this was a single-center study which may result in selection bias. Second, the cross-sectional design of the study suggests an association but does not establish a cause and effect relationship. Third, carotid scanning was evaluated by only one researcher. Nonetheless, the test was performed by standard protocols and specialists in the field. Finally, this is not a prospective study so the absence of long-term results has prevented us from obtaining future results of high-risk carotid imaging.

Conclusion

In summary, we found a relationship between MI and high-risk carotid profile defined as increased CIMT and the presence of carotid plaque in young patients. Our findings suggest that beyond having established risk factors, high-risk carotid imaging provides additional information to detect subclinical atherosclerosis in young patients. In light of this study, clinicians need to focus on carotid imaging apart from traditional risk factors when screening young patients for atherosclerosis. Furthermore, we should consider closer and more frequent follow-up of individuals with high-risk carotid imaging to prevent fatal and non-fatal cardiovascular events in young population.

Acknowledgement

We are really grateful to Biostatistics and Radiology Department of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital for giving close attention to the study and allocating time for the study.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital under the (decision no: 03.07.2014/6).

Informed Consent: Informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.U.S.; Design - M.U.S., H.K.; Supervision - M.U.S.; Materials - M.U.S.; Data Collection and/or Processing - M.U.S., H.K.; Analysis and/or Interpretation - M.U.S., H.K.; Literature Search - M.U.S.; Writing Manuscript - M.U.S.; Critical Review - M.U.S.

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

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

References

1. Gaziano JM. Global burden of cardiovascular disease. In: Braunwald E, Zipes DP, Libby P, editors. Heartdisease: A textbook of cardiovascular medicine. 6th ed. Philadelphia: WB Saunders Company; 2001.p.1-17.
2. Batsis JA, Lopez-Jimenez F. Cardiovascular risk assessment-from individual risk prediction to estimation of global risk and change in risk in the population. BMC Med 2010; 8: 29.
3. National Cholesterol Education Program (NCEP) Expert Panel on Detection. evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
5. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011; 365: 213-21.
6. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004; 110: 3075-80.

7. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010; 303: 1610-6.
8. Warwick GR, Benderson J, Albers JJ. Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. Clin Chem 1982; 28: 1379-88.
9. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987-1993. Am J Epidemiol 1997; 146: 483-94.
10. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. N Engl J Med 1999; 340: 14-22.
11. Linhart A, Dostálová G, Belohlávek J, Vítek L, Karetová D, Ingrischová M, et al. Carotid intima-media thickness in young survivors of acute myocardial infarction. Exp Clin Cardiol 2012; 17: 215-20.
12. Vrtovec B, Keber I, Gadzijev A, Bardorfer I, Keber D. Carotid intima-media thickness of young coronary patients. Coron Artery Dis 1999; 10: 407-11.
13. Coppola G, Corrado E, Piraino D, Carella M, Muratori L, Camarda P, et al. Carotid intimal-media thickness and endothelial function in young patients with history of myocardial infarction. Int Angiol 2009; 28: 120-6.
14. Erzen B, Sabovic M, Sebestjen M, Poredos P. Endothelia dysfunction, intima-media thickness, ankle-brachial pressure index,and pulse pressure in young post-myocardial infarction patients with various expressions of classical risk factors. Heart Vessels 2007; 22: 215-22.
15. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid intima-media thickness task force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21: 93-111.
16. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. Eur Heart J 2012; 33: 113-9.
17. Murphy DJ, Crinion SJ, Redmond CE, Healy GM, McNicholas WT, Ryan S, et al. Diagnostic accuracy of carotid intima media thickness in predicting coronary plaque burden on coronary computed tomography angiography in patients with obstructive sleep apnoea. J Cardiovasc Comput Tomogr 2017; 11: 227-33.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the european society of hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159-219.
19. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. Health Technol Assess 2003; 7: 1-94.
20. Goff DC, Jr., Lloyd-Jones DM, Bennett G et al. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013.
21. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21: 93-111.
22. Touboul PJ, Hernández-Hernández R, Küçükoğlu S, Woo KS, Vicaut E, Labreuche J, et al. Carotid artery intima media thickness, plaque and Framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA study. Int J Cardiovasc Imaging 2007; 23: 557-67.
23. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of non-invasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation 2004; 109: 1089-94.
24. Howard G, Burke GL, Evans GW, Crouse JR 3rd, Riley W, Arnett D, et al. Relations of intimal-medial thickness among sites within the carotid artery as evaluated by B-mode ultrasound. ARIC Investigators. Atherosclerosis Risk in Communities. Stroke 1994; 25: 1581-7.
25. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population based ultrasonography study. Atherosclerosis. 1990; 81: 33-40.
26. Irie Y, Katakami N, Kaneto H, Kasami R, Sumitsuji S, Yamasaki K, et al. Maximum carotid intima-media thickness improves the prediction ability of coronary artery stenosis in type 2 diabetic patients without history of coronary artery disease. Atherosclerosis 2012; 221: 438-44.
27. Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries ES, Smit JA, et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as predictors of vascular events in a high risk european population) study. J Am Coll Cardiol 2012; 60: 1489-99.
28. Geerts CC, Bots ML, Grobbee DE, Uiterwaal CS. Parental smoking and vascular damage in young adult offspring: is early life exposure critical? The atherosclerosis risk in young adults study. Arterioscler Thromb Vasc Biol 2008; 28: 2296-302.
29. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002; 346: 793-801.
30. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21: 93-111.
31. Fournier JA, Sanches A, Quero J, Perez Cortacero JA, Gonzales BA. Myocardial infarction in men aged 40 years or less: Prospective clinical-angiographic study. Clin Cardiol 1996; 19: 631-6.

İstanbul Med J 2019; 20(3): 224-30
DOI: 10.4274/imj.galenos.2018.32068

Factors Affecting the Etiology of Intractable Pruritus in Hospitalized Patients Without Primary Skin Lesions

Yatırılarak Etiyolojik Araştırma Yapılan Primer Deri Lezyonu Olmayan Şiddetli Kaşıntılı Hastalarda Kaşıntı Etiyolojisini Etkileyen Faktörler

Neslihan Akdoğan[1], Pınar İncel Uysal[1], Ayşe Öktem[1], Erdem Karabulut[2], Yıldız Hayran[1], Başak Yalçın[1]

[1]University of Health Sciences, Ankara Numune Training and Research Hospital, Clinic of Dermatology and Venereology, Ankara, Turkey
[2]Hacettepe University Faculty of Medicine, Department of Biostatistics, Ankara, Turkey

ABSTRACT

Introduction: Pruritus is a common symptom that has dermatologic, systemic, neurological, psychogenic, mixed, and unknown causes. The aim of this study was to identify the underlying origin of pruritus (UOP) in hospitalized patients having intractable pruritus and presenting with secondary scratch lesions (SSLs) and to assess the factors affecting UOP.

Methods: Data of 95 patients (male/female: 47/48) presenting with SSLs were examined retrospectively. Demographic and clinical characteristics, diagnostic procedures, and treatment agents were recorded. UOP was defined as dermatological and non-dermatological factors.

Results: The median (range) age and disease duration were 61 years (11-91) and 2 months (0.06-120), respectively. Pruritus was related to dermatological and non-dermatological reasons in 78% and 22% of patients. Univariate analysis revealed that factors showing an association between patients with and without underlying dermatological origin of [pruritus (UDOP)] were age, disease duration, disease onset, ≥3 months of continuous drug use, intake of drugs attributed to lead to pruritus, accompanying systemic diseases, polypharmacy, renal function tests, and the presence of sleep disorders (p=0.001, p=0.001, p=0.001, p=0.03, p=0.045, p=0.02, p=0.004, p=0.047 and p=0.01, respectively). Multivariate analyses revealed that acute onset of pruritus increased the risk of UDOP by 15.28 times (p=0.005, 95% confidence interval (CI): 2.30-101.67) compared to patients with chronic onset. The lack of sleep disorders increased the risk of UDOP by 8.22 times (p=0.01, 95% CI: 1.67-40.56) compared to patients who had sleep disorders.

Conclusion: Acute onset of pruritus and lack of sleep disorders were independent predictors of UDOP in patients with SSLs. The remaining patients without UDOP should be directed to the relevant departments for accurate diagnosis and management.

Keywords: Pruritus, etiology, skin

ÖZ

Amaç: Kaşıntı sık görülen bir belirti olup dermatolojik, sistemik, nörolojik, psikojenik, mikst ve bilinmeyen sebepleri vardır. Bu çalışmanın amacı sekonder deri lezyonları (SDL) ile prezente olan, dirençli kaşıntı nedeniyle hastanede yatan hastalarda kaşıntı etiyolojisini (KET) bulmak ve KET'i etkileyen faktörleri değerlendirmektedir.

Yöntemler: Retrospektif olarak SDL olan 95 hasta (erkek/kadın: 47/48) çalışmaya alındı. Demografik ve klinik özellikler, tanısal işlemler ve tedavi ajanları kaydedildi. KET dermatolojik ve dermatoloji dışı sebepler olarak tanımlandı.

Bulgular: Çalışmamızda ortalama (aralık) yaş 61 (11-91) yıl ve hastalık süresi 2 (0,06-120) aydı. Kaşıntı %78 hastada dermatolojik, %22 hastada dermatoloji dışı sebeplerle ilişkili bulundu. Tek değişkenli analiz yaş, ortalama hastalık süresi, akut veya kronik seyir, 3 aydan uzun süre sürekli ilaç kullanımı, kaşıntıya yol açabilecek ilaç kullanımı, eşlik eden sistemik hastalık, polifarmasi, böbrek fonksiyon testleri ve uyku bozukluğu varlığı ile altta yatan dermatolojik sebebe bağlı kaşıntısı (DSK) olan ve olmayan hastalarda ilişki gösterdi (sırasıyla p=0,001, p=0,001, p=0,001, p=0,03, p=0,045, p=0,02, p=0,004, p=0,047 ve p=0,01). Çok değişkenli analiz kronik kaşıntısı olan hastalarla karşılaştırıldığında akut kaşıntısı olan hastalarda DSK riskinin 15,28 kat (p=0,005, 95% CI): 2.30-101,67) arttığını gösterdi. Uyku bozukluğu olan hastalarla karşılaştırıldığında uyku bozukluğu yokluğunun DSK riskini 8,22 kat (p=0,01, 95% CI: 1,67-40,56) artırdığı görüldü.

Sonuç: Kaşıntının akut seyirli olması ve uyku bozukluğunun olmaması SDL olan kaşıntılı hastalarda DSK'nin bağımsız prediktörleridir. DSK olmayan hastalar tanı ve tedavi için uygun bölümlere yönlendirilmelidir.

Anahtar Kelimeler: Kaşıntı, etiyoloji, deri

Address for Correspondence/Yazışma Adresi: Neslihan Akdoğan MD, University of Health Sciences, Ankara Numune Training and Research Hospital, Clinic of Dermatology and Venereology, Ankara, Turkey
Phone: +90 312 508 56 43 **E-mail:** nslakdogan@gmail.com **ORCID ID:** orcid.org/0000-0002-1137-5399

Cite this article as/Atıf: Akdoğan N, İncel Uysal P, Öktem A, Karabulut E, Hayran Y, Yalçın B. Factors Affecting the Etiology of Intractable Pruritus in Hospitalized Patients Without Primary Skin Lesions. İstanbul Med J 2019; 20(3): 224-30.

Received/Geliş Tarihi: 19.07.2018
Accepted/Kabul Tarihi: 13.12.2018

Introduction

Pruritus is described as a sensation that will provoke scratching or the desire to scratch (1). It is defined either acute or chronic. Chronic form was described by the International Forum for the Study of Itch in 2007 as that lasting 6 or more weeks (2). Pruritic patients are divided into 6 groups according to the underlying etiologies such as dermatologic, systemic, neurologic, psychogenic/psychosomatic, mixed and other reasons (2). Well-known dermatologic conditions associated with pruritus are inflammatory skin diseases, infectious dermatoses, neoplastic conditions, genodermatoses, autoimmune bullous diseases, and some pregnancy dermatoses (3).

The underlying etiologies of patients with pruritus are sometimes detected easily. However, the exact diagnosis remains challenging when patients only present with secondary scratch lesions (SSLs) instead of presentation with primary skin lesions (PSLs) (4). Some patients may only present with SSLs without any PSLs. However, SSLs may arise from the manipulation of PSLs or from external forces such as scratching, trauma in the absence of PSLs. In accordance with the findings outlined above, it may not be possible to reach the underlying origin of pruritus (UOP) in patients with SSLs. Hence, the aim of the study was to identify the UOP and to assess the factors affecting UOP in hospitalized patients with intractable pruritus in the absence of PSLs.

Methods

Data of the patients with the diagnosis of pruritus of unknown etiology defined by the ICD-10 codes L29 (pruritus), L29.8 (other pruritus), L29.9 (pruritus, not elsewhere classified), and L28.2 (other prurigo) were retrospectively collected from hospital databases between October 2013 and November 2016. Regardless of the duration of pruritus, patients with acute or chronic onset and intractable pruritus were enrolled. Intractable pruritus is defined to be refractory to conventional therapies for pruritus (combination of oral antihistamines, topical mild or moderate potent corticosteroid ointments and moisturizers) given at least for 2 months and/or generalized distribution in patients for whom topical therapies were not appropriate and/or intense pruritus leading sleep disorders, disturbance of daily activities. Pruritic patients with underlying dermatoses were excluded. In all patients presented with SSLs in the absence of identifiable PSLs. SSLs were described as excoriation, lichenification, fissure, erosion, ulceration, scale, and crust.

Demographic data including age, gender, duration of pruritus, personal and familial medical history, onset of disease (acute/chronic), and previous and current topical and systemic treatment agents were recorded. Patients were questioned for sleep disorders due to pruritus. The presence of xerosis was checked. Patients were classified by age groups according to the World Health Organization's old age description (<60 years and >60 years) for statistical analysis (5). The duration of pruritus was expressed in months. A detailed medication (use of any drug due to a reason other than pruritus) history including ≥3 months of continuous drug use and newly initiated drug therapy in the past 30 days was obtained. Polypharmacy was defined as the concurrent use of ≥4 drugs. The European guideline was used to detect potential drugs that could lead to pruritus (6).

Collected laboratory investigation data comprised of serum levels of liver transaminases, renal function tests, blood eosinophil cell count, total serum immunoglobulin E (IgE) levels, and stool parasite tests. Eosinophilia was described as a peripheral blood eosinophil cell count >600 cells/microliter. The extent of eosinophilia was classified into 3 groups as mild (600-1500 cells/mL), moderate (1500-5000 cells/mL) or severe (>5000 cells/mL). A serum total IgE level >87 IU/mL was considered high. Stool specimens were collected over a 3-day period. Number of patients undergoing testing for malignant disease and testing for skin biopsy, lymph node biopsy, patch test or any other invasive diagnostic procedures were recorded. Numbers and details of the radiological studies and invasive diagnostic tests were based on the patients' first hospitalization for pruritus prior to the initiation of treatments. The result of skin biopsies was reviewed. The status of direct immunofluorescence microscopy (DIF) was questioned.

The number and content of consultations requested during hospitalization were examined. The duration of hospitalization was expressed in days. The diagnoses were confirmed by clinical features and histopathological findings. Patients were then classified according to the UOP such as dermatological and non-dermatological factors. The associations between patients with and without underlying dermatological origin of pruritus (UDOP) were assessed.

Statistical Analysis

All statistical analyses were performed using the software of Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 20.0. Demographic and clinical characteristics of the study population were analyzed using descriptive statistics. All numeric variables were expressed as median (range) since no numeric variables followed normality in this study. Categorical variables were described by frequency and percentage. Differences in numeric variables between patients with and without UDOP were analyzed by using the Mann-Whitney U test. The chi-square test ((χ^2) was employed to determine whether there were differences in categorical variables between independent groups. Multivariate logistic regression analysis was used to analyze variables with p value cut-off point of 0.15 via following elimination of confounding factors. The strength of the association between variables and UOP was assessed by odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). A p value of <0.05 was accepted statistically significant.

The study was approved by the Ankara Numune Training and Research Hospital Ethics Committee (decision no: E-16-1065, 19 October 2016). All procedures performed in the study were in accordance with the ethical principles of the 1964 Helsinki Declaration. Due to the retrospective design, patient consent was not obtained.

Results

Demographic and Clinical Characteristics of the Study Population

The study included 95 participants, including 47 males and 48 females who were examined by the consultant dermatologists. The median (range) age and disease duration was 61 years (11-91) and 2 months (0.06-120 months), respectively. The distribution of patients according to demographic and clinical characteristics, laboratory parameters,

Table 1. Demographic and clinical characteristics of the study population

Data	Patient group, n (%)
Age, years, median (range)	61 (11-91)
Age distribution (years)	
<60 years	47 (49.5%)
>60 years	48 (50.5%)
Gender	
Male	47 (49.5%)
Female	48 (50.5%)
Disease duration, months, median (range)	2 (0.06-120)
Disease onset	
Acute	40 (42%)
Chronic	55 (58%)
Intake of drugs	
≥3 months of continuous drug use	53 (56%)
Newly initiated drug therapy in the past 30 days	8 (8%)
Polypharmacy	26 (27%)
Laboratory results	
Abnormal liver transaminases	8 (8%)
Abnormal renal function tests	11 (12%)
Eosinophilia	29 (31%)
Elevated serum total IgE levels	17 (18%)
Negative stool parasite test	38 (40%)
Positive stool parasite test	1 (1%)
Unknown stool parasite test	56 (59%)
Radiological investigations	
Chest x-ray	73 (77%)
Computerized tomography	15 (16%)
Magnetic resonance imaging	1 (1%)
Ultrasonography of superficial lymph nodes	19 (20%)
Ultrasonography of abdomen	60 (63%)
Others	21 (22%)
Diagnostic invasive procedures	
Skin biopsy	73 (77%)
Lymph node biopsy	2 (2%)
Patch test	1 (1%)
Others	7 (7%)
Previous medications	
Topical corticosteroids	45 (47%)
Moisturizers	24 (25%)
Topical antihistamines	3 (3%)
Oral antihistamines	60 (63%)
Systemic corticosteroids	21 (22%)
Permethrin cream	9 (10%)
Topical antifungals	4 (4%)
Oral antifungals	5 (5%)
Topical antibiotics	8 (8%)
Oral antibiotics	5 (5%)
Oral cyclosporine	1 (1%)
Oral acitretin	1 (2%)
Azatiopurine	1 (1%)
Narrow-band UVB	3 (3%)
Omalizumab	1 (1%)
Gabapentin	1 (1%)
Untreated or unknown	15 (16%)
Current treatment options	
Topical corticosteroids	75 (79%)
Moisturizers	49 (52%)
Oral antihistamines	79 (83%)
Systemic corticosteroids	37 (39%)
Permethrin cream	8 (8%)
Topical antifungals	2 (2%)
Oral antifungals	1 (1%)
Topical antibiotics	15 (16%)
Oral cyclosporine	4 (4%)
Oral acitretin	1 (1%)
Azatiopurine	1 (1%)
Narrow-band UVB	4 (4%)
Omalizumab	1 (1%)
Gabapentin	15 (16%)
Antidepressants	15 (16%)
Oral antibiotics	6 (6%)
Dapsone	2 (2%)
Wound care	2 (2%)

Table 1 contiuned

n: number; UVB: Ultraviolet B phototherapy

Table 2. Frequency of accompanying diseases in this study

Diseases	n	%*
Diabetes mellitus	27	28
Hypertension	34	36
Cardiovascular diseases	11	12
Cardiac failure or arrhythmia	4	4
Pulmonary diseases	10	11
Renal diseases	4	4
Hypothyroidism	5	5
Neuropsychiatric diseases	15	16
Iron deficiency anemia	2	2
History of solid tumor	2	2
Others (gastritis, benign prostatic hyperplasia, cataracts, allergic rhinitis, adrenal insufficiency, rheumatoid arthritis, sarcoidosis, hemorrhoid, vitiligo, polymyalgia rheumatica)	25	26

*More than one systemic disease was seen in some patients
n: number, %: percentage

radiological investigations, diagnostic invasive tests, and previous and current treatment agents are shown in Table 1. Table 2 shows the frequency of accompanying diseases in this study.

Of all, 55 of 95 (58%) patients were using at least one drug for a reason other than pruritus since admission to the hospital. Besides, 45 of these 55 (82%) patients were using a drug which might induce pruritus. Although 22 of these 45 (49%) patients underwent withdrawal or change of the suspected drugs that was associated with pruritus, only 3 patients achieved complete remission of pruritus after drug cessation.

Of 95 patients, 24 (25%) patients exhibited xerosis, whereas 12 patients (13%) suffered from sleep disorders. All patients received at least one consultation during the hospitalization, mostly from internal medicine, psychiatry and ophthalmology (median: 1, range: 0-9). The median duration of hospitalization was 8 days (range:1-34).

Table 3. Etiological classification of all patients presenting with secondary scratch lesions according to underlying origin

Diseases underlying pruritus	**n=95 (%)**
Dermatological origin of pruritus	**n=74 (78%)**
Contact dermatitis	23
Drug reactions	18
Other inflammatory dermatoses	17
Autoimmune bullous diseases	8
Pregnancy dermatoses	3
Cutaneous lymphomas	2
Infectious dermatoses	3
Non-dermatological origin of pruritus	**n=21 (22%)**
Psychogenic origin of pruritus	8
Neurogenic origin of pruritus	3
Systemic origin of pruritus	
Drug-induced pruritus	2
Infection-induced pruritus	1
Mixed	
Psychogenic and neurogenic origin	4
Drug and infection induced pruritus	1
Pruritus of unknown origin	
Prurigo simplex	2

n: number; %: percentage

Table 4. Comparisons of numeric variables between patients with and without underlying dermatological origin of pruritus by univariate analysis

Variable	Patients with UDOP median (range)	Patients without UDOP median (range)	p
Age	56 (11-91)	73 (40-88)	0.001
Duration of pruritus	1 (0.06-120)	7 (0.130-120)	0.001
Blood eosinophil count	350 (0-5400)	300 (100-1000)	0.34
Duration of hospitalization	8 (1-37)	7 (2-16)	0.32

P values <0.05 is shown in bold
UDOP: Underlying dermatological origin of pruritus

Diseases Underlying Intractable Pruritus

A definitive diagnosis was confirmed by histopathological examination in 53 of 95 (56%) patients. The initial diagnoses by the dermatologist for the biopsy included allergic contact dermatitis (CD) (n=9), drug eruption (n=7), bullous pemphigoid (n=6), mycosis fungoides (n=5), cutaneous vasculitis (n=4), lichen planus (n=3), dermatitis herpetiformis (n=3), urticaria (n=3), psoriasis (n=2), lichenoid drug eruption (n=2), pemphigoid gestationis (n=2), actinic reticuloid (n=2), pityriasis rosea (n=1), Grover's disease (n=1), eosinophilic cellulitis (n=1), pemphigus vulgaris (n=1), and impetigo (n=1). However, detailed history, clinical and histopathological findings, and treatment responses led us to conclude on certain diagnosis in 42 of 95 (44%) patients who did not have definitive histopathological diagnoses. Intractable pruritus was associated with dermatological reasons in 74 of 95 (78%) patients and with non-dermatological reasons in 21 of 95 (22%) patients. The extended examination of all patients according to UOP is shown in Table 3.

The Mann-Whitney U test showed that, for patients with UDOP vs without UDOP, the median age and median disease duration were 56 (11-91) vs 73 (40-88) and 1 (0.06-120) vs 7 (0.13-120), respectively (p=0.001 and p=0.001, respectively) (Table 4). There was no difference between patients with UDOP and without UDOP in terms of the median eosinophil count and duration of hospitalization (p=0.34 and p=0.32, respectively).

χ^2 test revealed that there was an association between patients with and without UDOP, and disease onset, ≥3 months of continuous drug use, polypharmacy, intake of drugs attributed to lead to pruritus, accompanying systemic diseases, renal function tests and sleep disorders (p=0.001, p=0.03, p=0.004, p=0.045, p=0.02, p=0.047 and p=0.01, respectively). Univariate analysis showed that there was not any significant association between patients with and without UDOP, and gender, xerosis, eosinophilia, liver transaminases, and use of a drug initiated in the last 30 days (Table 5).

Multivariate logistic regression analyses revealed that no parameter was significantly associated with UOP, except disease onset and sleep disorders. Furthermore, acute onset of pruritus increased the risk of UDOP by 15.28 times (p=0.005, 95% CI: 2.30-101.67) compared to chronic onset. The lack of sleep disorders increased the risk of UDOP by 8.22-fold (p=0.01, 95% CI: 1.67-40.56) compared to patients who had sleep disorders. Therefore, acute pruritus onset and lack of sleep disorders were significant independent predictors of UOP in patients with intractable pruritus in this study (Table 6).

Discussion

Pruritus is one of the most frequent symptoms in many diseases. It can be associated with dermatological, systemic, neurological, and psychiatric diseases, however, its underlying etiology cannot be found in some patients despite detailed investigations (2). In our study, 78% of patients had a dermatological disease, whereas a dermatological origin was

Table 5. Associations between patients with and without underlying dermatological origin of pruritus and parameters

Characteristic	Patients with UDOP % (n=74)	Patients without UDOP % (n=21)	p
Age			**0.002**
<60 years	58% (n=43)	19% (n=4)	
>60 years	42% (n=31)	81% (n=17)	
Gender			
Female	46% (n=34)	67% (n=14)	0.09
Male	54% (n=40)	33% (n=7)	
Onset			**0.001**
Acute	51% (n=38)	10% (n=2)	
Chronic	49% (n=36)	90% (n=19)	
≥3 months of continuous drug use			**0.03**
Yes	50% (n=37)	76% (n=16)	
No	50% (n=37)	24% (n=5)	
Polypharmacy			**0.004**
Yes	20% (n=15)	52% (n=11)	
No	80% (n=59)	48% (n=10)	
Use of drug initiated in the last 30 days			0.12
Yes	11% (n=8)	0% (n=0)	
No	89% (n=66)	100% (n=21)	
Drugs attributed to cause pruritus			**0.045**
Yes	42% (n=31)	67% (n=14)	
No	58% (n=43)	33% (n=7)	
Eosinophilia			**0.07**
Present	35% (n=26)	14% (n=3)	
Absent	65% (n=48)	86% (n=18)	
Abnormal liver transaminases			**0.49**
Present	10% (n=7)	5% (n=1)	
Absent	90% (n=67)	95% (n=20)	
Abnormal renal function tests			**0.047**
Yes	8% (n=6)	24% (n=5)	
No	92% (n=68)	76% (n=16)	
Accompanying systemic diseases			**0.02**
Present	65% (n=48)	91% (n=19)	
Absent	35% (n=26)	9% (n=2)	
Sleep disorders			**0.01**
Present	8% (n=6)	29% (n=6)	
Absent	92% (n=68)	71% (n=15)	
Xerosis			**0.10**
Present	24% (n=18)	29% (n=6)	
Absent	5% (n=4)	19% (n=4)	
Not known	71% (n=52)	52% (n=11)	

P values <0.05 is shown in bold. Chi-square test was used to make comparisons between the relevant groups

UDOP: Underlying dermatological origin of pruritus

Table 6. Multivariate logistic regression analysis for variables in patients with and without underlying dermatological origin of pruritus after the elimination of confounding factors

Variable	p	OR (95% CI)
Disease onset	**0.005**	-
Acute	-	15.28 (2.30-101.67)
Chronic	-	1 (ref)
Sleep disorders	**0.01**	-
Yes	-	1 (ref)
No	-	8.22 (1.67-40.56)

OR: odds ratios, CI: confidence interval

not specified in the remaining 22% who had psychogenic, neurogenic, systemic, mixed, and unknown etiologies. Additionally, disease onset and the status of sleep disorders were significant independent predictors of UOP in patients with SSLs. The conduction of the present study in the dermatology unit of a tertiary hospital in a metropolitan region may lead to the detection of a high rate of dermatological disease in the absence of PSLs.

The most common disease associated with intractable pruritus was contact dermatitis in this study. Although allergic (A) CD is less common than irritant CD, ACD may be presented with a generalized distribution and intense pruritus due to its being an immune-mediated reaction (7). Thus, ACD should be suspected and evaluated in patients with pruritic eruptions.

Drug eruptions were the second common etiology associated with intractable pruritus following CD in this study. Drugs may lead to pruritus in the form of drug eruptions as a dermatological etiology or in the form of drug-induced pruritus acting as a non-dermatological etiology (6). Eighteen of 95 patients (19%) were suffering from drug eruptions, whereas 3 of 95 patients (3%) were attributed to have drug-induced pruritus that was diagnosed by the disappearance of pruritus after the cessation of the suspected drug in this study. Univariate analysis revealed that there was a significant association between patients with and without UDOP and ≥3 months of continuous drug use, intake of drugs attributed to lead to pruritus, and polypharmacy. However, there was no significant relationship between patients with UDOP and without UDOP and use of a drug initiated in the past 30 days. Therefore, one can speculate that drugs may affect the UOP if a patient is in ≥3 months of drug use, has polypharmacy or is taking any drugs attributed to lead to pruritus. Otherwise, drugs did not seem to affect the etiology of pruritus in patients who were in <1 month of drug use. Clinicians should take a detailed history of drug usage with its time of onset and total duration of use and should not forget that drugs may lead to pruritus without PSLs both in the forms of drug eruptions and in drug-induced pruritus. A recent guideline proposes that the suspected drug should be stopped if risk vs benefit analysis is reasonable to the patient and clinician with regards to drug-induced pruritus (8). Thus, dermatologists should be aware of potential differences in the clinical presentation, diagnostic approaches, and management of drug-associated pruritus forms. However, after the elimination of confounding factors, drug use did not have any effects on UOP in patients with SSLs in this study.

Apart from CD and drug reactions, other inflammatory dermatoses, detected in 17 patients, were the third most common UDOP in this study, which comprised of atopic dermatitis, urticaria, perforating dermatosis, urticarial and leukocytoclastic vasculitis. Indeed, the clinical appearance may have been changed or masked with the disappearance or camouflage of PSLs due to intense itching in these inflammatory dermatoses. Furthermore, patients may present with intractable pruritus in the pre-bullous phase of bullous pemphigoid and in dermatitis herpetiformis without PSLs, as in 8 patients in this study (9,10).

Besides dermatological etiologies, systemic diseases, neurological disorders and psychosomatic/psychiatric diseases are attributed to lead to pruritus (2,11). Several systemic diseases including iron deficiency anemia, hepatobiliary diseases, polycythemia vera, neoplasms and endocrine disorders have been reported to be especially associated with the chronic form of pruritus in the literature (12). Systemic etiologies were detected in 4 of 95 patients (4%) (one patient in the form of infection-induced, 3 patients in the form of drug-induced pruritus), suggesting that systemic diseases that were potentially associated with pruritus were relatively infrequent in our study population. However, it is not possible to ignore the impact of detected systemic diseases, such as diabetes mellitus, iron deficiency anemia, hypothyroidism, renal failure, on pruritus in patients with SSLs. Accordingly, univariate analysis showed that there was a significant association between patients with and without UDOP and accompanying systemic diseases. Systemic diseases showing relationship with pruritus may have contributed to the development of pruritus instead of its being primary reason. Additional research is needed to further clarify the exact role of accompanying diseases in the development of pruritus, and clinical significance, so as to discern if this knowledge can improve our attitude in intractable pruritus.

Psychogenic and neurogenic etiologies were considered in 15 of 95 patients (16%) in this study. It is known that psychiatric diseases may cause an increased response of the peripheral and central nervous system to pruritogenic stimuli, whereas neurogenic diseases may lead to hyperstimulation via pruritogens at the nerve fiber (13,14). To provide proper treatments, it is important to evaluate the psychogenic burden of pruritus when examining a patient with intractable and chronic pruritus. Hypo or hyperesthesia, symptoms of pain, and localized or generalized distribution may differentiate neurogenic form of pruritus in cases from other subgroups (13). It should not be forgotten that drugs may sometimes be more frequently associated with pruritus than the systemic diseases for which they are used. For example, topiramate may improve psychogenic pruritus, which also induced drug-induced pruritus (15).

Despite detailed investigations, UOP was not identified in 2 of 95 (2%) patients diagnosed with prurigo simplex through histopathology. Both of the two patients presented with chronic pruritus and were older than 60 years. Ständer et al. (2) proposed to classify this group as "others" and called them as "pruritus of undetermined origin" particularly in patients with chronic condition. Warlich et al. (16) showed that 32 of 510 (6.3%) patients with chronic pruritus were categorized into the group with unknown etiology. The present study demonstrated lower frequency of patients with unknown etiology compared to existing literature. If this study had included only patients with chronic onset and older ages, a higher rate of patients with unknown etiology might have been found. Additionally, the fact that patients may have been actually hospitalized to investigate the UOP might have diminished the number of unknown cases.

Although univariate analysis showed that there was no significant association between patients with and without UDOP, and xerosis, the contribution of xerosis to pruritus should not be overlooked in patients especially with chronic pruritus in the presence of SSLs. While pruritus is a common symptom in the elderly population, xerosis is the most frequent dermatological change leading to pruritus in this group (17). In the present study, 24 of 95 patients (25%), 11 of whom were elderly patients, had dry skin, whereas the status of xerosis was not known in 63 of 95 patients. Therefore, it would be appropriate to make certain comments on the impact of xerosis for the prediction of UOP in patients with SSLs.

According to the present study, for the acute onset of pruritus, it is more likely to find an etiology of dermatological origin for intractable pruritus in the absence of PSLs. A cross-sectional study showed that no difference was found between patients with acute and chronic pruritus in terms of the distribution of diagnoses and sleeplessness due to pruritus (18).

Pruritus is an unpleasant symptom that can negatively affect quality of life, and cause mood disturbances and disarranged sleep patterns in many patients. In this study, 12 of 95 patients (13%), for whom psychiatry consultation was requested, were suffering from sleep disorders due to pruritus. Oral antidepressant therapy was initiated in 7 of these 12 patients by the psychiatry department. Since oral antidepressants were considered to have antipruritic effects through their influence on serotonin and histamine levels, they were suggested for patients with chronic pruritus who gave no respond to other treatments (19). Univariate and multivariate analyses showed that there was a significant association between patients with and without UDOP, and sleep disorders. The lack of sleep disorders increased the risk of UDOP by 8.22-fold ($p=0.01$, 95% CI: 1.67-40.56) compared to patients having sleep disorders. Therefore, the presence of sleep disorders may have effects on UOP in patients with SSLs. Zachariae et al. (20) used an adapted form of Itch Severity scale in their study and demonstrated that the severity of pruritus was significantly correlated with impaired sleep quality among different origins of pruritus. Furthermore, the impact of several dermatoses including atopic dermatitis (21), psoriasis (22), chronic urticaria (23), and autoimmune bullous diseases (24) on sleep quality should not be ignored. Indeed, it should not be forgotten that patients with intractable pruritus may have impaired sleep quality in variable degrees regardless of the onset of pruritus.

The main limitations of this study were the retrospective design and the dependence of medical records of patients on hospital-based information. The absence of stool parasite examination in a large number of patients, the obscurity of previous medications in some patients, the lack of certain histopathological diagnoses in all biopsied cases are the other limitations for this study. Additionally, causality could not be evaluated due to its retrospective design. However, we think that our study contributes to the existing literature. It should not be forgotten

that besides dermatological reasons, intractable pruritus in the absence of PSLs may be associated with systemic reasons such as drugs and infections as well as psychogenic, neurogenic, mixed and unknown reasons. So, patients with intractable pruritus should be directed to the relevant departments for accurate diagnosis and correct treatment. Additionally, the onset of acute pruritus and lack of sleep disorders were significant independent predictors of UDOP in patients with SSLs. Further prospective investigations with larger cohorts are needed to characterize the UOP and to suggest more clear recommendations.

Ethics Committee Approval: The study was approved by the Ankara Numune Training and Research Hospital Ethics Committee (decision no: E-16-1065, 19 October 2016).

Informed Consent: Due to the retrospective design, patient consent was not obtained.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - N.A., Y.H.; Design - N.A.; Supervision - N.A., P.İ.U.; Resources - N.A., A.Ö., ; Materials - N.A.; Data Collection and/or Processing - N.A.; Analysis and/or Interpretation - N.A., E.K.; Literature Search - N.A.,B.Y.; Writing Manuscript - N.A.; Critical Review - N.A.

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

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

References

1. Savin JA. How should we define itching? J Am Acad Dermatol 1998; 39: 268-9.
2. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol. 2007; 87: 291-4.
3. Weisshaar E, Fleischer AB Jr, Bernhard JD. Pruritus and Dysesthesia. In: Bolognia JL JJ, Schaffer JV, editors. Dermatology. 3rd ed. London: Saunders; 2012. pp.111-25.
4. Ständer S. Classification of Itch. Curr Probl Dermatol 2016; 50: 1-4.
5. Kowal P, Peachey K. Information needs for research, policy and action on ageing and older adults. A report of the follow-up meeting to the 2000 Harare MDS Workshop. World Health Organization; 2001: 1-27.
6. Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. Acta Derm Venereol 2012;92:563-81.
7. Mowad MC, Marks JG Jr. Allergic contact dermatitis. In: Bolognia JL JJ, Schaffer JV, editors. Dermatology. 3rd ed. London: Saunders; 2012. pp. 233-48.
8. Millington GWM, Collins A, Lovell CR, Leslie TA, Yong ASW, Morgan JD, et al. British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. Br J Dermatol 2018; 178: 34-60.
9. Alonso-Llamazares J, Rogers RS 3rd, Oursler JR, Calobrisi SD. Bullous pemphigoid presenting as generalized pruritus: observations in six patients. Int J Dermatol 1998; 37: 508-14.
10. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part I. Epidemiology, pathogenesis, and clinical presentation. J Am Acad Dermatol 2011; 64: 1017-24.
11. Lee HG, Stull C, Yosipovitch G. Psychiatric disorders and pruritus. Clin Dermatol 2017; 35: 273-80.
12. Yonova D. Pruritus in certain internal diseases. Hippokratia. 2007; 11: 67-71.
13. Pereira MP, Kremer AE, Mettang T, Ständer S. Chronic pruritus in the absence of skin disease: pathophysiology, diagnosis and treatment. Am J Clin Dermatol 2016; 17: 337-48.
14. Altunay IK, Koslu A. Psychogenic pruritus. Turk J Dermatol 2008; 2: 116-20.
15. Signorelli MS, Cinconze M, Nasca MR, Marino M, Martinotti G, Di Giannantonio M, et al. Can topiramate induce pruritus? A case report and review of literature. CNS Neurol Disord Drug Targets 2015; 14: 309-12.
16. Warlich B, Fritz F, Osada N, Bruland P, Stumpf A, Schneider G, et al. Health-Related Quality of Life in Chronic Pruritus: An analysis related to disease etiology, clinical skin conditions and itch Intensity. Dermatology 2015; 231: 253-9.
17. Clerc CJ, Misery L. A Literature review of senile pruritus: from diagnosis to treatment. Acta Derm Venereol 2017; 97: 433-40.
18. Kopyciok ME, Ständer HF, Osada N, Steinke S, Ständer S. Prevalence and characteristics of pruritus: A one-week cross-sectional study in a German Dermatology Practice. Acta Derm Venereol 2016; 96: 50-5.
19. Kouwenhoven TA, van de Kerkhof PCM, Kamsteeg M. Use of oral antidepressants in patients with chronic pruritus: A systematic review. J Am Acad Dermatol 2017; 77: 1068-73.
20. Zachariae R, Lei U, Haedersdal M, Zachariae C. Itch severity and quality of life in patients with pruritus: preliminary validity of a Danish adaptation of the itch severity scale. Acta Derm Venereol. 2012; 92: 508-14.
21. Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Berger T, et al. Frequency and management of sleep disturbance in adults with atopic dermatitis: A Systematic Review. Dermatol Ther (Heidelb) 2017; 7: 349-64.
22. Jensen P, Zachariae C, Skov L, Zachariae R. Sleep disturbance in psoriasis - a case-controlled study. Br J Dermatol 2018; 179: 1376-84.
23. Balp MM, Khalil S, Tian H, Gabriel S, Vietri J, Zuberbier T. Burden of chronic urticaria relative to psoriasis in five European countries. J Eur Acad Dermatol Venereol 2018; 32: 282-90.
24. Pedroni MN, Hirotsu C, Porro AM, Tufik S, Andersen ML. The role of sleep in pemphigus: a review of mechanisms and perspectives. Arch Dermatol Res 2017; 309: 659-64.

İstanbul Med J 2019; 20(3): 231-3
DOI: 10.4274/imj.galenos.2018.70437

Acoustic Voice Analysis Findings in Ankylosing Spondylitis

Ankilozan Spondilit'te Akustik Ses Analizi Bulguları

Ahmet Volkan Sünter[1], Özgür Yiğit[1], Zeynep Alkan[1], Özer Burnaz[2]

[1]İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey
[2]İstanbul Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey

ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease involving the sacroiliac joint and the vertebral column. It can also affect other organs. We aimed to evaluate the voice quality objectively in patients with AS.

Methods: Forty-eight patients who were followed in physical therapy clinic with a diagnosis of AS were enrolled in the study. The control group included 18 healthy volunteers who did not have any voice problems or airway pathology. All patients underwent otorhinolaryngologic examination, laryngostroboscopic evaluation, acoustic voice analysis and pulmonary function test.

Results: Of the 48 patients included in the study, 35 were males and 13 were females. Of the 18 healthy volunteers included in the control group, 14 were males and four were females. The mean ages of the patient and control groups were 38.8±9.79 and 44.17±9.85 years, respectively. There was no statistically significant difference between the groups in terms of demographic characteristics. No cricoarytenoid joint involvement was observed in the patient group. The mean fundamental frequency (F_0) value in the patient group was significantly lower than the control group (p=0.043), while Shimmer values (%) were significantly higher (p=0.008). Additionally, harmonics-to-noise-ratio and signal-to-noise-ratio values were significantly lower in the patient group (p=0.032). No statistically significant difference was found in terms of other acoustic parameters.

Conclusion: In our study, F_0 in patients with AS was lower than the control group. This may be related to reduced respiratory capacity of patients with AS.

Keywords: Acoustic voice analysis, ankylosing spondylitis, fundamental frequency

ÖZ

Amaç: Ankilozan spondilit (AS) özellikle sakroiliak eklem ve vertebral kolonu tutan kronik enflamatuvar bir hastalıktır. Bunun yanında diğer organları da etkileyebilmektedir. Bu çalışmada AS'li hastalarda ses kalitesini objektif olarak değerlendirmeyi amaçladık.

Yöntemler: AS tanısı nedeniyle fizik tedavi bölümünde takip edilen 48 hasta çalışmaya dahil edildi. Kontrol grubu olarak ise herhangi bir ses problemi veya solunum yolu patolojisi bulunmayan 18 sağlıklı gönüllü çalışmaya dahil edildi. Tüm hastalara genel kulak burun boğaz muayenesi, laringostroboskopik değerlendirme, akustik ses analizi ve solunum fonksiyon testleri yapıldı.

Bulgular: Çalışmaya dahil edilen 48 hastanın 35'i erkek, 13'ü kadın olup kontrol grubuna dahil edilen 18 sağlıklı gönüllünün ise 14'ü erkek, 4'ü kadındı. Hasta grubunun yaş ortalaması 38,8±9,79 olarak bulunurken kontrol grubunun yaş ortalaması 44,17±9,85 idi. Gruplar arasında demografik özellikler açısından anlamlı bir farklılık gözlenmemiştir. Çalışma hastalarının hiçbirinde krikoaritenoid eklem tutulumu saptanmamıştır. Çalışma grubunda kontrol grubuna göre ortalama temel frekans (F_0) değerleri istatistiksel olarak anlamlı oranda daha düşük (p=0,043) bulunurken, Shimmer değerleri (%) anlamlı oranda daha yüksek (p=0,008) bulunmuştur. Harmonik-gürültü oranı (HNR) ve sinyal-gürültü oranı (SNR) değerleri ise yine çalışma grubunda istatistiksel olarak anlamlı oranda daha düşüktü (p=0,032). Diğer akustik parametrelerde istatistiksel olarak anlamlı bir değişiklik saptanmadı.

Sonuç: Çalışmamızda AS'li hastalarda sesin temel frekansı kontrol grubuna göre daha düşük bulunmuştur. Bu durum AS'li hastaların azalmış respiratuvar kapasiteleri ile ilgili olabilir.

Anahtar Kelimeler: Akustik ses analizi, ankilozan spondilit, temel frekans

Address for Correspondence/Yazışma Adresi: Ahmet Volkan Sünter MD, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey
Phone: +90 212 459 64 40 **E-mail:** avsunter@gmail.com **ORCID ID:** orcid.org/0000-0001-8601-0450

Cite this article as/Atıf: Sünter AV, Yiğit Ö, Alkan Z, Burnaz Ö. Acoustic Voice Analysis Findings in Ankylosing Spondylitis. İstanbul Med J 2019; 20(3): 231-3.

Received/Geliş Tarihi: 13.10.2018
Accepted/Kabul Tarihi: 22.11.2018

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that involves the sacroiliac joint and the vertebral column. It can involve other joints as well, but rarely can involve extra-articular soft tissues. In addition to joint problems, atypical manifestations such as uveitis, cardiac conduction disorders, pulmonary fibrosis and renal amyloidosis may be observed in patients. In addition to the most frequently involved sacroiliac joint, the joints of the larynx can be involved and the cricoarytenoid joint involvement is the most common. Hoarseness due to vocal cord paralysis may be the first symptom in patients. When lung involvement is present in these patients, lung capacity decreases and shortness of breath develops (1). As it is known, hoarseness may be due to laryngeal pathologies and extra-laryngeal pathologies may also affect voice quality. Decreased lung capacity may impair the quality of voice due to inability to breathe during phonation.

In our study, we aimed to investigate the changes in voice quality due to decreased lung capacity in patients with pulmonary involvement but without cricoarytenoid joint involvement by voice analysis.

Methods

Local Ethics Committee of İstanbul Training and Research Hospital approved this study (decision no: 2009-25). The patient group consisted of 48 AS patients who were followed up at the İstanbul Training and Research Hospital Physical Therapy and Rehabilitation Clinic without lung involvement. The control group consisted of 40 people without hoarseness and lung problems. All patients and voluntary individuals included in the study were explained in detail and written informed consent was obtained. Laryngeal examinations of the patient and control groups were performed by videolaryngostroboscopy (Karl Storz, Pulsar Model 20140020, Tuttlingen, Germany). Following exclusion of patients with vocal cord lesions that can cause hoarseness, vocal cord paralysis, history of laryngeal surgery, smoking and inhaler use, voice quality and function were analyzed using acoustic voice analysis (Dr. Speech, Version 4, Tiger DRS, USA). Pulmonary function test was performed, and patients with FEV1 less than 80 were considered to have pulmonary involvement and these patients were excluded from the study. Voice analysis was performed at least 3 times and the best performance was taken into consideration for analysis. Acoustic analysis parameters of all patients were evaluated statistically.

Statistical Analysis

Statistical analysis was performed with NCSS 2007 (NCSS, LLC, Utah, USA) package program. In addition to descriptive statistical methods (mean ± standard deviation), independent t-test was used for pairwise comparison of groups, x^2 test was used for comparison of qualitative data and Pearson correlation test was used to determine the relationship between variables. The results were evaluated at $p<0.05$ level.

Results

Thirty-five patients were male and 13 were female and their ages ranged from 16-60 years (mean age: 38.8±9.79 years). The control group consisted of 30 male and 10 female, and their ages ranged from 17 to 58 years (mean age: 37.3±8.65 years). The mean duration of disease was 4 years (2 months-37 years). Mean F_0 values were significantly lower in the patient group compared to the control group (p=0.043), whereas Shimmer values were significantly higher than the control group (p=0.008). Harmonics-to-noise-ratio and signal-to-noise-ratio (SNR) were statistically significantly lower in the patient group (p=0.032). There was no statistically significant difference between the mean maximum phonation time of the patient and control groups (p=0.985). There was no statistically significant difference between the s/z rates of the patient and control groups (p=0.250). There was no statistically significant difference between the Jitter (%) means of the patient and control groups (p=0.440) (Table 1). In addition, there was a significant difference in Shimmer and F_0 values with decreased respiratory capacity in respiratory function tests.

Table 1. Voice analysis findings of the study and control groups

	Patient group, n=48	Control group, n=30	t	p
F_0 (Hz)	157.37±43.63	183.14±49.46	-2.06	0.043
Jitter (%)	0.24±0.13	0.21±0.07	0.84	0.404
Shimmer (%)	2.72±1.24	1.88±0.63	2.72	0.008
HNR	20.08±2.4	21.6±2.81	-2.19	0.032
SNR	18.69±2.45	20.24±2.85	-2.20	0.032
MPT	12.89±6.38	12.86±5.91	0.02	0.985
s/z rate	0.18±0.25	0.26±0.3	-1.16	0.250

F_0: fundamental frequency, HNR: harmonics to noise ratio, SNR: signal to noise ratio, MPT: maximum phonation time

Discussion

There are various symptoms in AS depending on affected joint and these symptoms often involve multiple medical departments. Otologic involvement has been identified in the department of ear, nose and throat, and many studies and cases have been presented. Magaro et al. (2) reported conductive hearing loss due to otologic involvement, while other studies reported sensorineural hearing loss due to internal ear involvement (3-5).

Restriction of neck extension in cervical vertebrae due to AS leads to difficult intubation. The fact that the joints in the laryngeal structures are target points often cause vocal and swallowing difficulties in patients. The involvement of the cricoarytenoid joint is observed in rheumatic diseases, especially in rheumatoid arthritis, which is close to 25% (6). In addition, it can be observed rarely in AS patients (7,8). Although this involvement is usually bilateral, it may be in the form of unilateral joint involvement. In these patients, hoarseness and shortness of breath are the most common findings with the limitation of vocal cord movements. One study reported that cricoarytenoid joint involvement responded well to steroid therapy but had a tendency to recur after discontinuation of treatment (7-8).

Cricoarytenoid joint involvement may not always be accompanied by limitation of vocal cord movements. The rate of cricoarytenoid joint involvement increases with increasing duration of the disease. Even in one case, vocal cord fixation has emerged as the first symptom of the disease (9). Laryngeal electromyography may be useful in the differential

diagnosis of vocal cord paralysis in cases where vocal cord mobility is decreased and cricoarytenoid joint involvement is suspected.

Pulmonary involvement is also very common in AS patients, and restrictive type of respiratory problems develop due to reduced movement of the chest wall. Pulmonary function tests often show a marked decline in forced vital capacity. This is associated with decreased thoracic expansibility (1,10). Reduction of lung capacity is a common finding in patients with AS, even if it does not clinically cause symptoms. In these patients, severe respiratory problems occur as the duration of disease progresses.

The most important elements in the formation of voice are the expiratory air from the lungs, the vibratory vocal cords and the vocal tract that acts as resonator. It is known that the voice becomes weak due to decreased lung capacity. In patients with AS, decreased lung capacity, decreased vocal cord mobility, and decreased vocal tract volume may prevent the formation of a healthy voice. All these conditions may be closely related to the duration of the disease, but the degree of involvement in the joint is more important. When compared to the control group in our study, it was seen that the mean frequency of voice was significantly decreased and the shimmer values were significantly increased in the AS group. These changes were thought to be due to restrictive lung disease. Positive correlation between increased restrictive respiratory distress in the pulmonary function test and impairment in these values also support this.

However, in these patients, hoarseness may be confounded not only by joint restriction, but also due to involvement in other regions affecting the quality of the voice. Eliminating the problems in these regions as much as possible in the treatment will solve or reduce these accompanying problems.

Conclusion

In our study, the F_0 in AS patients was lower than the control group. This may be related to reduced respiratory capacity of AS patients.

Ethics Committee Approval: Local Ethics Committee of İstanbul Training and Research Hospital approved this study (decision no: 2009-25).

Informed Consent: All patients and voluntary individuals included in the study were explained in detail and written informed consent was obtained

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.V.S., Z.A.; Design - A.V.S., Ö.Y., Z.A., Ö.B.; Supervision - A.V.S., Ö.Y.; Resources - A.V.S., Ö.Y., Z.A., Ö.B.; Materials - A.V.S., Ö.Y., Z.A., Ö.B.; Data Collection and/or Processing - A.V.S., Ö.Y., Z.A., Ö.B.; Analysis and/or Interpretation - A.V.S., Ö.Y., Z.A., Ö.B.; Literature Search - A.V.S.; Writing Manuscript - A.V.S., Ö.Y.; Critical Review - A.V.S., Ö.Y.

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

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

References

1. Sampaio-Barros PD, Cerqueira EM, Rezende SM, Maeda L, Conde RA, Zanardi VA, et al. Pulmonary involvement in ankylosing spondylitis. Clin Rheumatol 2007; 26: 225-30.
2. Magaro M, Ceresia G, Frustaci A. Arthritis of the middle ear in ankylosing spondylitis. Ann Rheum Dis 1984; 43: 658-9.
3. Alatas N, Yazgan P, Oztürk A, San I, Iynen I. Audiological findings in patients with ankylosing spondylitis. J Laryngol Otol 2005; 119: 534-9.
4. Casellini C, Citera G, Rosemffet M, Ruggeri S, Saviotti A, Maldonado Cocco JA. Audiovestibular disorders in patients with ankylosing spondylitis. J Clin Rheumatol 2005; 11: 81-5.
5. De Miguel E, Tomas M, Benito S, Gavilan J, Gijon J. Ankylosing spondylitis and middle ear impairment. Ann Rheum Dis 1987; 46:174.
6. Beirith SC, Ikino CM, Pereira IA. Laryngeal involvement in rheumatoid arthritis. Braz J Otorhinolaryngol 2013; 79: 233-8.
7. Wojtulewski JA, Sturrock RD, Branfoot AC, Hart FD. Cricoarytenoid arthritis in ankylosing spondylitis Br Med J 1973; 3: 145-6.
8. Bienenstock H, Lanyi VF. Cricoarytenoid arthritis in a patient with ankylosing spondylitis. Arch Otolaryngol 1977; 103: 738-9.
9. Miller FR, Wanamaker JR, Hicks DM, Tucker HM. Cricoarytenoid arthritis and ankylosing spondylitis. Arch Otolaryngol Head Neck Surg 1994; 120: 214-6.
10. Feltelius N, Hedenstrom H, Hillerdal G, Hallgren R. Pulmonary involvement in ankylosing spondylitis. Ann Rheum Dis 1986; 45: 736-40.

İstanbul Med J 2019; 20(3): 234-40
DOI: 10.4274/imj.galenos.2018.37267

Evaluation of Factors Affecting Sexual Activity and Sexuality-Related Quality of Life in Different Stages of Pregnancy

Gebeliğin Değişik Dönemlerinde Cinsel Aktiviteyi ve Cinselliğe Bağlı Hayat Kalitesini Etkileyen Faktörlerin Değerlendirilmesi

Evren Çavuş, Fatma Beyazıt

Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Obstetrics and Gynecology, Çanakkale, Turkey

ABSTRACT

Introduction: Pregnancy is a special period in which physiological and psychological changes are observed in the body. Sexuality-related problems exhibit significant changes during pregnancy. In this study, we aimed to determine the distribution of changes in sexual behavior during pregnancy according to the trimesters and to determine the effects of these dysfunctions on quality of life.

Methods: This study was performed in order to investigate the sexual life of pregnant women during pregnancy and the factors that affect sexual function in women followed up in the outpatient of clinic Çanakkale Onsekiz Mart University, Department of Obstetrics and Gynecology between June 2017 and July 2017. The study included 300 pregnant women. Demographic data form and two questionnaires were applied to pregnant women. One of the questionnaires was aimed to determine the sexual function of pregnant women [Female Sexual Function Index (FSFI)] and the other was aimed to determine the quality of sexual life in pregnancy [Sexual Quality of Life-Female (SQoL-F) questionnaire].

Results: SQoL-F scores were found to be higher in the second trimester than in the first trimester (p=0.005). There was a statistically significant difference between the trimesters in terms of total FSFI scores and the highest score was in the second trimester (p=0.048). Subscales of FSFI scores were also evaluated and lubrication score was higher in the second trimester compared to other trimesters (p=0.009). Sexual success score in the second trimester was higher than in the first trimester (p=0.014).

Conclusion: In this study, we observed a significant decrease in sexual functions during pregnancy and fluctuations in sexual function between trimesters that are comparable with literature data. It is very important for health professionals to provide guidance in solving current problems by providing appropriate counseling services to pregnant women who express that they have problems during sexual intercourse.

Keywords: Pregnancy, quality of life, sexual dysfunction, sexuality

ÖZ

Amaç: Gebelik, vücutta fizyolojik ve psikolojik değişikliklerin görüldüğü özel bir süreçtir. Gebelik süresince cinsellikle ilgili yaşanan sorunlar gebelik trimesterlerine bağlı değişiklikler göstermektedir. Bu çalışmada gebelik süresince yaşanan cinsel işlevdeki değişimlerin trimesterlere göre dağılımını ve bu fonksiyon bozukluklarının hayat kalitesi üzerine etkilerini belirlemeyi amaçladık.

Yöntemler: Bu çalışma, Çanakkale Onsekiz Mart Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı gebe polikliniğine Haziran 2017 ve Temmuz 2017 tarihleri arasında başvuran gebelerin cinsel yaşamlarının ve bunu etkileyen etmenlerin incelenmesi amacıyla yapılmıştır. Çalışmaya 300 gebe kadın dahil edilmiştir. Gebelere demografik bilgilerinin belirlendiği bir form ve 2 anket formu uygulanmıştır. Anket formlarından biri gebelikte cinsel fonksiyonların düzeyini [Female Sexual Function Index (FSFI)] belirlemek, diğeri ise gebelikteki cinsel yaşamın kalitesini [(Cinsel Yaşam Kalite ölçeği-Kadın (CYKö-K)] belirlemeye yönelik idi.

Bulgular: CYKÖ skoru birinci trimester ile kıyaslandığında ikinci trimesterde daha yüksek idi (p=0.005). Trimesterler arasında total FSFI skorları açısından istatistiksel olarak anlamlı fark mevcuttu ve aynı zamanda en yüksek skor ikinci trimesterde idi (p=0,048). FSFI alt başlıkları kendi içlerinde değerlendirildiklerinde lubrikasyon skoru ikinci trimesterde diğer trimesterler ile kıyaslandığında daha yüksek idi (p=0,009). Cinsel başarı ikinci trimester skoru birinci trimester skorundan daha yüksek idi (p=0,014).

Sonuç: Bu çalışmada gebelikteki cinsel fonksiyonlardaki düşüş ve özellikle de trimesterler arası cinsel fonksiyonlardaki dalgalanma genel literatür verileriyle uyumlu olarak saptandı. Sağlık çalışanlarının cinsel ilişki sırasında sorun yaşadığını ifade eden gebelere uygun danışmanlık hizmeti vererek mevcut sorunların çözümünde rehberlik sağlamaları son derece önemlidir.

Anahtar Kelimeler: Gebelik, hayat kalitesi, cinsel işlev bozukluğu, cinsellik

Address for Correspondence/Yazışma Adresi: Fatma Beyazıt MD, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Obstetrics and Gynecology, Çanakkale, Turkey
Phone: +90 286 217 10 98 **E-mail:** fatmabeyazit@yahoo.com **ORCID ID:** orcid.org/0000-0002-0667-6090

Cite this article as/Atıf: Çavuş E, Beyazıt F. Evaluation of Factors Affecting Sexual Activity and Sexuality-Related Quality of Life in Different Stages of Pregnancy. İstanbul Med J 2019; 20(3): 234-40.

Received/Geliş Tarihi: 03.01.2018
Accepted/Kabul Tarihi: 19.12.2018

Introduction

Sexual life is an important part of an individual's health and quality of life (1,2). Sexual life includes gender, sexual identities and roles, sexual orientations, eroticism, pleasure, physical closeness and continuity of generation, and is an essential element of human life (3). Human sexuality and sexual quality of life (SQoL) are influenced by many factors. Race, ethnicity, social status, marital status, family and social support groups, vocational and educational levels are among the main factors affecting sexuality. Factors such as diseases, medical and surgical interventions, infertility, gynecological symptoms, gynecological cancers, changes in family life and domestic violence are other factors that affect the individual's sexual health and quality (3-5). Physiological life events such as menstrual cycle, pregnancy, birth, breastfeeding, menopause during a woman's life and old age can also affect the SQoL (3,6). Conditions such as previous and current diseases, previous pregnancies and births, and gestational week may affect sexual life of a woman during pregnancy (6,7). At the same time, emotional changes and psychological repercussions of physiological changes are other factors that influence sexual life (8,9).

Pregnancy is an important process in which physiological and psychological changes occur. Physiological and psychological changes that occur during pregnancy can affect the sexual life negatively. Sexuality, which is an essential element of human life, is negatively affected by pregnancy and this will negatively affect the quality of life of the individual (3,5,6).

In our study, we aimed to determine the factors affecting the sexual function of pregnant women at different stages of pregnancy (all three trimesters) and the effect of these factors on the SQoL in pregnant women.

Methods

This study was performed in accordance with the Declaration of Helsinki and Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved this study (decision no: 2017/11, date: 07.06.2017). Following approval, a cross-sectional study was performed on 300 pregnant women who admitted to the department of obstetrics and gynecology between June 2017 and July 2017, and who signed written informed consent.

Convenience sampling, a type of non-probability sampling, was used for sampling and was set as 100 pregnant women for every 3 trimesters who met inclusion criteria and who were willing to participate in the study. The inclusion criteria were determined as follows: being able to establish healthy communication, absence of risk factors (abortion risk, infection, third trimester bleeding, premature rupture of membranes, premature birth risk) during pregnancy, no restriction on the sexual life with the recommendation of a physician and being over 18 years of age. Pregnant women who did not agree to participate in the study, who were not sexually active, who still did not live with the same partner and who were younger than 18 years of age were excluded from the study.

Evaluations

The gestational ages of the pregnant women included in the study were determined according to the last menstrual period and were confirmed by ultrasound. The first trimester was determined as 4-14 weeks, the second trimester as 14-28 weeks and the third trimester as 28-42 weeks. Pregnant women were asked to fill out a data form for demographic information. In addition, 2 more questionnaires were applied. One of the questionnaires was to identify the sexual dysfunction in pregnancy (Female Sexual Function Index: FSFI). Sexual function scores of pregnant women were calculated with this index. SQoL-Female (F) was used to determine whether there was a difference between the SQoL before and after conception. Demographic data form was aimed to gather information on age, employment status, education level, type of marriage (arranged-love) and place of residence.

Female Sexual Function Index Questionnaire

The FSFI scale consists of 6 sub-headings including 19 questions asked to identify sexual functions. First and second questions are about sexual desire, 3-4-5-6th about sexual arousal, 7-8-9-10th about lubrication, 11-12-13th about orgasm, 14-15-16th about satisfaction and 17-18-19th about pain. The scores from the answers to these questions were used to determine the sexual function of the patients by having a score between 0 and 40. The reliability and validity study of the Turkish version of this scale, which was developed by Rosen et al. (10), was done by Aygin and Eti Aslan (11).

Sexual Quality of Life-Female Questionnaire Form

SQoL scale during pregnancy is a self-assessed, easy to use questionnaire consisting of 18 questions, each with a 6-point Likert scale (1= completely agree, 2= moderately agree, 3= slightly agree, 4= slightly disagree, 5= moderately disagree, 6= completely disagree). Each item is expected to be answered by the patient regarding the sex life in the last four weeks. The score range of this scale is 18-108. The scores of items 1, 5, 9, 13 and 18 are reversed before the total score is calculated. Raw scores must be transformed onto a standardized scale of 0 to 100 using the following formula: "Scale score= the sum of the component items (minus) the lowest possible score * 100 possible raw score range". The answers to the questions are collected as points and these points are used to calculate the SQoL by converting to percentage values. The higher the score, the better the SQoL. The validity and reliability study of the Turkish version of SQoL-F was published by Tuğut and Gölbaşı (5) in 2010.

Statistical Analysis

All data were analyzed using SPSS version 20 (Chicago, IL, USA) program. The data were presented as median (minimum-maximum) or mean ± standard deviation depending on the normality of data distribution. Mann-Whitney U test was used for pairwise comparisons. P values <0.05 were considered significant. Kruskal-Wallis test was used to compare FSFI scores between three trimesters. Pairwise comparison of three trimesters was performed using Mann-Whitney U test following Bonferroni correction to make comparisons regarding lubrication, sexual satisfaction, total FSFI score and SQoL-F score before and after conception, which were significantly different between the FSFI scores. Pairwise comparisons of four sub-headings, which have a difference between them in the Kruskal-Wallis test, were performed between the three trimesters.

Results

A total of 300 pregnant women were included in the study and the mean age of these pregnant women was 28.61±5.6 years. The mean age of pregnant women according to trimesters is shown in Table 1. Regarding mean gravida, mean gravida was 1.90±1.1 in the first trimester group, 1.94±1.1 in the second trimester group and 1.87±1.0 in the third trimester group. The mean parity was 0.68±0.79 in the first trimester group, 0.71±0.87 in the second trimester group and 0.66±0.75 in the third trimester group. Other demographic data of pregnant women, including education level and place of residence, are detailed in Table 1.

Regarding total FSFI scores, median total FSFI was 22.8 (20.0-25.1) in the first trimester group, 23.6 (21.7-26.1) in the second trimester group and 22.0 (16.1-25.5) in the third trimester group. There was no significant difference between total FSFI scores of pregnant women in all 3 groups (Figure 1). Regarding FSFI subscales, median FSFI sexual desire scores were not statistically significant (p=0.51). When FSFI subscales were evaluated in terms of trimesters, it was found that there was a statistically significant difference between the trimesters only in the lubrication and sexual satisfaction subscales (p=0.039 and p=0.012, respectively). The relationship between other subscales and trimesters is given in Table 2.

Pregnant women in all 3 trimesters were evaluated before and after pregnancy in terms of SQoL-F scores. The median SQoL-F values before pregnancy were 55.5 (46.6-87.7) in the first trimester, 78.2 (57.7-93.3) in the second trimester and 74.9 (51.1-94.4) in the third trimester. The median SQoL-F values after pregnancy were 55.5 (44.4-80.0) in the first trimester, 64.4 (52.2-88.8) in the second trimester and 64.9 (57.7-92.2) in the third trimester (Table 2).

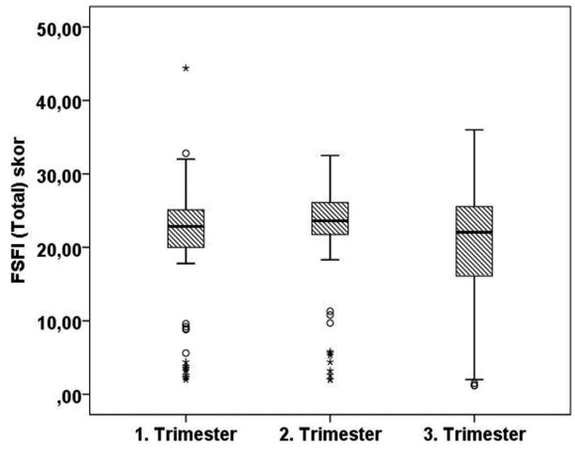


Figure 1. Mean FSFI total score of pregnant women according to trimesters
FSFI: Female Sexual Function Index

Table 1. Demographic characteristics of pregnant women in the study by trimesters

		1st trimester, (n=100)	2nd trimester, (n=100)	3rd trimester, (n=100)
Age (years)		28.4	28.6	29.3
Duration of Marriage (years)		6.07	5.43	5.99
Gravida (n)		1.90	1.94	1.87
Parity (n)		0.68	0.71	0.66
Number of Living Children (n)		0.69	0.70	0.66
Education Level (n)	Not literate/Elementary school	12	13	16
	Secondary/High school	54	53	55
	University/Postgraduate	34	34	29
Employment status (n)	Employed	32	33	32
	Unemployed	68	67	68
Place of residence (n)	Village	6	13	13
	District	35	38	44
	Province	59	49	43
Smoking (n)	Yes	9	18	21
	No	91	82	79
Alcohol (n)	Yes	2	3	2
	No	98	97	98
Residence (n)	Tenant	62	59	52
	Owner	38	41	48
Type of marriage (n)	Love	83	83	81
	Arranger	17	17	19
Disease (n)	No	86	90	85
	Yes	14	10	15
Drug use (n)	Yes	32	36	42
	No	68	64	58

Considering whether previous birth histories of pregnant women included in the study had an effect on FSFI scores, only pain scores in the second trimester were significantly higher in multiparous women compared with nulliparous women (p=0.009). Otherwise, there was no significant difference in the total median FSFI scores between three trimesters in multiparous and nulliparous women (Table 3).

The pregnant women were divided into 3 groups in terms of age (<25 years, 25-30, and >30 years). The effect of age on sexual functions was evaluated by using FSFI scores. The FSFI total median score in the first trimester group was 22.9 (20.5-24.7) in the <25 years group, 23.2 (19.6-26.8) in the 25-30 years group and 22.8 (20.0-24.9) in the >30 years group. Similar calculations were made for other trimesters. There was no significant difference between the groups in terms of FSFI scores.

There was no significant difference between the education levels of the pregnant women and the FSFI and SQoL-F scores between the trimesters (p>0.05 for all groups).

Considering the effect of parity on SQoL-F scale, median SQoL-F score in the nulliparous group before pregnancy was 68.8 (51.1-93.3) and 71.1 (51.1-91) in the multiparous group. There was no significant difference between the groups (p=0.96). In pregnant women, SQoL-F score was

Table 2. Median FSFI subscale and SQoL-F scores by trimester

	1st trimester (T1)	2nd trimester (T2)	3rd trimester (T3)	p	p	p	p
	Median, (25-75%)	Median, (25-75%)	Median, (25-75%)	-	-	-	-
SQOL-F	55.5 (44.4-80.0)	64.4 (52.2-88.8)	64.9 (57.7-92.2)	0.003	0.005	0.02	0.63
FSFI							
Desire	3.6 (3.0-4.8)	3.6 (3.0-4.8)	3.6 (2.4-4.8)	0.51	-	-	-
Arousal	3.9 (2.8-4.8)	4.2 (3.0-4.8)	4.0 (1.9-4.8)	0.56	-	-	-
Lubrication	3.6 (3.3-4.2)	3.9 (3.3-4.5)	3.6 (3.0-4.5)	0.039	0.009	0.53	0.10
Orgasm	4.0 (3.2-4.4)	4.0 (3.6-4.8)	3.6 (2.4-4.4)	0.76	-	-	-
Satisfaction	4.0 (3.2-4.8)	4.8 (3.8-5.2)	4.2 (2.4-5.2)	0.012	0.014	0.62	0.08
Pain	3.2 (2.0-4.0)	3.2 (2.0-4.0)	3.2 (1.2-4.8)	0.91	-	-	-
Total score	22.8 (20.0-25.1)	23.6 (21.7-26.1)	22 (16.1-25.5)	0.048	0.13	0.24	0.018

FSFI: female sexual function index, SQoL-F: sexual quality of life-female

Table 3. Effect of parity on FSFI score

Trimester		Nulliparous	Multiparous	p
1st trimester	FSFI	Median, (%25-75)	Median, (%25-75)	-
	Desire	4.2 (3.0-4.8)	3.6 (3.0-4.8)	0.50
	Arousal	3.9 (2.7-4.8)	3.6 (2.8-4.6)	0.92
	Satisfaction	4.0 (3.2-4.8)	4.0 (3.2-5.2)	0.57
	Lubrication	3.6 (3.0-3.9)	3.6 (3.3-4.2)	0.35
	Orgasm	4.0 (3.2-4.4)	4.0 (3.0-4.4)	0.89
	Pain	3.2 (2.0-4.0)	2.8 (1.8-4.4)	0.92
	Total	22.8 (19.6-25.1)	22.9 (20.1-25.1)	0.83
2nd trimester	Desire	3.6 (3.3-4.8)	3.6 (3.0-4.5)	0.43
	Arousal	4.2 (3.1-4.5)	3.9 (3.0-4.9)	0.56
	Satisfaction	4.8 (4.0-5.2)	4.8 (3.6-5.2)	0.68
	Lubrication	3.9 (3.3-4.5)	4.0 (3.6-4.8)	0.35
	Orgasm	4.0 (3.4-4.6)	4.2 (3.6-4.8)	0.26
	Pain	2.8 (1.8-3.6)	3.6 (2.4-4.6)	0.009
	Total	23.4 (21.4-25.0)	24.2 (21.9-26.7)	0.30
3rd trimester	Desire	3.6 (2.4-4.8)	3.6 (2.4-4.5)	0.67
	Arousal	3.6 (1.5-4.8)	3.8 (2.1-4.5)	0.91
	Satisfaction	4.8 (2.0-5.2)	3.6 (2.4-4.8)	0.59
	Lubrication	3.6 (3.3-4.8)	3.6 (3.0-4.2)	0.53
	Orgasm	3.6 (1.2-4.4)	3.6 (3.2-4.2)	0.52
	Pain	2.8 (1.2-4.8)	3.6 (1.8-4.8)	0.62
	Total	22.6 (16.0-25.7)	21.0 (16.3-25.2)	0.77

FSFI: female sexual function index

Table 4. Evaluation of the relationship between FSFI scores and SQoL-F

	Before pregnancy, SQoL-F		During pregnancy, SQoL-F	
	r	p	r	p
1st trimester FSFI score	0.064	0.52	0.22	0.03
2nd trimester FSFI score	0.279	0.005	0.288	0.004
3rd trimester FSFI score	0.242	0.015	0.268	0.007

FSFI: female sexual function index, SQoL-F: sexual quality of life-female

61.6 (48.8-90.0) in the nulliparous group and 63.3 (50.0-87.7) in the multiparous group (p=0.96).

There was no statistically significant difference between the first trimester FSFI score and SQoL-F score before pregnancy (p=0.52). There was a significant difference between FSFI and SQoL-F in all other trimesters. However, the correlations were found to be low to moderate. The correlations between FSFI and SQoL-F in terms of the trimesters are given in Table 4.

Discussion

It is a known fact that pregnancy is effective on female sexual life. A decrease in sexual activity during pregnancy has been shown in studies (6,12-14). Physiological and psychological changes brought about by pregnancy may affect sexual function and satisfaction. In this respect, it is not surprising that in the literature, the studies on the sexual dysfunctions of pregnant women increase day by day. In these studies, correlations between sexuality related parameters and FSFI scores were investigated and data on sexual function changes in pregnancy were tried to be obtained.

The frequency of sexual activity among trimesters in pregnant women varies. The main reason for this is both hormonal and physiological changes due to pregnancy. Although the sexual activity level in the second trimester seems to be increasing compared to the other trimester, the frequency of sexual intercourse has generally decreased compared to non-pregnant individuals. Although in this study we obtained different data related to sexuality during pregnancy, we did not collect data about the frequency of sexual activity in pregnancy. However, studies on this subject reported that pregnant women avoid sexual activity during pregnancy (6,15-17). It has been reported in studies that the incidence of sexual intercourse, with a mean of 3.2 per week before pregnancy, decreases to 1.8 per week with pregnancy (14). Similar results have been obtained in studies on SQoL during pregnancy and it has been shown that the SQoL has decreased during pregnancy. However, in studies conducted by Quirk et al. (18) and Maasoumi et al. (19), the mean scores of SQoL during pregnancy were higher compared to our study. We think that such a difference can be caused by social and racial diversities.

In this study, FSFI scores in the second trimester of pregnancy were found to be higher compared to the FSFI scores in the first and third trimesters of pregnancy. This finding is similar to the literature data (6,12,14,16,17,20-22). It is known that although sexual function and related conditions vary in the second trimester and significantly decrease in the third trimester, it changes or decreases slightly in the first trimester (13,21). In this study, we also found that FSFI scores in the third trimester were significantly decreased compared to other trimesters. Similarly, FSFI scores in first trimester were slightly higher than FSFI scores in the third trimester, but this was not statistically significant. The reason for the lack of statistical significance could be the low number of cases we included in the study.

In our study, we found that there were significant differences in the lubrication and satisfaction scores of the FSFI scores. Literature studies show that there are also differences between the trimesters in terms of desire, arousal and orgasm scores (6,15,16). Although we found that lubrication, one of the sexual functions, was higher in the second trimester compared to the first trimester there are also studies indicating a decrease (13,21). However, we think that the increase in lubrication in the second trimester is compatible with physiological and psychological changes during pregnancy.

One of the most important findings in our study is the increased sexual satisfaction FSFI score detected in the second trimester. When compared to other trimesters, the sexual satisfaction score was highest in the second trimester. This finding is also compatible with pregnancy physiology. Because this trimester is the period when the pregnant woman feels most comfortable. Sexual intercourse in this trimester will positively affect the pregnant woman both physiologically and psychologically. Therefore, the sexual satisfaction score will also be high in this trimester. Literature studies offer limited data especially for this subgroup. However, as previously mentioned, increased nausea and vomiting rates in the first trimester and infant awareness in the third trimester are among the most important causes of low satisfaction rates in the first and third trimesters (6). However, during pregnancy, both the partner and the pregnant have some concerns about pregnancy complications and these concerns may cause emotional changes among the couples.

It is known that the SQoL changes negatively as gestational week and number of births increase (7,9). In our study, SQoL and FSFI scores fluctuated with increased gestational week. Second trimester scores were higher than first and third trimester scores. There was no decrease as the gestational week progressed but fluctuations were observed in the values. Again in our study, there was no statistically significant effect of the parity on FSFI scores. The reason for this is that the parity scores were evaluated as nulliparous and multiparous in our study. Therefore, our study is inadequate in evaluating the differences among the pregnant women who give more than one birth.

In the studies conducted, it was shown that the SQoL of pregnant women whose spouses are primary school graduates is lower when compared with pregnant women having spouses with high school graduates or higher education level (1,3). In our study, we did not evaluate the education level of the spouses of pregnant women, we evaluated the relationship between the educational levels and sexual functions of pregnant women and found that the educational status of pregnant women had no effect on the SQoL or sexual functions. For this reason, we believe that it is appropriate to educate women about sex life and SQoL before and during pregnancy independently of their education level.

Another result we found in this study is that the SQoL is highest in the second trimester. In the first trimester, the SQoL is the lowest. The first priority of the pregnant woman with the onset of pregnancy shifts from her spouse to her child, this causes temporary suppression of sexual desire and wishes in pregnant woman (21). The pregnant, who became sexually passive, suppresses these feelings with the sense that she will have a baby and cannot respond positively to her partner's sexual desires. Therefore, the decrease in the SQoL in pregnant women in the first trimester can be considered as a natural finding. With the transition to the second trimester, the pregnant woman is now accustomed to the pregnancy process, and her priority is directed back to her husband and naturally to her sexual life. In this period, in parallel with the increase in sexual function, the SQoL is affected positively, and the pregnant woman entered a period close to the psychological and physical well-being. However, as the time progresses, the diameter of the abdomen increases in parallel with the growth of the baby, and this starts to affect the SQoL negatively. For all these reasons, the changes in the SQoL that we found in our study are extremely natural.

In the literature, the number of studies related to SQoL in pregnancy is extremely limited. Studies have shown that the decrease in the SQoL is due to changes in sexual function observed in pregnancy (decrease in pleasure and decrease in satisfaction from sexuality) (23-25). However, in this study, we found a significant decrease in the SQoL in the first trimester and a higher quality of sexual life scores in the second trimester. These results, which we find partially different from the literature, can be affected by various factors such as differences in study designs, follow-up period of pregnant women and cultural differences.

It has been investigated in many different studies whether the parameters such as nulliparity or multiparity were effective on the SQoL. There are studies showing that the number of births decreases SQoL scores, and there are also studies showing that previous birth history is not effective in this respect (7,8,10). Pregnant women who gave birth before gets faster through pregnancy psychology and this has a positive effect on sexual life in their subsequent pregnancies. The pregnant woman who gets rid of emotional period early in the first trimester becomes more active and willing in terms of sexual life. Although we found that having a child before had a positive effect on the SQoL in our study, this was not statistically significant.

Conclusion

As a result, social and cultural factors significantly affect the sexual life of couples during pregnancy. In particular, the education levels of couples, employment status, marriage period and even their ethnic identity can affect the sexual functions during pregnancy. However, nausea and vomiting, fatigue and feeling of tiredness that are frequently observed during pregnancy are other factors that negatively affect sexuality in pregnant women. Although there are differences in sexual desire in the first trimester of pregnancy, the general opinion is that there is a decrease in sexual function due to the decrease of libido. The woman's belly begins to grow as the pregnancy progresses, and she starts to experience difficulties in sex positions. This is the most common cause of sexual dysfunction observed in the third trimester.

Considering that sexuality is an important part of health care, we believe that the problems related to sexual dysfunctions of pregnant women should be detected and resolved at an early stage, and that this will help to improve the sexual health of the pregnant woman and her partner and their SQoL.

Ethics Committee Approval: This study was performed in accordance with the Declaration of Helsinki and Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved this study (decision no: 2017-11, date: 07.06.2017).

Informed Consent: Written consent was obtained.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - E.Ç., F.B.; Design - E.Ç.; Supervision - F.B.; Resources - E.Ç., F.B.; Materials - E.Ç.; Data Collection and/or Processing - E.Ç.; Analysis and/or Interpretation E.Ç., F.B.; Literature Search - E.Ç.; Writing Manuscript - E.Ç.; Critical Review - F.B.

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

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

References

1. Leonardi-Warren K, Neff I, Mancuso M, Wenger B, Galbraith M, Fink R. Sexual health: exploring patient needs and healthcare provider comfort and knowledge. Clin J Oncol Nurs 2016; 20: 162-7.
2. Kisa S, Zeyneloğlu S, Yilmaz D, Güner T. Quality of sexual life and its effect on marital adjustment of Turkish women in pregnancy. J Sex Marital Ther 2014; 40: 309-22.
3. Andreucci CB, Bussadori JC, Pacagnella RC, Chou D, Filippi V, Say L, et al. Sexual life and dysfunction after maternal morbidity: a systematic review. BMC Pregnancy Childbirth 2015; 15: 307.
4. Bretschneider CE, Doll KM, Bensen JT, Gehrig PA, Wu JM, Geller EJ. Sexual health before treatment in women with suspected gynecologic malignancy. J Womens Health (Larchmt) 2017; 26: 1326-32.
5. Tuğut N, Gölbaşı Z. A validity and reliability study of Turkish version of the sexual quality of life questionnaire-female. Cumhuriyet Med J 2010; 32: 172-80.
6. von Sydow K. Sexuality during pregnancy and after childbirth: a metacontent analysis of 59 studies. J Psychosom Res 1999; 47: 27-49.
7. Leite AP, Campos AA, Dias AR, Amed AM, De Souza E, Camano L. Prevalence of sexual dysfunction during pregnancy. Rev Assoc Med Bras (1992) 2009; 55: 563-8.
8. Kingsberg S, Althof SE. Evaluation and treatment of female sexual disorders. Int Urogynecol J Pelvic Floor Dysfunct 2009; 20(Suppl 1): 33-43.
9. Moodley J, Khedun M. Sexual activity during pregnancy: a questionnaire-based study. Southern african journal of epidemiology and infection 2011; 26: 33-5.
10. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The female sexual function index (FSFI): A multidimensional selfreport instrument for the assessment of female sexual function. J Sex Marital Ther 2000; 26: 191-208.
11. Aygin D, Eti Aslan F. Kadın cinsel işlev ölçeğinin Türkçe'ye uyarlanması. Türkiye Klinikleri J Med Sci 2005; 25:393-9.

12. Bartellas E, Crane JM, Daley M, Bennett KA, Hutchens D. Sexuality and sexual activity in pregnancy. BJOG 2000; 107: 1306-8.

13. Lee JT. The meaning of sexual satisfaction in pregnant Taiwanese women. J Midwifery Womens Health 2002; 47: 278-86.

14. Onah HE, Iloabachie GC, Obi SN, Ezugwu FO, Eze JN. Nigerian male sexual activity during pregnancy. Int J Gynaecol Obstet 2002; 76: 219-23.

15. Perkins RP. Sexuality in pregnancy: what determines behavior? Obstet Gynecol 1982; 59: 189-98.

16. de Pierrepont C, Polomeno V, Bouchard L, Reissing E. (What do we know about perinatal sexuality? A scoping reviewon sexoperinatality-part 1). J Gynecol Obstet Biol Reprod (Paris) 2016; 45: 796-808.

17. Jones C, Chan C, Farine D. Sex in pregnancy. CMAJ 2011; 183: 815-8.

18. Quirk F, Haughie S, Symonds T. The use of the sexual function questionnaire as a screening toolfor women with sexual dysfunction. J Sex Med 2005; 2: 469-77.

19. Maasoumi R, Lamyian M, Montazeri A, Azin SA, Aguilar-Vafaie ME, Hajizadeh E. The sexual quality of life-female (SQOL-F) questionnaire: translation and psychometric properties of the Iranian version. Reprod Health 2013; 10: 25.

20. Orji EO, Ogunlola IO, Fasubaa OB. Sexuality among pregnant women in South West Nigeria. J Obstet Gynaecol 2002; 22: 166-8.

21. Oruç S, Esen A, Laçin S, Adigüzel H, Uyar Y, Koyuncu F. Sexual behaviour during pregnancy. Aust N Z J Obstet Gynaecol 1999; 39: 48-50.

22. Ryding EL. Sexuality during and after pregnancy. Acta Obstet Gynecol Scand 1984; 63: 679-82.

23. Fok WY, Chan LY, Yuen PM. Sexual behavior and activity in Chinese pregnant women. Acta Obstet Gynecol Scand 2005; 84: 934-8.

24. Bartellas E, Crane JM, Daley M, Bennett KA, Hutchens D. Sexuality and sexual activity in pregnancy. BJOG 2000; 107: 964-8.

25. Johnson CE. Sexual health during pregnancy and the postpartum. J Sex Med 2011; 8: 1267-84.

İstanbul Med J 2019; 20(3): 241-5
DOI: 10.4274/imj.galenos.2018.11129

Evaluation of Pseudophakic Patients with Epiretinal Membrane: Our Experience

Kliniğimize Başvuran Psödofakik Epiretinal Membranlı Olguların Değerlendirilmesi

Mustafa Suat Alıkma, Erkan Ünsal

İstanbul Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this study was to evaluate the clinical features of pseudophakic patients with idiopathic epiretinal membrane (ERM) and to compare the optical coherence tomography (OCT) macular characteristics of the eye with ERM with the normal eye.

Methods: Patients with bilateral pseudophakic eyes and ERM in one eye who were admitted to our clinic between 2017 and 2018 were evaluated according to gender, age, visual acuity and OCT findings and the relationship between these findings were evaluated statistically.

Results: Eighty-two eyes of 41 patients with a mean age of 71.4±6.4 years (range: 60-86) who were admitted to our clinic between 2017 and 2018 were included in the study. All eyes were pseudopkahic. The patients with systemic and ocular disease history were not excluded. Nineteen (46%) patients were female and 22 (54%) were male. ERM was on the right side in 21 (51%) eyes and on the left side in 20 (49%) eyes. The mean visual acuity of the eyes with ERM was 0.35±0.24 (0.1-1.0) LogMAR. The mean central macular thickness of the eyes with ERM was 355.4±75.4 (234-554) microns. Regarding the parafoveal region (1-3 mm), the superior quadrant thickness was 371.4±60.3 (range: 287-558) microns, nasal quadrant thickness was 371±52.5 (range: 311-549) microns, inferior quadrant thickness was 365.6±44.3 (range: 307-494) micron and temporal quadrant thickness was 365.1±52.2 (range: 280-510) micron. In the eyes with ERM, the macular volume was 11.3±1.1 (9.7-15) mm^3 by OCT. There was a statistically significant difference between eyes with and without ERM in terms of central macular thickness, macular volume, superior, temporal, inferior and nasal quadrant thicknesses of parafoveal region (1-3 mm) ($p<0.05$).

Conclusion: ERM is a disease related to advanced age. Since the disease occurs at the vitreoretinal interface, it causes some changes in optic cohorence tomography.

Keywords: Epiretinal membrane, vitreoretinal interface, vision loss

ÖZ

Amaç: Kliniğimize başvuran idiyopatik psödofakik epiretinal membranlı (ERM) olguların klinik muayene bulguları ve optik koherens tomografi (OKT) ile değerlendirilen maküla özellikleri ile aynı olguların normal gözleri karşılaştırılarak değerlendirme amaçlanmıştır.

Yöntemler: 2017 ve 2018 yılları içerisinde kliniğimize başvuran, bilateral psödofakik ve tek gözlerinde ERM bulunan olgular cinsiyet, yaş, görme keskinliği ve OKT bulgularına göre değerlendirilerek bu bulgular arasındaki ilişki istatistiksel açıdan değerlendirildi.

Bulgular: 2017 ve 2018 yılları içerisinde kliniğimize başvuran yaş ortalaması 71,4±6,4 yıl (60-86 arasında) olarak tespit edilen 41 hastanın 82 gözü çalışmaya dahil edildi. Çalışmaya idiyopatik ERM'si olan psödofakik olgular alındı. Sistemik ve oküler hastalık anamnezi olan olgular çalışma kapsamına alınmadı. Hastaların 19'u (%46) kadın ve 22'si (%54) erkek olarak tespit edildi. Çalışmada ERM bulunan gözlerden 21'i (%51) sağ göz ve 20'si (%49) sol göz olarak tespit edildi. Olguların görme keskinlikleri ortalama olarak 0,35±0,24 (0,1-1,0 arasında) LogMAR olarak tespit edildi. ERM bulunan gözlerin ortalama santral maküla kalınlığı 355,4±75,4 (234-554 arasında) mikron, parafoveal bölgede 1-3 mm mesafedeki dairesel alanda superior kadran kalınlığı 371,4±60,3 (287-558 arasında) mikron, nazal kadran kalınlığı 371±52,5 (311-549 arasında) mikron, inferior kadran kalınlığı 365,6±44,3 (307-494 arasında) mikron, temporal kadran kalınlığı 365,1±52,2 (280-510 arasında) mikron olarak tespit edildi. ERM bulunan gözlerde maküler volüm OKT ile 11,3±1,1 (9,7-15 arasında) mm^3 olarak tespit edildi. ERM bulunan ve bulunmayan gözlerdeki santral maküla kalınlıkları, maküler volüm, parafoveal bölgede 1-3 mm mesafedeki dairesel alanda superior, temporal, inferior ve nazal kadran kalınlıkları arasında istatistiksel olarak anlamlı fark saptandı ($p<0,05$).

Sonuç: ERM ileri yaş ile ilgili bir hastalıktır. Hastalık vitreoretinal ara yüzeyde oluştuğu için OKT'de bazı değişikliklere yol açar.

Anahtar Kelimeler: Epiretinal membran, vitreoretinal ara yüzey, görme azlığı

Address for Correspondence/Yazışma Adresi: Mustafa Suat Alıkma MD, İstanbul Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 532 171 55 71 **E-mail:** m.suatalikma@gmail.com **ORCID ID:** orcid.org/0000-0002-3621-1892

Cite this article as/Atıf: Alıkma MS, Ünsal E. Evaluation of Pseudophakic Patients with Epiretinal Membrane: Our Experience. İstanbul Med J 2019; 20(3): 241-5.

Received/Geliş Tarihi: 15.08.2018
Accepted/Kabul Tarihi: 13.12.2018

Introduction

Epiretinal membrane (ERM) is a vitreoretinal interface disease that leads to a decrease in visual acuity, macropia, micropsy and metamorphopsia symptoms. These symptoms have been associated with macular surface deterioration and macular thickness increase (1,2). Diagnosis is made clinically and by means of optical coherence tomography (OCT) (3,4). ERM is formed on the internal limiting membrane (ILM) and has a fibrocellular structure (5). ERM diagnosis and classification is based on clinical findings (6).

ERM is etiologically classified as primary and secondary ERM (3). ERM without pathological ophthalmic examination other than posterior vitreous detachment is called primary idiopathic ERM (7,8). Secondary ERM can occur as a result of many etiological factors such as ocular trauma, cryopexy, intraocular surgeries and vascular pathologies related to the retinal artery and veins (4). Although the disease is generally benign, it may cause functional defects by causing shrinkage in the retina and veins, structural changes in retinal pigment epithelium, photoreceptor cells and veins, and causing intraretinal edema (9-11).

In this study, we aimed to evaluate the age, visual acuity and OCT findings of bilateral pseudophakic patients with ERM and to evaluate the relationship between these features.

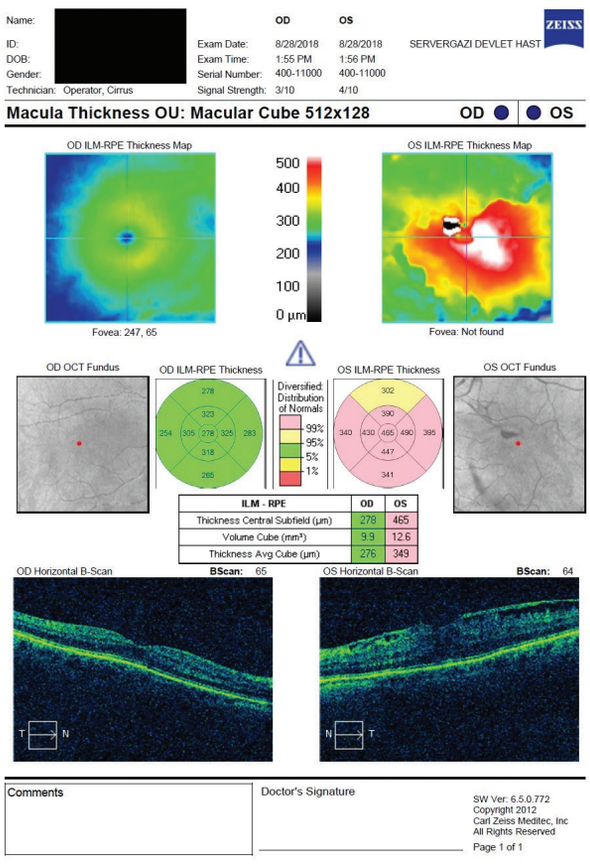


Image 1. OCT output of the patient with ERM in one eye.

OCT: optical coherence tomography, ERM: epiretinal membrane, OD: oculus dexter, OS: oculus sinister, ILM-PRE: internal limiting membrane-retinal pigment epithelium

Methods

In our study, patients who were admitted to our clinic between August 2017 and August 2018 and who had unilateral stage 2 ERM in their clinical examination were evaluated. Only bilateral pseudophakic patients were evaluated in order to evaluate the ERM-related visual acuity levels of the patients included in the study and to provide the retinal evaluation with OCT. Retinal imaging was performed with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) to confirm the diagnosis of ERM and to evaluate macular volume and thickness of central macular and parafoveal quadrants (Image 1). The patients had no history of ocular surgery, except for cataract surgery. The patients with ophthalmologic disease history and detected pathology on ophthalmologic examination were not included in the study. Patients with hypertension, coronary artery disease and diabetes mellitus (DM) were excluded. Age, gender and visual acuity were recorded.

Among OCT findings, central macular thickness, mean retinal thickness in superior, nasal, inferior and temporal parafoveal quadrants (1-3 mm), distance between ILM and in retina pigment epithelium in the central macular region and macular volume within 6 mm horizontal and 6 mm vertical fovea-centered square area were recorded. OCT measurements and measurement classifications were performed according to the studies by Chan et al. (12) and Sabouri et al. (13).

Visual acuity levels according to the Snellen chart, intraocular pressures in mmHg, detailed anterior segment and fundus examinations were recorded in all patients. The history of systemic and ocular disease of all patients was questioned. Patients with a history of systemic and ocular disease and patients with surgical history except for uncomplicated cataract surgery were excluded from the study. For statistical evaluation, the visual acuities recorded according to the Snellen chart were converted to the corresponding LogMAR values. In the statistical evaluation, the relationship between visual findings, OCT findings and visual acuity in eyes with and without ERM were evaluated.

İstanbul Training and Research Local Ethics Committee approval was obtained for this study (decision no: 882, date: 25.11.2016). The study was conducted in accordance with the Declaration of Helsinki. Written and oral consent were obtained from the patients included in the study and their data were evaluated within the scope of the study.

Statistical Analysis

Statistical analysis was performed using paired t-test in SPSS ver. 25 for Windows (SPSS Inc., Chicago, Illinois, USA) software. Descriptive statistics were given as number and percentage for categorical variables. Regarding correlation analysis, Pearson or Spearman correlation tests were used, where appropriate. $p<0.05$ was considered statistically significant.

Results

The study included 82 eyes of 41 patients (19 women and 22 men) with a mean age of 71.4±6.4 (range: 60-86) years. The patients were pseudophakic and had ERM in one eye. Patients who had hypertension,

coronary artery disease and DM were excluded. The visual acuities of the eyes with and without ERM were 0.35±0.24 (range: 0.1-1.0) LogMAR and 0.0±0.1 (range: 0.0-0.1) LogMAR, respectively.

When the findings of the eyes with and without ERM were compared, it was observed that there was a significant difference between two groups in terms of visual acuity, central macular thickness, and thickness of the superior, temporal, nasal and inferior parafoveal (1-3 mm) quadrants ($p<0.05$) (Table 1).

Regarding statistical relationship between visual acuity and central macular thickness (Figure 1), thickness of the superior (Figure 2), temporal (Figure 3), nasal (Figure 4) and inferior (Figure 5) parafoveal quadrants (1-3 mm), and macular volume (Figure 6) in the eyes with ERM, statistically significant negative correlation was found between visual acuity level and these parameters (p=0.000, r=-0.689; p=0.004, r=-0.445; p=0.000, r=-0.577; p=0.004, r=-0.440; p=0.006, r=-0.422; p=0.001, r=-0.517) (Table 2).

Table 1. Mean values of optical coherence tomography parameters between eyes with and without epiretinal membrane and statistical significance levels between them

Parameter	Eyes with epiretinal membrane	Eyes with epiretinal membrane	p
Central macula, µm	355.4±75.4 (234-554)	250.4±34.2 (183-317)	p=0.00
Superior quadrant, µm	371.4±60.3 (287-558)	323.8±30.7 (260-375)	p=0.00
Temporal quadrant, µm	365.1±52.2 (280-510)	318.1±32.9 (264-394)	p=0.00
Inferior quadrant, µm	365.6±44.3 (307-494)	322.1±26.9 (267-371)	p=0.00
Nasal quadrant, µm	371±52.5 (311-549)	325.4±27.6 (275-374)	p=0.00
Cube volume (mm3)	11.3±1.1 (9.7-15)	9.9±0.7 (8.1-11.5)	p=0.00

Table 2. The statistical assessment results of visual acuity and OCT findings in eyes with epiretinal membrane

	Central macula	Cube volume	Temporal	Superior	Nasal	Inferior
BCVA	p=0.000, r=-0.689	p=0.001, r=-0.517	p=0.000, r=-0.577	p=0.004, r=-0.445	p=0.004, r=-0.440	p=0.006, r=-0.422

BCVA: best corrected visual acuity, OCT: optical coherence tomography

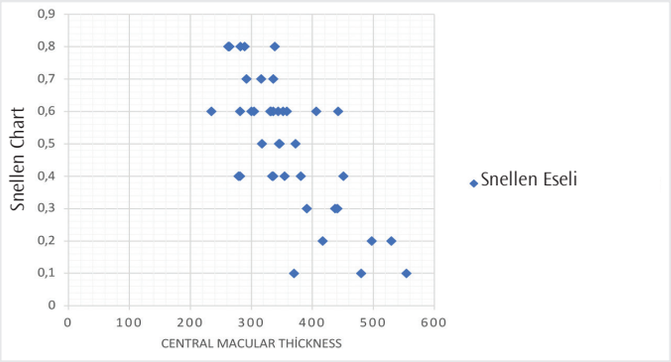


Figure 1. The distribution of visual acuity according to the Snellen chart and central macular thickness of the eyes with epiretinal membrane

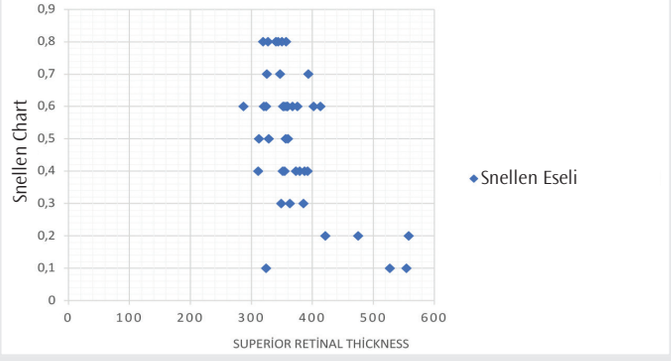


Figure 2. The distribution of visual acuity according to the Snellen chart and thickness of the superior parafoveal quadrant of the eyes with epiretinal membrane

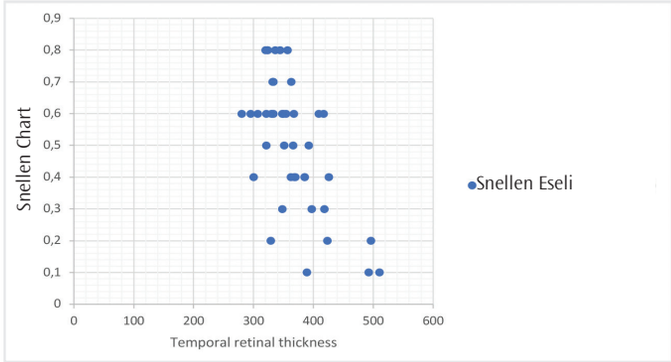


Figure 3. The distribution of visual acuity according to the Snellen chart and thickness of the temporal parafoveal quadrant of the eyes with epiretinal membrane

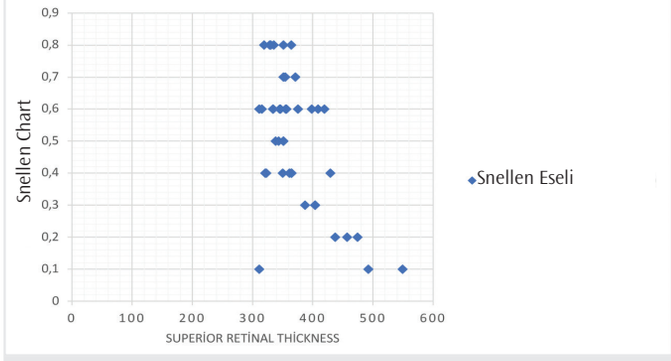


Figure 4. The distribution of visual acuity according to the Snellen chart and thickness of the nasal parafoveal quadrant of the eyes with epiretinal membrane

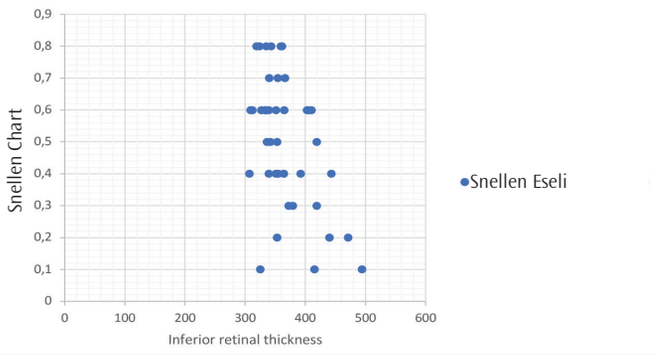


Figure 5. The distribution of visual acuity according to the Snellen chart and thickness of the inferior parafoveal quadrant of the eyes with epiretinal membrane

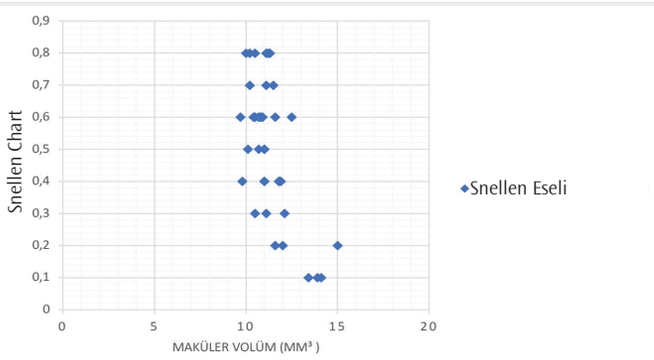


Figure 6. The distribution of visual acuity according to the Snellen chart and macular volume in optical coherence tomography of the eyes with epiretinal membrane

Discussion

Although the majority of the cases diagnosed as ERM were over 50 years of age, ERM was found in 2-6.4% autopsy studies (14). Fraser-Bell et al. (15) reported an ERM incidence of approximately 5.3% in an epidemiological study. In an epidemiological study by Miyazaki et al. (16), the incidence of ERM in adults over 40 years of age was 4%. All of the cases in our study were pseudophakic patients over the age of 60 years. Similar to other studies, ERM was associated with advanced age in our study. In a study by Klein et al. (17) evaluating the relationship between the disease and gender, they stated that the disease was more common in women than men. In our study, there was no statistically significant difference between men and women.

Stevenson et al. (1) reported that macular thickness was increased in patients with ERM. Chen et al. (18) showed that there was an increase in macular thickness in the ERM cases and that there was a correlation between the increase in macular thickness and visual acuity. Kumagai et al. (19) reported that macular thickness decreased and visual acuity improved after ERM surgery. In our study, central macular thickness, and thickness of the superior, temporal, nasal and inferior parafoveal quadrants (1-3 mm) in eyes with ERM were statistically higher than the same parameters in eyes without ERM. In addition, the mean visual acuity level in the eyes with ERM was statistically lower than in the eyes without eyes.

Pilli et al. (20) demonstrated the relationship between the increase in central macular thickness and the deterioration of macular morphology and decreased visual acuity. In their histological study, Paovic et al. (21) reported that visual acuity decreased in the central macular thickness increase due to ERM-related macular edema. Dawson et al. (22) reported that visual acuity decreased with central macular thickness increase and visual acuity increased in patients with decreased central macular thickness following macular surgery. The relationship between central macular thickness and visual acuity levels of the patients in our study was evaluated. In our study, there was also a statistically significant relationship between visual acuity level and central macular thickness. In our study, there was also a statistically significant relationship between visual acuity and central macular thickness, and thickness of the superior, temporal, nasal and inferior parafoveal quadrants (1-3 mm) in eyes with ERM.

Reduction in visual acuity due to ERM and primary treatment of metamorphopsia were defined as pars plana vitrectomy (PPV) (23). In a study performed by Karabaş et al. (24), they defined the rate of visual acuity increase after PPV as 90% in primary idiopathic ERM and 62.8% in secondary ERM cases. Tanawade et al. (25) reported in their study that visual acuity increased after PPV in 31.25% of cases, did not change in 31.25% and decreased in 37.5%. Okomoto et al. (2) reported that metamorphopsia complaints could be resolved with PPV.

Conclusion

ERM is usually a disease related to advanced age. ERM is considered one of the vitreoretinal interface diseases. With or without intraretinal edema, the membrane causes visual symptoms as a result of an increase in macular thickness. The main treatment of the disease was defined as PPV. Examination of the vitreoretinal interface and evaluation of OCT in elderly patients presenting with low level of vision is very important in terms of overlooking disease. Surgical approach is a treatment option in patients with low visual acuity, micropsia, macropsy and metamorphopsia.

Ethics Committee Approval: İstanbul Training and Research Local Ethics Committee approval was obtained for this study (decision no: 882, date: 25.11.2016).

Informed Consent: Written and oral consent were obtained from the patients included in the study and their data were evaluated within the scope of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S.A.; Design - M.S.A.; Supervision - E.Ü.; Resources - E.Ü.; Materials - M.S.A.; Data Collection and/or Processing - M.S.A.; Analysis and/or Interpretation - M.S.A.; Literature Search - E.Ü.; Writing Manuscript - M.S.A.; Critical Review - E.Ü.

Conflict of Interest: The authors have no conflict of interest to declare.

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

References

1. Stevenson W, Prospero Ponce CM, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical coherence tomography-based diagnosis and classification. Clinical Ophthalmol 2016; 10: 527-34.

2. Okamoto F, Okamoto Y, Hiraoka T, Oshika T. Effect of vitrectomy for epiretinal membrane on visual function and vision-related quality of life. Am J Ophthalmol 2009; 147: 869-74.

3. Inoue M, Kadonosono K. Macular diseases: epiretinal membrane. Dev Ophthalmol 2014; 54: 159-63.

4. Yazici AT, Alagöz N, Celik HU, Bozkurt E, Alagöz C, Cakir M, et al. Idiopathic and secondary epiretinal membranes: do they differ in terms of morphology? An optical coherence tomography-based study. Retina 2011; 31: 779-84.

5. Kampik A. Pathology of epiretinal membrane, idiopathic macular hole, and vitreomacular traction syndrome. Retina 2012; 32(Suppl 2): 194-8.

6. Stevenson W, Prospero Ponce CM, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical coherence tomography-based diagnosis and classification. Clin Ophthalmol. 2016; 10: 527-34.

7. Legarreta JE, Gregori G, Knighton RW, Punjabi OS, Lalwani GA, Puliafito CA. Three-dimensional spectral-domain optical coherence tomography images of the retina in the presence of epiretinal membranes. Am J Ophthalmol 2008; 145: 1023-30.

8. Pournaras CJ, Donati G, Brazitikos PD, Kapetanios AD, Dereklis DL, Stangos NT. Macular Epiretinal Membranes. Semin Ophthalmol 2000; 15: 100-7.

9. Miguel AI, Legris A. Prognostic factors of epiretinal membranes: A systematic review. J Fr Ophtalmol 2017; 40: 61-79.

10. Konidaris V, Androudi S, Alexandridis A, Dastiridou A, Brazitikos P. Optical coherence tomography-guided classification of epiretinal membranes. Int Ophthalmol. 2015; 35: 495-501.

11. Altan Ç, Güngel H, Pınarcı E. Primer ve sekonder epiretinal membranların optik koherens tomografi bulgularının karşılaştırılması. Retina-Vitreus 2009; 17: 263-8.

12. Chan A, Duker JS, Ko TH, Fujimoto JG, Schuman JS. Normal macular thickness measurements in healthy eyes using stratus optical coherence tomography. Arch Ophthalmol 2006; 124 : 193-8.

13. Sabouri MR, Kazemnezhad E, Hafezi V. Assessment of macular thickness in healthy eyes using cirrus HD-OCT: A Cross-Sectional Study. Med Hypothesis Discov Innov Ophthalmol. 2016; 5: 104-11.

14. Sjarda R, Michels R. Macular pucker. In: Ryan S, editör. Retina. St. Louis: Mosby; 1994.p.2301-11.

15. Fraser-Bell S, Guzowski M, Rochtchina E, Wang JJ, Mitchell P. Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study. Ophthalmology 2003; 110: 34-40.

16. Miyazaki M, Nakamura H, Kubo M, Kiyohara Y, Iida M, Ishibashi T, et al. Prevalence and risk factors for epiretinal membranes in a Japanese population: the Hisayama study. Graefe's Archive for clinical and experimental ophthalmology 2003; 241: 642-6.

17. Klein R, Klein BE, Wang Q, Moss SE. The epidemiology of epiretinal membranes. Trans Am Ophthalmol Soc 1994; 92: 403-30.

18. Chen L, Liu M, Xie AM, Liu Y. A study on change of macular retinal thickness and its relationship with vision before and after operation to idiopathic macular epiretinal membranes. Int J Clin Exp Med 2015; 8: 18571-80.

19. Kumagai K, Hangai M, Ogino N. Progressive thinning of regional macular thickness after epiretinal membrane surgery. Invest Ophthalmol Vis Sci 2015; 56: 7236-42.

20. Pilli S, Lim P, Zawadzki RJ, Choi SS, Werner JS, Park SS. Fourier-domain optical coherence tomography of eyes with idiopathic epiretinal membrane: correlation between macular morphology and visual function. Eye (Lond) 2011; 25: 775-83.

21. Paovic J, Paovic P, Paovic AS. Correlation between epiretinal membrane bridging, visual acuity and central macular thickness. J Cytol Histol. 2017; 8: 1-6.

22. Dawson SR, Shunmugam M, Williamson TH. Visual acuity outcomes following surgery for idiopathic epiretinal membrane: an analysis of data from 2001 to 2011. Eye (Lond) 2014; 28: 219-24.

23. Thompson JT. Vitrectomy for epiretinal membranes with good visual acuity. Trans Am Ophthalmol Soc 2004; 102: 97-103.

24. Karabaş L, Özkan B, Altıntaş Ö, Çağlar Y. Epiretinal membranlarda etyoloji ve vitreoretinal cerrahi sonuçlarımız. Ret-Vit 2006; 14: 193-6.

25. Tanawade RG, Tsierkezou L, Bindra MS, Patton NA, Jones NP. Visual outcomes of pars plana vitrectomy with epiretinal membrane peel in patients with uveitis. Retina 2015; 35: 736-41.

İstanbul Med J 2019; 20(3): 246-9
DOI: 10.4274/imj.galenos.2018.48640

Primary Mucosal Malignant Melanoma: Two Case Reports

Primer Mukozal Malign Melanom; İki Olgu Sunumu

Kevser Esmeray Çifci[1], Yeşim Karagöz[1], Çağrı Erdim[1], Cem Leblebici[2], Özgür Kılıçkesmez[1]

[1]Sarıca Farabi Training and Research Hospital, Clinic of Radiology,Kocaeli, Turkey
[2]İstanbul Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey

ABSTRACT

Primary mucosal malignant melanomas originate from melanocytes in mucosal membranes, which are located in the respiratory, gastrointestinal and urogenital tract. Mucosal melanomas are extremely rare and have a more aggressive and poor prognosis than skin melanoma. Local or distant metastasis, recurrence probability and mortality rates are higher. Although there are many epidemiological and etiological differences between mucosal melanomas and skin melanomas, there is no clear predisposing factor for mucosal melanomas. Mucosal melanomas constitute 1.3-1.4% of all melanomas, and 25-50% of these cases are head and neck tumors. The symptoms are non-specific and vary according to the location of the lesion. Knowing the typical radiological imaging characteristics of mucosal melanomas and its consideration in the differential diagnosis in clinical evaluation will increase the chance of early diagnosis and will positively affect the survival of patients.

We present the radiological imaging characteristics and clinical course of a 57-year-old male patient who presented with a complaint of parotid mass and who died in a short period of time with widespread metastases, and a 72-year-old male patient who presented with epistaxis and who had no metastasis in the postoperative follow-up, but had a local recurrence.

Keywords: Mucosal melanoma, extracutaneous, MRI

ÖZ

Primer mukozal malign melanomlar respiratuvar, gastrointestinal ve ürogenital traktta bulunan mukozal membranlardaki melanositlerden köken alır. Mukozal melanomlar oldukça nadirdir ve deri melanomuna göre daha agresif ve kötü prognozludur. Bölgesel veya uzak metastaz ve rekürrens olasılıkları ve mortaliteleri daha yüksektir. Mukozal melanomlar ile deri melanomları arasında epidemiyolojik ve etiyolojik pek çok fark bulunmakla birlikte mukozal melanomlar için net olarak tanımlanmış bir predispozan faktör bulunmamaktadır. Mukozal melanomlar tüm melanomların %1,3-1,4'ünü oluşturur ve bu olguların %25-50'si baş-boyun kaynaklı tümörlerdir. Semptomlar non-spesifik olup lezyonun yerleşim yerine göre değişmektedir. Mukozal melanomların tipik radyolojik görüntüleme özelliklerinin bilinmesi ve klinik değerlendirmede ayırıcı tanıda akla gelmesi, erken tanı şansını artıracak ve hasta sağ kalımını olumlu etkileyecektir.

Parotis lojunda kitle şikayetiyle başvuran ve kısa zamanda yaygın metastazlar ile hayatını kaybeden 57 yaşında erkek hasta ve epistaksis ile başvuran ve postoperatif takibinde metastazı bulunmayan, fakat lokal nüks saptanan 72 yaşında erkek hastanın radyolojik görüntüleme özelliklerini ve klinik gidişini sunmaktayız.

Anahtar Kelimeler: Mukozal melanom, ekstrakütanöz, MRG

Introduction

Primary mucosal malignant melanomas originate from melanocytes in mucosal membranes, which are located in the respiratory, gastrointestinal and urogenital tract. Mucosal melanomas are very rare and have a more aggressive and poor prognosis than skin melanoma (1). Although there are many epidemiological and etiological differences between mucosal melanomas and skin melanomas, there is no clear predisposing factor for mucosal melanomas (2).

Knowing the typical imaging characteristics of mucosal melanomas, which are very rare and have poor prognosis and its consideration in differential diagnosis, will contribute to early diagnosis.

Address for Correspondence/Yazışma Adresi: Kevser Esmeray Çifci MD, Sarıca Farabi Training and Research Hospital, Clinic of Radiology, Kocaeli, Turkey
Phone: +90 505 324 11 39 **E-mail:** kevser.esmeray@yahoo.com **ORCID ID:** orcid.org/0000-0002-8518-7390

Cite this article as/Atıf: Çifci KE, Karagöz Y, Erdim Ç, Leblebici C, Kılıçkesmez Ö. Primary Mucosal Malignant Melanoma: Two Case Reports. İstanbul Med J2019; 20(3): 246-9.

Received/Geliş Tarihi: 08.05.2017
Accepted/Kabul Tarihi: 18.06.2018

The aim of this study was to present two cases of primary mucosal malignant melanoma and to discuss its clinical and radiological features.

Case Reports

Case 1

A 52-year-old male patient presented with swelling in the parotid gland region. Ultrasonographic examination revealed hypoechoic solid nodular lesions in the parotid gland. After detecting malignant melanoma infiltration with fine needle aspiration biopsy, positron emission tomography-computed tomography (PET-CT) examination was performed, and intense fluorodeoxyglucose uptake was observed in the parotid gland in two foci and gallbladder. Abdominal magnetic resonance imaging (MRI) showed a polypoid mass lesion with contrast enhancement in the gallbladder (Figure 1). Although primary malignant melanomas originating from parotid and gallbladder were very rare, the gallbladder was considered as the primary focus after histopathological examination. After the surgeries were performed, the patient was treated with radiotherapy and chemotherapy, and the patient was accepted in remission and early follow-up was performed with PET-CT at 3-month intervals. The PET-CT evaluation of the patient, who did not have recurrence for fourteen months, revealed metastases in the rectum and the small curvature of the stomach, and this diagnosis was confirmed by biopsy. Three months later, PET-CT revealed disseminated metastases in the soft tissue and cerebellum metastasis (Figures 2a,b,c), and the patient died in a short time. Figure 2a shows the typical hyperintensity of melanoma metastasis on T1-weighted imaging (WI). Figure 2c shows intense, diffuse and homogenous uptake and hypervascular nature of the melanoma metastasis. The survival of the patient from presentation was 22 months. Written informed consent was not obtained from the patients due to retrospective design of the study.

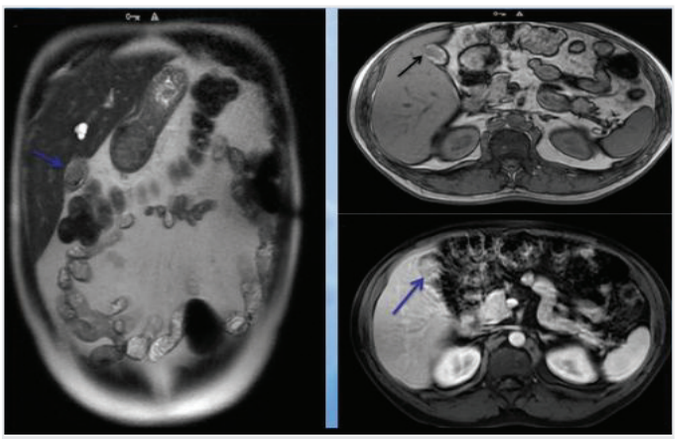


Figure 1. Primary malignant melanoma infiltration of the gallbladder with isointense appearance on coronal T2-weighted images, hyperintense appearance on axial T1-weighted images and prominent contrast enhancement on fat-suppressed T1-weighted images

Case 2

A 70-year-old male patient was admitted to our otolaryngology clinic with complaint of epistaxis. Examination revealed polypoid mass in the right inferior concha. In the pre-operative imaging of the patient, CT scan revealed a mass lesion extending from the inferior right concha to the posterior of the nasopharynx. Contrast-enhanced facial MRI showed polypoid lesion with no extramucosal extension, which was isointense with mucosa on T1-W sequence and hypointense on T2-weighted sequence, which had similar enhancement pattern with

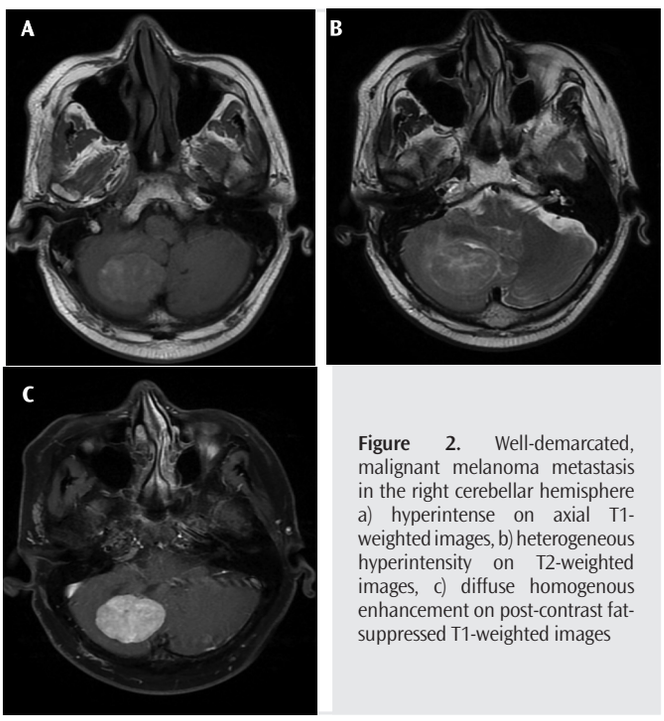


Figure 2. Well-demarcated, malignant melanoma metastasis in the right cerebellar hemisphere a) hyperintense on axial T1-weighted images, b) heterogeneous hyperintensity on T2-weighted images, c) diffuse homogenous enhancement on post-contrast fat-suppressed T1-weighted images

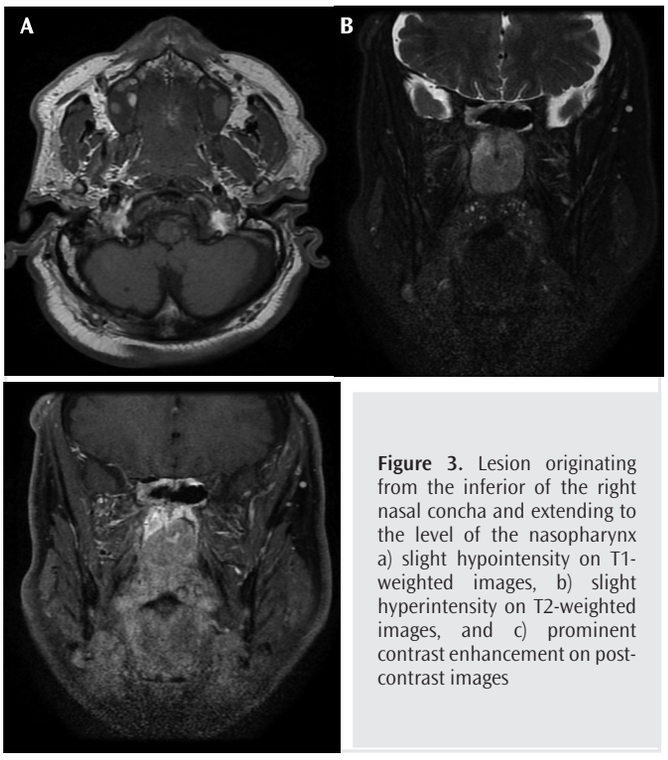


Figure 3. Lesion originating from the inferior of the right nasal concha and extending to the level of the nasopharynx a) slight hypointensity on T1-weighted images, b) slight hyperintensity on T2-weighted images, and c) prominent contrast enhancement on post-contrast images

mucosa on the post-contrast images and which could not be clearly differentiated from inflammatory polyp (Figures 3a,b,c). Frozen section consultation was reported as "15 mm diameter tumor, 5 mm mucosal extension with negative margins and non-specific chronic inflammation at the posterior tumor margin and right maxillary sinus resection". In immunohistochemical studies, neoplastic cells were identified as S100 (+) and HMB45 (+) malignant melanoma. No distant metastasis was detected in PET-CT. Skin melanoma was not found in the dermatological examination of the patient. At the post-operative 2nd month follow-up examination, recurrence was considered and biopsy was performed. The biopsy result was reported as recurrent malignant melanoma in the posterior half of the nasal cavity. Written informed consent was not obtained from the patients due to retrospective design of the study.

Discussion

Mucosal melanomas are more aggressive than skin melanomas. These are more likely to have local or distant metastasis and recurrence, and have a higher mortality. Mucosal melanomas account for 1.3-1.4% of all melanomas, and 25-50% of these cases originate from head and neck tumors. Nasal cavity, oral cavity and paranasal sinuses are the most common sites of the mucosal melanomas in the head and neck region (3). The second common site is the gastrointestinal tract, which accounts for 25% of all mucosal melanoma cases. The most common localizations in the gastrointestinal tract are the anorectal mucosa, the esophagus and the small intestine. Urogenital tract melanomas have the same incidence as the gastrointestinal tract by forming 20% of all mucosal melanomas, but due to the fact that vulvovaginal melanomas are in this group, the incidence of these melanomas is high in women (4). Primary extracutaneous melanomas in the parenchymatous organs have been reported in very few cases. Melanomas seen in the retroperitoneal region and parenchymatous organs, such as the lung and prostate, constitute only 5% of the extracellular malignant melanomas (4,5).

The symptoms are non-specific and vary according to the location of the lesion. The most common symptom in the head and neck region is bleeding and unilateral nasal obstruction. In the anorectal area, it is commonly seen as a polypoid mass and may cause rectal bleeding, abdominal pain and difficulty in defecation.

Vulvar melanomas are the most common type of urogenital melanoma and share similar symptoms with other malignancies in this region. Symptoms include pruritus, irritation, and vaginal discharge. Vulvar melanomas are seen as an ulcerated, bleeding mass lesion in clinical examination and are often not pigmented (1-5,6). The metastasis pattern in mucosal melanomas varies according to the location of the primary site. In vaginal melanomas, early peritoneal invasion occurs due to the close anatomical relation and distant metastases may occur without regional lymph node involvement. Sinonasal melanomas often metastasize to the liver. Lymph node involvement is seen in 60% of anorectal melanomas and the first region of invasion of anal melanomas is inguinal lymph nodes (3-7).

Radiological evaluation is required for diagnosis, staging, preoperative planning and treatment follow-up in metastatic patients receiving systemic treatment. MRI is the primary imaging modality for the evaluation of local disease. CT and PET-CT have limited utility in the evaluation of local disease, and they play a primary role in the detection of metastatic disease (2). MRI appearance of the mucosal melanoma varies according to the histological features of the lesion and the presence of bleeding. Melanotic melanomas are hyperintense on T1-WI and iso-hypointense on T2-WI due to the paramagnetic effect of melanin. Amelanotic melanomas are usually hypointense on T1-WI and hyperintense on T2-WI. In addition to conventional MRI sequences, dynamic contrast-enhanced MRI shows marked enhancement in the early phase due to the hypervascularity of the lesion. Diffusion WI shows high signal intensity and low ADC values (2-8). The only curative treatment option for mucosal melanoma is wide surgical resection. Chemotherapy is used for systemic treatment or in addition to surgery in metastatic disease, and radiotherapy is used to control the local disease and prevent local recurrence (9,10).

Conclusion

Primary mucosal malignant melanomas are very rare and have poor prognosis. Knowing typical radiological features in respiratory, gastrointestinal and urogenital tract lesions, and considering it for differential diagnosis in clinical evaluation will increase the chance of early diagnosis.

Informed Consent: Written informed consent was not obtained from the patients due to retrospective design of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.E.Ç.; Design - Ç.E.; Supervision - Y.K., Ö.K.; Resources - K.E.Ç.; Materials - C.L.; Data Collection and/or Processing - Y.K.; Analysis and/ or Interpretation - Ç.E.; Literature Search - K.E.Ç.; Writing Manuscript - K.E.Ç.; Critical Review - K.E.Ç., Y.K., Ç.E., C.L., Ö.K.

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

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

References

1. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol 2012; 5: 739-53.
2. Keraliya AR, Krajewski KM, Braschi-Amirfarzan M, Tirumani SH, Shinagare AB, Jagannathan JP, et al. Extracutaneous melanomas: a primer for the radiologist. Insights into imaging 2015; 6: 707-17.
3. Seetharamu N, Ott PA, Pavlick AC. Mucosal melanomas: a case-based review of the literature. Oncologist 2010; 15: 772-81.
4. Baderca F, Cojocaru S, Lazar E, Lazureanu C, Lighezan R, Alexa A, et al. Amelanotic vulvar melanoma: case report and review of the literature. Rom J Morphol Embryol 2008; 49: 219-28.
5. Carvajal RD, Spencer SA, Lydiatt W. Mucosal melanoma: a clinically and biologically unique disease entity. J Natl Compr Canc Netw 2012; 10: 345-56.
6. Baderca F, Vincze D, Balica N, Solovan C. Mucosal melanomas in the elderly: challenging cases and review of the literature. Clin Interv Aging 2014; 9: 929-37.

7. O'Regan K, Breen M, Ramaiya N, Jagannathan J, DiPiro PJ, Hodi FS, et al. Metastatic mucosal melanoma: imaging patterns of metastasis and recurrence. Cancer Imaging 2013; 13: 626-32.

8. Liu QY, Zeng YP, Lin XF, Liu ZF, Wu XF, Li HG. MRI findings in primary vaginal melanoma - a report of four cases. Clin Imaging 2015; 39: 533-7.

9. Gunbey HP, Gunbey E, Sayit AT, Aslan K. Magnetic Resonance Imaging (MRI) appearances of primary amelanotic malign melanoma in the nasal cavity: A rare case. J Clin Diagn Res 2015; 9: 1-3.

10. Bridger AG, Smee D, Baldwin MA, Kwok B, Bridger GP. Experience with mucosal melanoma of the nose and paranasal sinuses. ANZ J Surg 2005; 75: 192-7.

İstanbul Med J 2019; 20(3): 250-2
DOI: 10.4274/imj.galenos.2018.77785

Difficult Tracheotomy in Advanced Anaplastic Thyroid Carcinoma

İleri Anaplastik Tiroid Karsinomunda Zor Trakeotomi

Sedat Aydın, Mustafa Paksoy, Elif Uysal

İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Otolaryngology, İstanbul, Turkey

ABSTRACT

Anaplastic thyroid carcinoma (ATC) is a rare and rapidly progressive malignancy of the thyroid gland with a poor prognosis. The cause of death in these patients is mostly due to invasion of the airway with mass and metastasis to the airway. The local destructive invasion of the mass and the compression of the trachea in a short time may lead to severe dyspnea and stridor in the patient. Tracheotomy is a palliative surgical approach that can be performed after endotracheal intubation in patients with severe respiratory distress. This patient with advanced ATC was admitted to the emergency department due to severe respiratory distress. After endotracheal intubation, the tracheotomy was performed with difficulty and the safety of respiratory tract was achieved. In such patients, respiratory airway management is presented with current literature review.

Keywords: Anaplastic thyroid carcinoma, tracheotomy, thyroid gland, difficult, dyspnea

ÖZ

Anaplastik tiroid karsinomu (ATK) tiroid bezinin nadir görülen kötü prognozlu, hızlı ilerleyen bir malignitesidir. Bu hastalarda ölüm sebebi çoğunlukla hava yolunun kitle ile invazyonu ve metastaz sebebiyle olur. Kitlenin lokal destrüktif invazyonu ile kısa sürede trakeada oluşturduğu bası hastada şiddetli dispne ve stridora yol açabilir. Trakeotomi ileri derecede solunum sıkıntısı olan hastalarda endotrakeal entübasyon sonrasında uygulanabilecek palyatif bir cerrahi yaklaşımdır. İlerlemiş ATK olan bu olgumuz ileri derecede solunum sıkıntısı sebebiyle acil servise başvurdu. Endotrakeal entübasyon sonrasında güçlükle uygulanan trakeotomi ile solunum yolu güvenli hale gelmiştir. Bu tür hastalarda solunum yolu yönetimi güncel literatür gözden geçirilerek sunulmuştur.

Anahtar Kelimeler: Anaplastik tiroid karsinomu, trakeotomi, tiroid bezi, zor, dispne

Introduction

Anaplastic thyroid carcinoma (ATC) constitutes 2-5% of all thyroid malignancies and has a very poor prognosis. It usually emerges in the 6th and 7th decades of life with a rapidly growing mass in the neck. As a result of the invasion of this mass to the local tissues, mostly hoarseness, stridor and dyspnea are observed. Airway problems occur due to tracheal invasion or external pressure in the early stages of the disease (1,2). American Thyroid Society (ATA) guide recommends surgical resection in areas where the tumor can be resected and that chemoradiotherapy be given as initial therapy in patients with extensive tumor spread, followed by completion surgery if possible (3,4). Survival rates are 20% at one year after diagnosis and 5% at five years, and the mean life expectancy after diagnosis is 6-15 months. In most of these patients, the cause of death is metastasis and airway problems (5-8).

Airway control is difficult in a tumor with such poor prognosis. Airway problems may be the complaints of patients or may develop during the treatment process. Physicians often have difficulty in deciding when to open tracheotomy or perform surgical decompression. Prior to the publication of the ATA treatment guideline, the literature was limited in providing airway control in ATC (3). This guideline recommends opening tracheotomy under general anesthesia under appropriate conditions in patients with severe respiratory distress in ATC only. In this article, we aimed to present a tracheotomy approach to a patient with ATC who presented with respiratory distress.

Case Report

A 49-year-old male patient was diagnosed with ATC after a biopsy in the health center he had applied to because of developed pain and swelling on his neck 6 months ago. He presented to the emergency department

Address for Correspondence/Yazışma Adresi: Sedat Aydın MD, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Otolaryngology, İstanbul, Turkey
Phone: +90 216 441 39 00 **E-mail:** sedataydin63@yahoo.com **ORCID ID:** orcid.org/0000-0003-4939-5026

Cite this article as/Atıf: Aydın S, Paksoy M, Uysal E. Difficult Tracheotomy in Advanced Anaplastic Thyroid Carcinoma. İstanbul Med J 2019; 20(3): 250-2.

Received/Geliş Tarihi: 19.07.2018
Accepted/Kabul Tarihi: 11.09.2018

of our hospital because of the increasing swelling in his neck and severe respiratory distress and stridor presenting in a short time. In the examination of the patient who had no pathology in his medical history and family history, it was observed that he had difficult respiration and inspiratory stridor in the inspection. The mass was covering the whole neck and anatomic triangulation points could not be differentiated. It was stiff, fixed, about 15x20 cm and mostly lateralized to the right side of the neck. The flexible nasopharyngoscopy revealed bilateral cord vocal paralysis and increased secretion in the piriform sinuses. The opening between the two vocal folds was 2-3 mm. Previous neck and thorax computed tomography of the patient were reported as "15x17 cm mass lesion, involving both thyroid lobes and isthmus, having irregular margins and exhibiting heterogeneous enhancement, and margins cannot be clearly distinguished from the surrounding muscles and soft tissues, and sternocleidomastoid muscles" (Figures 1 and 2). Informed consent was obtained from the patient. The mass pushed the trachea to the right and was compressing the airway from the anterolateral side. An urgent tracheotomy was planned for breathing difficulty. However, because important triangulation points in the neck were lost, it was thought that tracheotomy would be safer after endotracheal intubation and endotracheal intubation was performed under general anesthesia. Then, a conventional Kocher incision was planned in case apron flap incision was required. During the subcutaneous flap elevation, which was difficult due to bleeding, stiff and hemorrhagic thyroid mass adherent to strap muscles and other surrounding tissues were encountered. The incision was extended to the apron flap incision as previously thought, in order to control the mass. It was seen that the mass deviated the trachea to the right, extending to the posterior end of the sternum. Thyroid cartilage of the larynx was detected as an anatomical triangulation point in the neck. It was aimed to reach tracheal rings by following this structure downwards. In the meantime, with the help of the "harmonic scalpel®" vascular sealing device that provided technological innovation, the thyroid right lobe and the mass thought to be derived from this lobe were partially excised and the tracheal cartilages were reached. The trachea was entered from the place where the second ring was thought to be (Figure 3). The patient was sedated and was taken to the intensive care unit with intravenous antibiotic and fluid support. Because the patient had postoperative induration and discharge in his neck, antibiotic treatment was continued as ultrasound revealed suspected abscess. The patient died in the intensive care unit after 14 days due to sudden bradycardia and cardiac arrest.

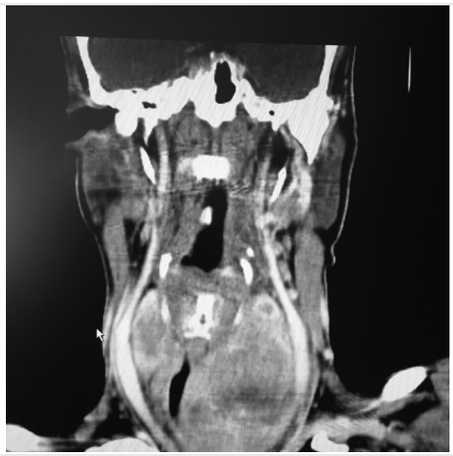


Figure 1. In coronal view of computed tomography scan of head and neck; a mass of 15x17 cm with irregular margins and heterogeneous contrast enhancement is observed, which invades both thyroid lobe and isthmus, and thus cannot be clearly distinguished from surrounding soft tissues

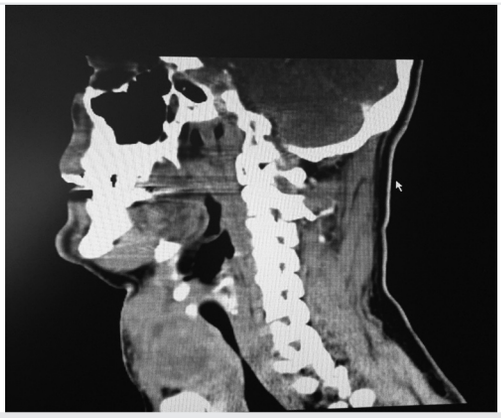


Figure 2. In sagittal view of computed tomography scan of head and neck; it is observed that the same mass has filled the thyroid space and narrowed the tracheal lumen

Discussion

Treatment options of ATK include surgery, chemotherapy, radiotherapy and combined therapies. However, the assessment of patients' airway is of critical importance. The cause of death in patients with ATC is often distant metastases with airway involvement, bilateral vocal cord paralysis and respiratory problems. The tracheotomy or cricothyrotomy procedure provides palliative and transient airway solution. This issue should be discussed with the patient and his/her relatives and consent must be taken. The survival in patients who underwent tracheotomy was

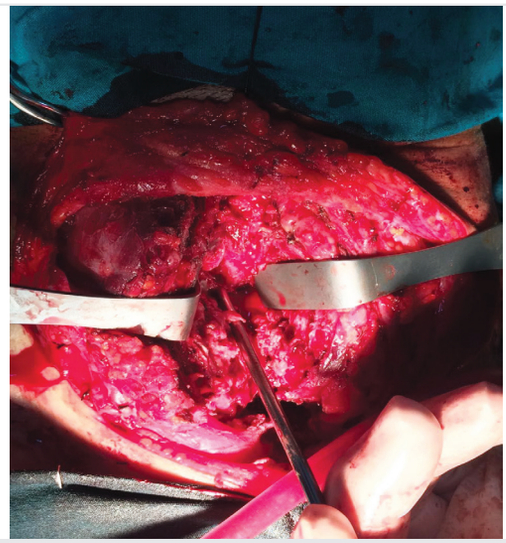


Figure 3. A view of tracheotomy after partially tumor excision of the istmus region, severe destructive mass in the trachea drastically eliminated the anatomical guiding points

found to be shorter than in patients who underwent "debulking" surgery (9). However, it is important to note that in patients with ATC, respiratory problems are likely to occur until the tracheotomy stage. Because of the presence of malignancy and radiotherapy in these patients, wound healing in the tracheotomy region is not fast and healthy. For this reason, the tumor tissue can continue to grow from the tracheotomy line or its surroundings, leading to bleeding (10). In our case, abscess formation was detected after tracheotomy.

The fact that the mass causes respiratory distress in patients with ATC means that the mass grows and closes the surgical access ways to the trachea in the midline of the neck. Another problem is the displacement of the trachea due to the compression effect of the mass during tracheotomy. ATA recommends that tracheotomy should be performed under operating conditions and under general anesthesia as we did in our case (3-11).

As the ATC is progressing rapidly, a large mass is often encountered in the neck midline when respiratory distress occurs in patients. Because of this mass, "debulking" surgery is required to reach the trachea. Displacement of the trachea, stiffness and blood supply of the mass should be considered during this surgery. At this stage, the importance of preoperative radiological evaluation of the patient is revealed. The shortest and easiest way of access to the tr achea should be evaluated preoperatively and the size of the surgery should be determined preoperatively. During "debulking" surgery, electrocautery should be used to reduce both the duration of surgery and post-operative bleeding. Standard tracheotomy cannulae can be short in these patients because reaching the trachea with "debulking" surgery also increases the distance between the skin and the trachea. In this stage, length-adjustable cannulas or intubation tube can be used (9). It is important to fix the cannula or tube to prevent dislocation (12). In our case, since length-adjustable tracheotomy cannula was not available at the time, a 7.0 endotracheal intubation tube was used and it was fixed to the surrounding neck skin.

In addition, the light to be advanced through the trachea can be followed by fiberoptic endoscopy during tracheotomy to help locate the trachea, which is displaced by external pressure (9). In our case, trachea was revealed after "debulking" surgery and there was no need for fiberoptic endoscopy guidance.

In conclusion, after the laryngeal examination with flexible nasopharyngoscopy and tracheotomy is planned for maintaining airway safety in cases of ATC admitting to emergency departments with severe respiratory distress, one first should get ready for a problematic tracheotomy following endotracheal intubation in the operating room conditions, as in our case. We believe that tracheotomy would be safe by reaching tracheal cartilages guided by thyroid notch and thyroid cartilage with a large incision, in difficult tracheotomy cases where triangulation points disappear, as in our case.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.A.; Design - S.A.; Supervision - S.A., M.P., E.U.; Resources - S.A., E.U.; Materials - S.A., M.P., E.U.; Data Collection and/or Processing - S.A., M.P., E.U.; Analysis and/or Interpretation - S.A., E.U.; Literature Search - S.A., M.P.; Writing Manuscript - S.A., E.U.; Critical Review - S.A.

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

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

References

1. Ain KB. Anaplastic thyroid carcinoma: a therapeutic challenge. Semin Surg Oncol 1999; 16: 64-9.
2. Wein RO, Weber RS. Anaplastic thyroid carcinoma: palliation or treatment? Curr Opin Otolaryngol Head Neck Surg 2011;19:113-8.
3. Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, et al. American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012; 22: 1104-39.
4. Işık A, Fırat D, Yılmaz I, Peker K, Idız O, Yılmaz B, et al. A survey of current approaches to thyroid nodules and thyroid operations. Int J Surg 2018; 54: 100-4.
5. Veness MJ, Porter GS, Morgan GJ. Anaplastic thyroid carcinoma: dismal outcome despite current treatment approach. ANZ J Surg 2004; 74: 559-62.
6. Rodriguez JM, Pinero A, Ortiz S, Moreno A, Sola J, Soria T, et al. Clinical and histological differences in anaplastic thyroid carcinoma. Eur J Surg 2000; 166: 34-8.
7. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches. Ann Surg Oncol 2006; 13: 453-64.
8. Lang BH, Lo CY. Surgical options in undifferentiated thyroid carcinoma. World J Surg 2007; 31: 969-77.
9. Mani N, McNamara K, Lowe N, Loughran S, Yap BK. Management of the compromised airway and role of tracheotomy in anaplastic thyroid carcinoma. Head Neck 2016; 38: 85-8.
10. Ranganath R, Shah MA, Shah AR. Anaplastic thyroid cancer. Curr Opin Endocrinol Diabetes Obes 2015; 22: 387-91.
11. Haddad RI, Lydiatt WM, Ball DW, Busaidy NL, Byrd D, Callender G, et al. Anaplastic thyroid carcinoma, Version 2.2015, J Natl Compr Canc Netw 2015; 13: 1140-50.
12. Shaha AR, Ferlito A, Owen RP, Silver CE, Rodrigo JP, Haigentz M Jr, et al. Airway issues in anaplastic thyroid carcinoma. Eur Arch Otorhinolaryngol 2013; 270: 2579-83.

İstanbul Med J 2019; 20(3): 253-5
DOI: 10.4274/imj.galenos.2018.75735

A Localized Painful Rash Induced by Linagliptin in a Patient with type 2 Diabetes

Tip 2 Diyabetli Bir Hastada Linagliptine Bağlı Lokalize Ağrılı Döküntü

İsmail Yıldız[1], Ramazan Gen[2], Leyla Batmaz[2], Kerem Sezer[2], Esen Akbay[2], Mahmut Serbülent İbanoğlu[2], Yasemin Yuyucu Karabulut[3]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Endocrinology and Metabolism, Tekirdağ, Turkey
[2]Mersin University Faculty of Medicine, Department of Endocrinology and Metabolism, Mersin, Turkey
[3]Mersin University Faculty of Medicine, Department of Patology, Mersin, Turkey

ABSTRACT

The number of patients with type 2 diabetes using dipeptidyl peptidase-4 (DPP-4) inhibitors is increasing across the world.

Although this class of antidiabetic medications is generally safe and associated with less side effects compared to other oral antidiabetic medications, they could also cause some side effects such as skin rashes. Herein we report a case of type 2 diabetes patient who developed a painful maculopapular rash induced by linagliptin, a widely used DPP-4 inhibitor.

A localized painful maculopapular rash developed on the palmar faces of the patient's hands almost 1 day after the initiation of the drug. The patient was using intensive insulin therapy before linagliptin was started. There was no eruption on the other body parts except the palmar faces of the hands. Following the discontinuation of the drug, the rash disappeared in about four days. The patient had no history of urticaria and did not use an ACE inhibitor. As far as we know, this is the first case report of a skin rash induced by linagliptin in the Turkish literature. This case report highlights a rare and lesser known side effect of linagliptin, a new member of DPP-4 inhibitors.

Keywords: Linagliptin, DPP-4 inhibitor, rash skin eruption, type 2 diabetes mellitus

ÖZ

Dipeptidil peptidaz-4 (DPP-4) inhibitörleri kullanan tip 2 diyabet hastalarının sayısı dünya genelinde artmaktadır.

Bu antidiyabetik ilaç sınıfı genelde güvenli olmakla birlikte diğer oral antidiyabetik ilaçlarla karşılaştırıldığında daha az yan etki ile ilişkili olsa da, deri döküntüleri gibi bazı yan etkilerle ilişkili olabilirler. Burada yaygın olarak kullanılan bir DPP-4 inhibitörü olan linagliptin ile indüklenen ağrılı makülopapüler döküntü gelişen tip 2 diyabetli bir hastayı sunuyoruz.

Linagliptin başlandıktan 1 gün sonra hastamızın ellerinin palmar yüzünde lokalize ağrılı makülopapüler bir döküntü gelişti. Linagliptin başlanmadan önce hasta intensif insülin tedavisi altındaydı. Vücudun diğer bölgelerinde herhangi bir döküntü yoktu. Linagliptin kesildikten sonra 4 gün içerisinde döküntü kayboldu. Hastanın ürtiker öyküsü yoktu ve Anjiyotensin dönüştürücü enzim inhibitörü kullanmıyordu. Bildiğimiz kadarıyla bu, Türk literatüründe Linagliptine bağlı deri döküntüsü geliştirdiği rapor edilen ilk olgudur. Bu olgu sunumu, DPP-4 inhibitörlerinin nadir görülen ve daha az bilinen bir yan etkisini vurgulamaktadır.

Anahtar Kelimeler: Linagliptin, DPP-4 inhibitörleri, makülopapüler cilt döküntüsü, tip 2 diabetes mellitus

Introduction

A localized painful maculopapular rash developed on the palmar faces of both hands of a patient almost one day after the initiation of linagliptin, a new member of dipeptidyl peptidase inhibitors-4 (DPP-4). The patient was using intensive insulin therapy before linagliptin was started. There was no eruption on the other body parts except the palmar faces of the hands. When the drug was discontinued, the rash immediately disappeared in about four days. The patient had no urticaria and did not use an angiotensin converting enzyme (ACE) inhibitor.

Contrary to other DPP-4 inhibitors, linagliptin is generally used for diabetic patients who have different stages of renal failure. This case shows that linagliptin can also induce skin reactions like other DPP-4 inhibitors.

Case Report

A-54-year old female patient with newly diagnosed type 2 diabetes was admitted to our outpatient clinic due to nausea, vomiting, polyuria, and polydipsia. She had a history of essential hypertension. She had not any

Address for Correspondence/Yazışma Adresi: İsmail Yıldız MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Endocrinology and Metabolism, Tekirdağ, Turkey
Phone: +90 553 454 15 40 **E-mail:** ismailyil1987@gmail.com **ORCID ID:** orcid.org/0000-0002-4990-0216

Cite this article as/Atıf: Yıldız İ, Gen R, Batmaz L, Sezer K, Akbay E, İbanoğlu MS, Yuyucu Karabulut Y.A Localized Painful Rash Induced by Linagliptin in a Patient with type 2 Diabetes. İstanbul Med J 2019; 20(3): 253-5.

Received/Geliş Tarihi: 18.02.2018
Accepted/Kabul Tarihi: 13.07.2018

fever, skin rash or other signs of infectious diseases. Except for reduced skin turgor and tonus, the physical examination was normal.

On biochemical analysis, her fasting plasma glucose, hemoglobin A1c (HbA1c), white blood cell (WBC) count, serum creatinine, blood urea nitrogen (BUN), and C-reactive protein levels were 300 mg/dL, 9.8%, 17.000 (70% neutrophil), 1.7 mg/dL, 60 mg/dL, and 3 mg/L (<5 mg/L), respectively. She did not have ketonuria or acidosis and the serum potassium level was normal.

One day after starting rehydration with isotonic saline infusion for acute renal injury and intensive insulin therapy for hyperglycemia, the skin turgor and tonus, fasting and postprandial plasma glucose, serum creatinine, BUN, and WBCs count returned to normal values.

On the 3rd day after admission, metformin was added to the insulin treatment, but dyspeptic complaints and watery diarrhea developed. For this reason, metformin was stopped and linagliptin, a DPP-4 inhibitor, was added.

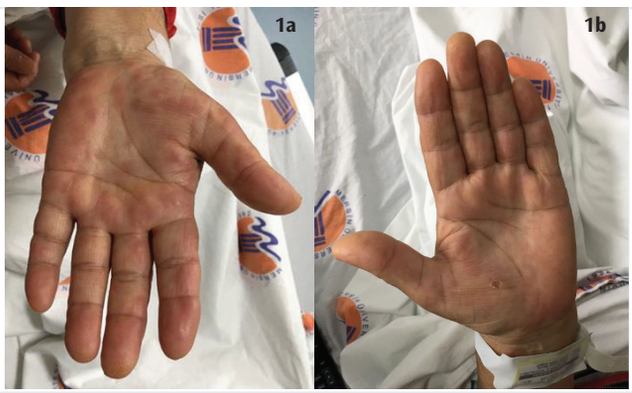


Figure 1. a) Hyperemic maculopapular rash on the palmar faces of the hands, b) disappearance of the rash after the cessation of the linagliptin

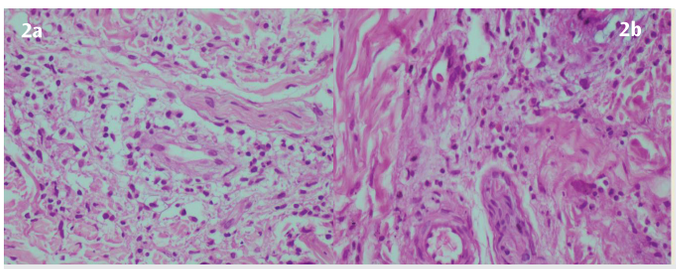


Figure 2. a, b) Eosinophils

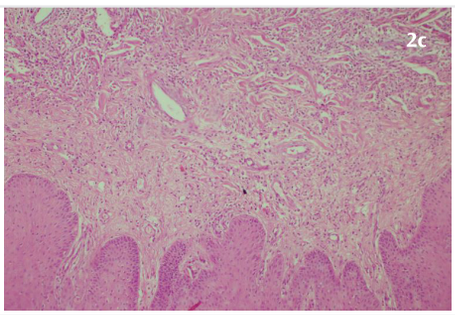


Figure 2. c) A histopathologic view (haematoxylin and eosin staining) of an eosinophilic superficial dermatitis taken from the skin biopsy of the patient

However, one day later, the patient developed a painful, hyperemic, maculopapular rash (Figure 1) without itching on the palmar faces of the both hands. The rash was thought to be related to linagliptin and treatment was therefore stopped.

The patient's informed consent form was taken. A skin biopsy performed by a dermatologist revealed an eosinophilic superficial dermatitis (Figure 2). So, a diagnosis of an allergic skin reaction against linagliptin was made and treatment with betamethasone ointment was started. Four days after the treatment of linagliptin, this treatment was stopped, treatment with betamethasone ointment was started, and pain and maculopapular rash disappeared completely.

Discussion

DPP-4 inhibitors are orally active drugs used for the treatment of type 2 diabetes (1). DPP-4 is a cell-surface protease that inactivates the incretin hormones, the glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP). The incretins play an important role in glucose homeostasis, stimulating insulin secretion, suppressing glucagon release, and slowing gastric emptying.

The DPP-4 inhibitors increase the circulating concentrations of incretin hormones (GIP, GLP-1) and also decrease plasma glucose concentrations in type 2 diabetes patients (2-5). In clinical trials on type 2 diabetic patients, the addition of a DPP-4 inhibitor decreases fasting glucose and HbA1c and improves insulin secretion (6,7).

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin reactions including Stevens-Johnson syndrome. The onset of these reactions generally occurs within the first 3 months of the initiation of the treatment with sitagliptin, and even some reactions occur after the first dose of the drug (8). Nakatani et al. (9) have reported a drug-induced generalized skin eruption in a diabetes mellitus patient receiving sitagliptin plus metformin. Attaway et al. (10) also have reported a case of bullous pemphigoid associated with sitagliptin.

There are a few reports about the anaphylactic reactions and skin lesions occurring after the use of sitagliptin or vildagliptin. Although a few reports are available in English literature demonstrating skin reactions induced by linagliptin, Esposito et al. (11) have recently reported a case of bullous pemphigoid induced by linagliptin. Also, Psomadakis et al. (12) have reported a case of linagliptin-associated blistering and ulceration. In the present case, linagliptin was used in addition to intensive insulin therapy. After the initiation of linagliptin, the patient developed maculopapular lesions on the palmar aspects of the hands, which resolved in four days after stopping the drug.

In our patient, although metformin was used for a short period of time (2 days), the skin eruption occurred just after adding linagliptin to the treatment. The occurrence of skin eruption after starting linagliptin and the disappearance of the eruption after the discontinuation of linagliptin suggests that linagliptin might be the cause of skin eruption in our patient.

Despite the long term history of metformin use, drug-induced rash after metformin therapy has rarely been reported, and the most commonly

reported skin reactions due to metformin are psoriasis form eruption (13) and leukocytoclastic vasculitis (14). Therefore, the skin reaction in our patient is thought to be due to linagliptin.

Conclusion

The present case suggests that linagliptin may also cause skin reactions similar to other DPP-4 inhibitors, such as sitagliptin and vildagliptin, which can lead to skin reactions such as bullous pemphigoid in particular.

Therefore, patients taking this class of drugs with or without a history of urticaria should be considered and treatment should be discontinued after skin reactions occur. However, it is not well known whether cross reaction would develop after switching to another DPP-4 inhibitor in patients with skin rash occurring after starting a DPP-4 inhibitor. However, close follow-up of patients who have skin reactions after the use of DPP-4 inhibitor or who have been switched to another DPP-4 inhibitor is necessary to prevent serious skin reactions. This case also suggests that local glucocorticoid ointments are generally effective in the treatment of localized skin reactions induced by DPP-4 inhibitors.

Informed Consent: The patient's informed consent form was taken.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - İ.Y., R.G., L.B., M.S.İ.; Design - İ.Y., K.S., E.A.; Supervision - İ.Y., R.G., E.A.; Resources - İ.Y., L.B. M.S.İ.; Analysis and/or Interpretation - İ.Y., R.G., L.B., ; Literature Search - İ.Y., K.S., M.S.İ., Y.Y.K.; Writing Manuscript - İ.Y., R.G., L.B.; Critical Review - R.G., K.S., E.A.

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

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

References

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696-705.
2. Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, et al. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 2005; 90: 4888-94.
3. Pratley RE, Jauffret-Kamel S, Galbreath E, Holmes D. Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. Horm Metab Res 2006; 38: 423-8.
4. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia 2006; 49: 2564-71.
5. Herman GA, Bergman A, Stevens C, Kotey P, Yi B, Zhao P, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. J Clin Endocrinol Metab 2006; 91: 4612-9.
6. Ahren B, Pacini G, Foley JE, Schweizer A. Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes Care 2005; 28: 1936-40.
7. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007; 9: 733-45.
8. JANUVIA™ (sitagliptin) Prescribing Information. MERCK and CO, Inc. Whitehouse Station, NJ; 2007.
9. Nakatani K, Kurose T, Hyo T, Watanabe K, Yabe D, Kawamoto T, Seino Y. Drug-induced generalized skin eruption in a diabetes mellitus patient receiving a dipeptidyl peptidase-4 inhibitor plus metformin. Diabetes Ther 2012; 3: 14.
10. Attaway A, Mersfelder TL, Vaishnav S, Baker JK. Bullous pemphigoid associated with dipeptidyl peptidase IV inhibitors. A case report and review of literature. J Dermatol Case Rep 2014; 8: 24-8.
11. Esposito I, Moretta G, Peris K, De Simone C. Linagliptin-induced bullous pemphigoid. Int J Dermatol 2017; 56: 1467-9.
12. Psomadakis C, Shahzad N, Katz J. Linagliptin-associated blistering and ulceration. BMJ Case Rep 2017: 2017.
13. Koca R, Altinyazar HC, Yenidünya S, Tekin NS. Psoriasiform drug eruption associated with metformin hydrochloride: a case report. Dermatol Online J 2003; 9: 11.
14. Ben Salem C, Hmouda H, Slim R, Denguezli M, Belajouza C, Bouraoui K. Rare case of metformin-induced leukocytoclastic vasculitis. Ann Pharmacother 2006; 40: 1685-7.

İstanbul Med J 2019; 20(3): 256-60
DOI: 10.4274/imj.galenos.2018.89421

Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome Associated with Ampicillin-Sulbactam and Clindamycin: A Case Report

Ampisilin-Sulbaktam ve Klindamisin-İlişkili Eozinofili ve Sistemik Semptomlarla Giden İlaç Reaksiyonu Sendromu: Olgu sunumu

Öner Özdemir[1], Gökçe Genç[2]

[1]Sakarya University Training and Research Hospital, Clinic of Pediatrics, Division of Allergy and Immunology, Adapazarı, Turkey
[2]Sakarya University Training and Research Hospital, Clinic of Pediatrics, Adapazarı, Turkey

ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening delayed type allergic reaction characterized by fever, skin rash, lymphadenopathy, eosinophilia and internal organ involvement. A 4-year-old male patient was admitted to the hospital with fever and rash. His medical history revealed use of an antibiotic combination (ampicillin + sulbactam and clindamycin) 2 weeks ago. Physical examination revealed hepatomegaly, splenomegaly, lymphadenopathy, fever and macular rash. The patient was diagnosed with DRESS syndrome with laboratory and clinical findings. The responsible medication was discontinued and corticosteroid was added to the treatment. DRESS syndrome should be kept in mind in patients with history of drug use, fever, skin rash and solid organ involvement.

Keywords: DRESS, eosinophilia, allergy, drug, hypersensitivity

ÖZ

Eozinofili ve sistemik semptomlarla giden ilaç reaksiyonu (DRESS) sendromu ateş, deri döküntüsü, lenfadenopati, eozinofili, iç organ tutulumu ile karakterize, yaşamı tehdit eden bir gecikmiş tip allerjik reaksiyonudur. Dört yaşında bir erkek hasta ateş ve döküntü ile hastaneye yatırıldı. Öyküsünde 2 hafta önce antibiyotik kombinasyonu (ampisilin + sulbaktam ve klindamisin) kullanımı mevcuttu. Fizik incelemede hepatomegali, splenomegali, lenfadenopati, ateş ve maküler döküntü saptandı. Laboratuvar ve klinik bulguları ile hastaya DRESS sendromu tanısı konuldu. Sorumlu ilaç kesildi ve tedaviye kortikosteroit eklendi. İlaç kullanım öyküsü, ateş, deri döküntüsü ve solid organ tutulumu olan hastalarda DRESS sendromu ayırıcı tanıda akılda tutulmalıdır.

Anahtar Kelimeler: DRESS, eozinofili, alerji, ilaç, hipersensitivite

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, drug-induced, lethal, delayed drug hypersensitivity reaction in childhood (1-3). Clinical findings include drug-induced rash, eosinophilia in peripheral blood count, and systemic symptoms such as fever, lymph node involvement and other solid organ involvement (liver, kidney, lung, etc.) (1,2). Although the most common cause is anti-epileptic drugs, it is associated with many drugs such as antibiotics (3,4).

Although the exact incidence of DRESS syndrome is unknown, it is thought to be 1.2-6 cases/million/year (5,6). DRESS syndrome, especially for anti-convulsant drugs, is thought to be an immunological response to reactive metabolites that develop after a pharmacological defect in drug detoxification (6). This immunological response can also be triggered by viral infections such as Herpes infections (6-8). Here, we aimed to present our rare case in which we discuss the contribution of synchronous human parvovirus-B19 (HPV-B19) infection in the development of DRESS syndrome associated with the use of antibiotic combination (ampicillin + sulbactam and clindamycin).

Case Report

A 4-year-old male patient was admitted to our clinic because of prolonged and persistent fever. The patient had a fever that started 10 days prior to his admission. In his medical history, it was learned that he had been treated with empirical antibiotic (ampicillin + sulbactam and clindamycin) for 6 days and his fever persisted. The patient had no problems in his prenatal, natal and family history. On

Address for Correspondence/Yazışma Adresi: Öner Özdemir MD, Sakarya University Training and Research Hospital, Clinic of Pediatrics, Division of Allergy and Immunology, Adapazarı, Turkey
Phone: +90 264 444 54 00 **E-mail:** oner.ozdemir.md@gmail.com **ORCID ID:** orcid.org/0000-0002-5338-9561

Cite this article as/Atıf: Özdemir Ö, Genç G. DRESS Syndrome Associated with Ampicillin-Sulbactam and Clindamycin: A Case Report. İstanbul Med J 2019; 20(3): 256-60.

Received/Geliş Tarihi: 26.04.2018
Accepted/Kabul Tarihi: 03.09.2018

his physical examination, his general condition was good and he was conscious. His vital signs were as follows: body temperature: 38.2 °C, pulse: 125/min and blood pressure: 90/60 mm/Hg. The patient had new-onset maculo-papular rash on his face and whole body (Figures 1,2). Facial rashes and peelings on the palm and fingers suggested HPV-B19 infection, however, dermatitis in the DRESS syndrome was also suspected (Figure 3). Physical examination also revealed diffuse maculo-papular rash, 2 cm hepatomegaly, 3 cm splenomegaly, bilateral cervical and inguinal lymphadenopathy without clear fever focus. Other system examination findings were normal. Laboratory findings were as follows: hemoglobin: 10.2 g/dL, white blood cell count: 14.400/mm^3, platelet count: 330.000/mm^3. Peripheral blood smear revealed eosinophilia (4%, absolute eosinophil count: 545/mm^3) and reactive (atypical) lymphocytes. Complete biochemistry and urinalysis were normal, and blood and urine cultures were negative. C-Reaktif Protein was 36 mg/L and sedimentation was 44 mm/h. Although HPV-B19 İmmunoglobulin M (IgM) was positive in serology, HPV-B19 IgG could not be studied. The polymerase chain reaction (PCR) for parvovirus was negative. The patient's history and clinical findings were consistent with DRESS syndrome. According to the RegiSCAR scoring, our patient had >5 points (seven) (Table 1). The drugs (ampicillin + sulbactam and clindamycin) that were considered to be responsible were discontinued immediately. Corticosteroid (1 mg/kg/day, methylprednisolone) and feniramine maleate (2 mg/kg/day) were started. After the first doses of treatment, the patient's fever receded. Hepatomegaly, splenomegaly and lymphadenopathies regressed with one-week steroid therapy. Corticosteroid was reduced and discontinued, and feniramine was discontinued without reduction within 1 week. The patient, who showed clinical improvement, was discharged for outpatient follow-up. In order to get rid of the effects of drugs and to get optimal results, a patch test was planned within 2 to 6 months after the discharge, however, it could not be done because the family moved to another city. Both oral and written consent were obtained from the patient's parents for this case report.

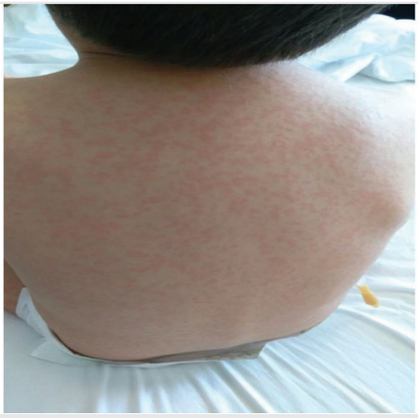


Figure 1. Maculo-papular rashes are seen in the back of our patient

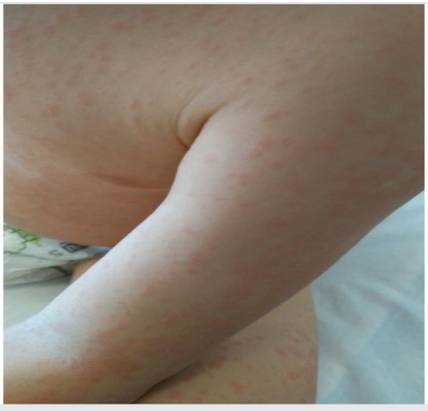


Figure 2. Maculo-papular rashes in the trunk, arm and thigh

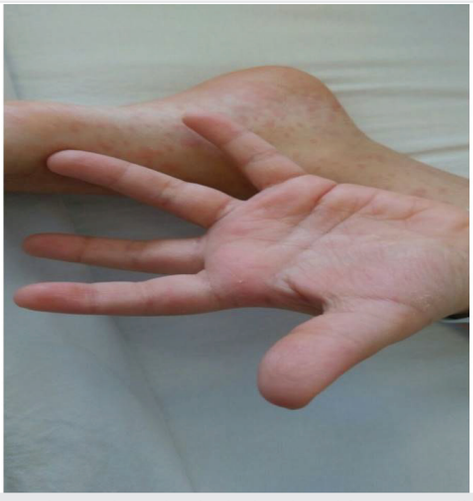


Figure 3. Maculo-papular rashes in the hands and feet, and peeling in the hand

Discussion

The diagnostic criteria for DRESS syndrome have been described in the literature (9). Presence of more than 3 following criteria in a patient is considered diagnostic for DRESS syndrome: sudden onset of skin rash, >38 ºC fever, lymphadenomegaly in at least two regions, at least one solid organ involvement, and laboratory findings (hematological abnormalities: eosinophilia, lymphocytosis, thrombocytopenia and atypical lymphocytes) (4-10).

High fever occurs in almost all cases and begins at the same time as the rash. The rash is usually in the form of maculo-papular exanthema. Bullae, pustule, purpura, plaque, erythrodermia and even exfoliative dermatitis may be observed (4,5,11,12). In DRESS syndrome, the most commonly affected solid organ is liver, kidney, lung and heart, respectively (5,13). Eosinophilic infiltration is seen in the involved organs (5). Transaminases and serum creatinine increases due to involvement (4,5,14). In our case, there were maculo-papular rash after drug use and fever for at least 10 days. In our patient, eosinophilia (>500/mm^3) was also present in the peripheral smear. The presence of hepatomegaly and splenomegaly in our patient showed solid organ involvement. Renal functions, chest X-ray, respiratory and cardiovascular examination were normal. The patient with prolonged fever and rash after drug use was evaluated as DRESS syndrome with clinical findings and RegiScar scoring. Clinical findings in DRESS syndrome occur 2-8 weeks after taking the drug (4). In our patient, this period was approximately 2 weeks.

Our case met the criteria with fever, rash, liver involvement, lymphadenopathy and eosinophilia. The RegiSCAR scoring system developed by Kardaun et al. (15) for the diagnosis of DRESS syndrome

has a total score between -4 and 9, and is divided into no cases (<2 points), possible (2-3 points), probable (4-5 points) and definite DRESS syndrome (>5 points) (Table 1). The RegiScar scoring was as follows in our patient: fever: 0 point, lymphadenopathy: 1 point, eosinophilia: 0 point, atypical lymphocytes in peripheral smear: 1 point, skin rash: 2 points, liver and spleen involvement: 2 points, rash resolution >15 days: 0 point and excluding other causes: 1 point, a total of 7 points. The diagnosis of DRESS syndrome was confirmed by >5 points in RegiScar evaluation.

The most commonly responsible drugs from DRESS syndrome are aromatic (phenytoin, phenobarbital, carbamazepine, etc.) anti-convulsants. Rarely, other anti-epileptics, antibiotics such as sulfonamide, dapsone, allopurinol, anti-inflammatory drugs have also been reported as the cause (4,6,13-17). In a study performed by Kundak et al. (14), DRESS syndrome following amoxicillin use was defined. Again, in the RegiScar study by Kardaun et al. (15), which included 201 possible DRESS cases, one of the cases who developed DRESS with 13 antibiotics was the patient who used ampicillin/sulbactam. In addition, our patient also used clindamycin and this antibiotic was reported in the near future to cause DRESS syndrome in the literature (17). The fact that the same group of antibiotics was used together in our case suggests that antibiotics may be responsible for the development of the clinical picture. Although it is reported in the literature that DRESS syndrome is usually developed with anti-convulsant drugs, DRESS syndrome following antibiotic use reported in previous articles from our country and other countries, as in our case, is important in terms of demonstrating this possibility (14,17).

The role of antibiotics in the development of DRESS syndrome can be demonstrated by antibiotic-mediated lymphocyte transformation test and patch test since drug provocation in such clinical situations is risky and not recommended (18,19). These tests should be done if necessary, in order to determine the agent and to avoid them in the future, although the results are not very reliable. Positive results are more valuable than negative results. The negative and positive predictive values of these tests are not known. Although patch test with anti-epileptics such as carbamazepine gives good results, it has been reported that the positive predictive value of other drugs such as allopurinol varies between 0-10% (19-22). Although there are no serious side effects associated with patch test, there are rare reports of serious side effects with recurrence in the literature (23). As the patient could not come to the follow-up due to moving from the city, patch test for antibiotics could not be performed.

Table 1. Evaluation of our patient according to RegiSCAR scoring system used for diagnosis and classification of DRESS syndrome

Score (points)	**-1**	**0**	**1**	**2**	**Min.**	**Max.**
Fever ≥38.5 °C	**N/U**	**Y**	**-**	**-**	**-1**	**0**
Enlarged lymph nodes	-	N/U	Y	-	0	1
Eosinophilia	-	N/U		-	0	2
Eosinophil	-	700-1.499/mm^3	≥1.500/mm^3	-	-	-
Eosinophil (if leukocyte <4.000/mm3	-	10-19.9%	20%	-	-	-
Atypical lymphocytosis	-	N/U	Y	-	0	1
Skin involvement	-	-	-	-	-2	2
Extent (body surface area %)	-	N/U	>%50	-	-	-
Rash suggesting DRESS	N	U	Y	-	-	-
Skin biopsy suggesting DRESS	N	Y/ U	-	-	-	-
Organ involvement*	-	-	-	-	0	2
Liver	-	N/U	Y	-	-	-
Kidney	-	N/U	Y	-	-	-
Lungs	-	N/U	Y	-	-	-
Heart/Muscle	-	N/U	Y	-	-	-
Pancreas	-	N/U	Y	-	-	-
Other organs	-	N/U	Y	-	-	-
Rash resolution ≥15 days	N/U	Y	-	-	-1	0
Excluding other causes	-	-	-	-	0	1
Anti-nuclear antibody (ANA)	-	-	-	-	-	-
Blood culture	-	-	-	-	-	-
Serology for HAV/HBV/HCV	-	-	-	-	-	-
Chlamydia/Mycoplasma (If three tests of the following tests were performed and all were negative)	-	-	Y	-	-	-
Total Score				-	- 4	9

Total score: no cases (<2 points), possible (2-3 points), probable (4-5 points) and definite DRESS syndrome (>5 points). *After exclusion of other causes 1: one organ involvement, 2: shows two or more organ overalls.

DRESS: Drug reaction with eosinophilia and systemic symptoms, N: no, U: unknown/unclassified, Y: yes, HAV: Hepatit A virus, HBV: Hepatit B virus, HCV: Hepatit C virus, min: minimum, max: maximum

Although DRESS syndrome is a type of delayed type (type IV) drug hypersensitivity reaction, its ethiopathogenesis is not clear today. Among the factors implicated in ethiopathogenesis are enzyme defects of drug metabolism, lymphocyte activation, eosinophilia and viral agents (especially human herpesvirus-6 and 7) (5). In addition, it was observed that cytomegalovirus and Epstein-Barr virus infections from the herpesvirus family were also reported to be related or triggering causes (4-7). Although there has been no previously reported case of HPV-B19 in the literature (24,25) except for 1-2 cases, the presence of symptoms (fever, rash, and peeling on hands and feet), HPV-B19 IgM positivity (despite PCR negativity and IgG not examined) in our case suggests that parvovirus can also be a related factor. As a result of the microbiology consultation, it was learned that PCR performed in the early period of viremia and/or PCR kit being not very sensitive might be the reason for PCR negativity and that PCR could not always show that the patient was not infected.

HPV-B19 cases reported in the literature, as reported by Regnier et al. (24), suggested that infection might cause clinical situations that can mimic DRESS syndrome or that this infection occur during the clinical course of DRESS syndrome (reactivation) and prolongs the course of disease and complicates the clinical status. Regnier et al. (24) and Coughlin et al. (25) reported that HPV-B19 infection was detected in three cases after DRESS disease or after recurrent transaminitis (hepatic transaminase elevation). The steroid therapy was continued for 20 weeks in one case and for 7 weeks in the other. In our case, transaminase values were within normal limits from the beginning to the end of the disease course. This, in addition to the IgM positivity, makes us think the effect of HPV-B19 on the clinical picture of our patient as the transaminases were within normal limits and PCR was negative. Perhaps, anti-HPV-B19 IgM positivity may also be coincidental. In conclusion, it is difficult to explain whether the clinical picture of DRESS in our case is due to virus-drug interaction or the effect of drugs on its own.

The basic for the management of DRESS syndrome is the immediate discontinuation of the suspected drug or drugs and the supportive treatment (3). Topical corticosteroids, moisturizers and H1-anti-histamines in case of mild symptoms, prednisolone 1 mg/kg/day in the presence of severe symptoms (5-fold increase in transaminases, pneumonia, hemophagocytosis, cardiac involvement, solid organ involvement, etc.), 0.5-2 g/kg/dose Intravenous Ig (IVIG) in case of life-threatening symptoms (hemophagocytosis, encephalitis, severe hepatitis, renal insufficiency, respiratory failure, etc.) and combination of steroid, antiviral agents and/or IVIG is recommended in the presence of severe symptoms with major viral reactivation (5,18). In our case, corticosteroid was given from 1 mg/kg/day due to solid organ involvement. The patient's fever, rash and organomegaly were dramatically regressed. Corticosteroids were reduced and discontinued within 1 week. The patient who showed clinical improvement was discharged with outpatient follow-up.

Conclusion

DRESS syndrome, which is a life-threatening reaction when its diagnosis is delayed, should be considered in the differential diagnosis in patients with prolonged fever, rash, lymphadenopathy, solid organ involvement and prior drug use.

Informed Consent: Both oral and written consent were obtained from the patient's parents for this case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.Ö.; Design - Ö.Ö., G.G.; Supervision - Ö.Ö.; Resources - Ö.Ö., G.G.; Materials - G.G.; Data Collection and/or Processing - G.G.; Analysis and/ or Interpretation - Ö.Ö.; Literature Search - G.G.; Writing Manuscript - Ö.Ö., G.G.; Critical Review - Ö.Ö.

Conflict of Interest: There is no conflict of interest with any institution or company.

Financial Support: The authors declared that they did not receive financial support for this study.

References

1. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L. The DRESS syndrome: A literature review. Am J Med 2011; 124: 588-97.
2. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome, Part I: Clinical perspectives. J Am Acad Dermatol 2013; 68: 693-705.
3. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? Br J Dermatol 2007; 156: 609-11.
4. Ucal-Bakkal S, Kocak-Tufan Z, Bulut C. A case of DRESS syndrome mimicking sepsis. Klimik Dergisi 2011; 24: 132-4.
5. Canitez Y, Poyraz Efe H, Sapan N. Carbamazepine-related DRESS syndrome; a rarely seen drug hypersensitivity reaction: Türkiye Çocuk Hast Derg 2015; 1: 147-51.
6. Oskay T, Karademir A, Ertürk OI. Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6, 7. Epilepsy Res. 2006; 70: 27-40.
7. Nanishi E, Hoshina T, Ohga S, Nishio H, Hara T. Drug reaction with eosinophilia and systemic symptoms during primary Epstein-Barr virus infection. J Microbiol Immunol Infect 2015; 48: 109-12.
8. Criado PR, Avancini J, Santi CG, Medrado AT, Rodrigues CE, de Carvalho JF. Drug reaction with eosinophilia and systemic symptoms (DRESS): A complex interaction of drugs, viruses and the immune system. Isr Med Assoc J 2012; 14: 577-82.
9. Yılmaz EA, Özmen S, Tuygun N. Lamotrijin ilişkili DRESS sendromu: bir vaka sunumu. Çocuk Dergisi 2009; 9: 142-6.
10. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol 2008; 22: 1044-9.
11. Peyriere H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2006; 155: 422-8.
12. Saha M, Gorai S, Madhab V. Oxcarbazepine-induced drug rash with eosinophilia and systemic symptoms syndrome presenting as exfoliative dermatitis. J Pharmacol Pharmacother 2016; 7: 142-5.
13. Knowles SR, Dewhurst N, Shear NH. Anticonvulsant hypersensitivity syndrome: An update. Expert Opin Drug Saf 2012; 11: 767-78.
14. Kundak S, Öner Eİ, Bağ İnce Ö. Sülfasalazin ile birlikte Amoksisilin kullanımına bağlı gelişen DRESS sendromu. Turkiye Klinikleri J Dermatol 2016; 26: 184-90.
15. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169(5):1071-80.

16. Girelli F, Bernardi S, Gardelli L, Bassi B, Parente G, Dubini A, et al. A new case of DRESS syndrome induced by Sulfasalazine and triggered by Amoxicillin. Case Rep Rheumatol 2013; 2013: 409152.

17. Karakayalı B, Yazar AS, Çakir D, Cetemen A, Kariminikoo M, Deliloglu B, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome associated with cefotaxime and clindamycin use in a 6 year-old boy: a case report. Pan Afr Med J 2017; 28: 218.

18. Descamps V, Ben-Saïd B, Sassolas B, Truchetet F, Avenel-Audran M, Girardin P, et al. Management of drug reaction with eosinophilia and systemic symptoms (DRESS). Ann Dermatol Venereol 2010; 137: 703-8.

19. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. J Am Acad Dermatol 2013; 68: 709.

20. Santiago F, Goncalo M, Vieira R, Coelho S, Figueiredo A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Derm 2010; 62: 47-53.

21. Elzagallaai AA, Knowles SR, Rieder MJ, Bend JR, Shear NH, Koren G. Patch testing for the diagnosis of anticonvulsant hypersensitivity syndrome: a systematic review. Drug Safety 2009; 32: 391-408.

22. Pinho A, Coutinho I, Gameiro A, Gouveia M, Gonçalo M. Patch testing - a valuable tool for investigating non-immediate cutaneous adverse drug reactions to antibiotics. J Eur Acad Dermatol Venereol 2017; 31: 280-7.

23. Shebe K, Ngwanya MR, Gantsho N, Lehloenya RJ. Severe recurrence of drug rash with eosinophilia and systemic symptoms syndrome secondary to rifampicin patch testing in a human immunodeficiency virus-infected man. Contact Dermatitis 2014; 70: 125-7.

24. Regnier S, Descamps V, Boui M, Lebrun-Vignes B, Descamps D, Grossin M, et al. (Parvovirus B19 infection mimicking drug-induced hypersensitivity syndrome). Ann Dermatol Venereol 2000; 127: 505-6.

25. Coughlin CC, Jen MV, Boos MD. Drug hypersensitivity syndrome with prolonged course complicated by Parvovirus infection. Pediatr Dermatol 2016; 33: 364-5.

İstanbul Med J 2019; 20(3): 261-3
DOI: 10.4274/imj.galenos.2018.81488

Human Metapneumovirus Infection in a Patient with Recurrent Wheezing: Case Report

Tekrarlayan Hışıltılı Hastada İnsan Metapnömovirüs Enfeksiyonu: Olgu Sunumu

Öner Özdemir[1], Onur Bircan[2]

[1]Sakarya University Training and Research Hospital, Clinic of Allergy and Immunology, Adapazarı, Turkey
[2]Sakarya University Faculty of Medicine, Department of Pediatrics, Adapazarı, Turkey

ABSTRACT

Lower respiratory tract infections are responsible for 28% of preventable and treatable childhood deaths under 2 years of age in the world. In recent years, due to advances on the factors of respiratory tract infections, new agents such as human metapneumovirus (hMPV), coronaviruses, human bocavirus, parvovirus type 4 and type 5, and polyomavirus have been identified in addition to classical respiratory tract viruses. hMPV was first identified in the Netherlands in 2001. hMPV can lead to clinical manifestations ranging from mild upper respiratory tract infection, bronchiolitis and asthma attack, severe pneumonia to acute respiratory distress syndrome. In this article, a 23-month-old patient, who was followed-up with recurrent wheezing, respiratory distress, hypoxemia and in whom hMPV was identified as an etiologic agent, was presented for the purpose of drawing attention to the recent identification of the agent and its rare occurrence in the clinical practice.

Keywords: Bronchiolitis, human metapneumovirus, pneumonia, wheezing

ÖZ

Dünyada 2 yaş altı önlenebilir ve tedavi edilebilir çocuk ölümlerinin %28'inden alt solunum yolu enfeksiyonları sorumludur. Son yıllarda solunum yolu enfeksiyonlarının etmenlerine yönelik yapılan çalışmalardaki gelişmelere bağlı olarak klasik solunum yolu virüslerinin yanında insan metapnömovirüs (iMPV), koronavirüsler, insan bocavirüs, parvovirüs tip 4 ve tip 5 ve poliyomavirüs gibi yeni etmenler de tespit edilmiştir. iMPV ilk kez 2001 yılında Hollanda'da tespit edilmiştir. iMPV hafif üst solunum yolu enfeksiyonundan, bronşiolit ve astım atağına, ciddi pnömoniden akut respiratuvar distress sendromuna kadar varan klinik tablolara yol açabilir. Bu makalede tekrarlayan hışıltı atağı, solunum sıkıntısı ve oksijen ihtiyacı nedeniyle takip edilen ve etken olarak iMPV saptanan 23 aylık hasta, etkenin son yıllarda yeni tanımlanması ve klinikte nadir görülüp tespit edilmesine dikkat çekmek amacıyla sunulmuştur.

Anahtar Kelimeler: Bronşiolit, insan metapnömovirüs, pnömoni, hışıltı

Introduction

Lower respiratory tract infections (LRTIs) are responsible for 28% of preventable and treatable child deaths under 2 years in the world (1). The most common causes of LTRIs below 2 years are viruses (2). Recent advances in respiratory tract infections have led to isolation of new agents such as human metapneumovirus (hMPV), coronaviruses, human bocavirus, parvovirus type 4 and type 5, and polyomavirus in addition to classical respiratory tract viruses such as influenza, parainfluenza, adenovirus and respiratory syncytial virus (RSV) (3). HMPV was first isolated from the airways in the Netherlands in 2001 as a new paramyxovirus (4). HMPV causes LRTIs such as bronchiolitis and pneumonia besides upper respiratory tract infection.

In this article, a 23-month-old patient, who was followed-up with recurrent wheezing, respiratory distress, hypoxemia and in whom hMPV was identified as the etiologic agent, was presented for the purpose of drawing attention to the recent identification of the agent and its rare occurrence in the clinical practice.

Case Report

A 23-month-old boy was admitted to the hospital due to respiratory distress. He had a history of recurrent wheezing for a year and severe wheezing episodes, and he was hospitalized 3 times. He was on nebulized salbutamol, budesonide and montelukast therapy. The patient's respiratory distress had persisted for the last two weeks despite treatment. His vital signs were as follows: body temperature: 36.7 ºC,

Address for Correspondence/Yazışma Adresi: Öner Özdemir MD, Sakarya University Training and Research Hospital, Clinic of Allergy and Immunology, Adapazarı, Turkey
Phone: +90 264 444 54 00 **E-mail:** oner.ozdemir.md@gmail.com **ORCID ID:** orcid.org/0000-0002-5338-9561

Cite this article as/Atıf: Özdemir Ö, Bircan O. Human Metapneumovirus Infection in a Patient with Recurrent Wheezing: Case Report. İstanbul Med J 2019; 20(3): 261-3.

Received/Geliş Tarihi: 17.07.2018
Accepted/Kabul Tarihi: 07.11.2018

respiratory rate: 50/minute (min), oxygen saturation (sPO_2): 96%, and pulse: 136/min. Physical examination revealed diffuse rhonchi in both lungs, and basal crepitant crackles. Laboratory results were as follows: white blood cells: 19.000/mm^3 (range: 4.000-10.200/mm^3), neutrophil count: 9.760/mm^3, Hemoglobin: 13.1g/dL (range: 12-18 g/dL), platelet count: 405.000/mm^3 (range: 142.000-424.000/mm^3), C-reaktif protein (CRP): 54.4 mg/dL (range: 0-5 mg/dL), sedimentation: 16/hr. (normal: <20). There was left perihilar fullness in the chest X-ray (Figure 1). The patient was started on salbutamol and ipratropium bromide treatment due to respiratory distress, and cefuroxime axetil treatment with a pre-diagnosis of bronchopneumonia with suspected bacterial agent. After the third day of treatment, systemic steroid (1 mg/kg/day) was initiated due to ongoing rhonchi. In order to investigate the etiology of recurrent wheezing episodes, immunoglobulin (Ig) G, A, M, E, IgG subgroups, specific antibody responses to past infections (anti-CMV IgG, anti-Rubella IgG and anti-HBs), CD3 in flow cytometric evaluation (T-cell), CD4, CD8, CD19 (B-cell), CD16 and CD56 (NK-cell) lymphocyte subgroups, isohemagglutinin (anti-A and anti-B) tests were performed and results were evaluated as normal. Purified protein derivative test (2 times) was negative. The sweat test was in normal range with 5.6 (range: 0-60) mmol/L. On the 10th day of the follow-up, his antibiotic treatment was discontinued and the dose of nebulized salbutamol and ipratropium bromide was reduced. On the 11th day of admission, his clinical condition improved and he complained of recurrent fever and vomiting while trying to cease the bronchodilator treatment. Urine and stool examination (adenovirus, rotavirus and microscopic examination) were evaluated as normal. At follow-up, complaints of 39 ºC fever, wheezing and respiratory distress, tachypnea and hypoxemia occurred, and the sPO_2 of the patient decreased to 88%. Supportive oxygen therapy was initiated. Blood cultures were obtained and a respiratory viral panel examination with polymerase chain reaction (PCR) was performed from the nasopharynx swab (Rotor-Gene Q platform,Qiagen, Germany). A total of 20 viruses were screened from 10 virus groups (influenza, rhinovirus, coronavirus, parainfluenza, hMPV A/B, bocavirus, RSV, adenovirus, enterovirus, and parechovirus). Despite negative blood cultures, hMPV was isolated from nasopharyngeal swab using PCR method. The patient was diagnosed as having hMPV-induced LRTI (bronchiolitis attack) and was discharged following observed improvement in hypoxemia and chest X-ray with conservative treatment (Figure 2). Oral patient consent was obtained from the family.

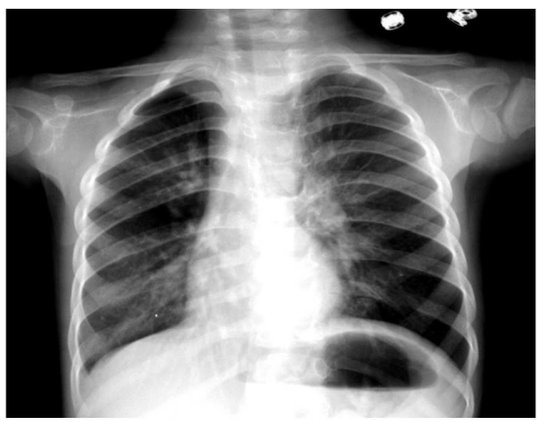


Figure 1. Left perihilar fullness, infiltrative appearance in the right lower and middle zones suggesting pneumonia and bilateral significant hyperaeration are noteworthy

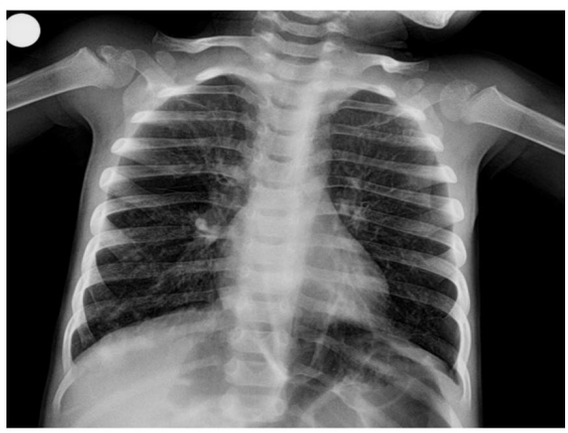


Figure 2. Prominent bronchovascular structures

Discussion

HMPV is an RNA virus from the paramyxovirus family. People are the only source of infection for the virus. The disease is transmitted through the respiratory tract secretions of infected persons by droplets or direct contact (5). Personal hygiene and contact precautions are the main preventive methods for the prevention of virus transmission (6). Its frequency increases in winter and spring months. The most frequent months are March and April (7). The incidence is higher in boys than in girls. Unlike the RSV, it is more common in children between 6-21 months. Prodrome period lasts for 5-6 days and the clinical symptoms occur after (8). The typical course is the LRTI findings starting after a short asymptomatic period following the symptoms of the upper respiratory tract that lasts for two days. In many patients, wheezing lasts for several days, however, as in our patient, it may lead to LRTI (bronchiolitis) after an asymptomatic period, and may cause recurrent wheezing, and wheezing attacks and cough may continue for weeks in individuals with similar diseases (9,10).

The most common clinical findings are cough, runny nose, fever, restlessness, anorexia, wheezing and rarely nausea, vomiting and diarrhea. Auscultation findings include wheezing (52%), and less frequently rhonchi (20%) and crackles (8%) (11). Radiographically, chest X-ray can show consolidation, perihilar infiltration, atelectasis and hyperinflation (12). Lymphopenia, transaminase elevation and CRP elevation can be detected in the laboratory tests (13). HMPV can lead to clinical manifestations ranging from mild upper respiratory tract infection, bronchiolitis and asthma attack, severe pneumonia to acute respiratory distress syndrome (9). The most common reason for hospitalization in hMPV infection is bronchiolitis and pneumonia (14).

In a study by Williams et al. (11), 59% of the patients hospitalized for LRTI and diagnosed as having hMPV were evaluated as bronchiolitis, 8% as pneumonia, 18% as croup and 14% as asthma attack. Xepapadaki et al. (14) found hMPV in 16% of the patients hospitalized for bronchiolitis. In our patient, the clinical findings started as recurrent wheezing, followed

by nasal discharge, subfebrile fever, nausea, vomiting and diarrhea, followed by a fever of 39 ºC, respiratory distress and recurrent wheezing. There were no significant laboratory findings in our patient's blood tests except increased CRP (54.4 mg/dL). There was a perihilar infiltration in the chest X-ray.

Although the gold standard method is cell culture, the PCR test is widely used in diagnosis. It is not clinically useful since reproduction in viral cell culture can last 10-14 days (12). There was no growth in blood, urine and throat cultures of our patient. The hMPV was found to be positive by real-time PCR method in screening with viral respiratory panel.

There is no antiviral drug or vaccine approved for the treatment and prophylaxis of hMPV infection. Oxygen support therapy, and intravenous fluid therapy in patients with reduced oral intake, vomiting and diarrhea are supportive treatments. Bronchodilator and steroid therapy may be used in cases of asthma exacerbation. Antibiotic therapy may be necessary in cases of bacterial superinfection. There are studies suggesting that ribavirin and intravenous Ig treatment inhibit hMPV infection *in vitro*. There are case reports of ribavirin and intravenous Ig treatment used in the treatment of immunosuppressive patients (12,15). The patient was given antibiotherapy due to the initial diagnosis of bacterial pneumonia, and conservative treatment was continued despite clinical deterioration after the diagnosis of hMPV-induced LRTI (bronchiolitis). The patient was discharged with healing after intravenous hydration, mask oxygen therapy and nebulized salbutamol.

Our patient was probably infected with hMPV infection while he was inpatient for correction of respiratory distress due to recurrent wheezing, but he was undergoing the prodrome period of the disease. In the first week of hospitalization for wheezing, the infection presented with upper respiratory tract symptoms in the asymptomatic period and became symptomatic with subsequent LRTI findings. In our patient, it is important to detect recurrent wheezing attack and to reveal the clinical picture that is caused by hMPV. Again, according to the literature, it is significant to show that the supportive treatment will be sufficient and the clinic is improved in the patient.

Conclusion

In cases of recurrent wheezing and asthma bronchitis exacerbations, hMPV infection should be considered and the clinical picture that it may cause should be known by other physicians, such as allergy and chest diseases specialists, dealing with respiratory diseases.

Informed Consent: Oral patient consent was obtained from the family.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.Ö.; Design - Ö.Ö.; Supervision - Ö.Ö.; Resources - O.B.; Materials - O.B.; Data Collection and/or Processing - Ö.Ö., O.B.; Analysis and/ or Interpretation - Ö.Ö.; Literature Search - O.B.; Writing Manuscript - Ö.Ö., O.B.; Critical Review - Ö.Ö.

Conflict of Interest: There is no conflict of interest with any institution or company.

Financial Support: The authors declared that they did not receive financial support for this study.

References

1. WHO: Integrated management of childhood ilness. http://www. who.int/child-adolescent-health 2003.
2. Özdoğan Ş. Çocuklarda toplum kökenli pnömoniye yaklaşım: Amerikan Çocuk Enfeksiyon Derneği Rehberi. Ş.E.E.A.H Tıp Bülteni 2015; 49: 163-73.
3. Akçalı S, Yılmaz N, Güler Ö, Şanildağ T, Anıl M. Alt solunum yolu enfeksiyonu olan çocuklarda solunum yolu viral etkenlerinin sıklığı. Turk Pediatri Ars 2013; 48: 215-20.
4. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered Human Pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001; 7: 719-24.
5. Peiris JS, Tang WH, Chan KH, Khong PL, Guan Y, Lau YL, et al. Children with respiratory disease associated with Metapneumovirus in Hong Kong. Emerg Infect Dis 2003; 9: 628-33.
6. TangYi- Wei, Crowe JE, Uyar Y. Respiratory Syncytical Virus and Human Metapneumovirus. In: Murray PR, Baron EJ, Pfaller MA, Jorgensen JH, Yolken RH, editors. 9.baskı. Ankara: Atlas Kitapçılık; 2009. 1361-77.
7. Parlakay AÖ, Kara A. Yeni solunum yolu virüsleri. Çocuk Sağlığı ve Hastalıkları Dergisi 2010; 53: 59-65.
8. Broor S, Bharaj P, Chahar HS. Human Metapneumovirus: a new respiratory pathogen. J Biosci 2008; 33: 483-93.
9. Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, et al. Human Metapneumovirus infections in hospitalized children. Emerg Infect Dis 2003; 9: 634-40.
10. Falsey AR, Erdman D, Anderson LJ, Walsh EE. Human Metapneumovirus infections in young and elderly adults. J Infect Dis 2003; 187: 785-90.
11. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, et al. Human Metapneumovirus and lower respiratory tract disease in otherwise healty infants and children. N Engl J Med 2004; 350: 443-50.
12. Schuster JE, Williams JV. Human Metapneumovirus. Pediatr Rev 2013; 34: 558-65.
13. Alto WA. Human Metapneumovirus: a newly described respiratory tract pathogen. J Am Board Fam Pract 2004; 17: 466-9.
14. Xepapadaki P, Psarras S, Bossios A, Tsolia M, Gourgiotis D, Liapi-Adamidou G, et al. Human Metapneumovirus as a causative agent of acute bronchiolitis in infants. J Clin Virol 2004; 30: 267-70.
15. Wyde PR, Chetty SN, Jewell AM, Boivin G, Piedra PA. Comparison of the inhibition of Human Metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 2003; 60: 51-9.

İstanbul Med J 2019; 20(3): 264–6
DOI: 10.4274/imj.galenos.2018.16769

Diplopia Due to Orbital Myositis: Diagnosis with Magnetic Resonance Imaging

Orbital Myozite Bağlı Çift Görme: Manyetik Rezonans Görüntüleme ile Birlikte Tanısı

Aslı Tanrıvermiş Sayıt[1], Muzaffer Elmalı[1], İnci Güngör[2]

[1]Ondokuz Mayıs University Faculty of Medicine, Department of Radiology, Samsun, Turkey
[2]Ondokuz Mayıs University Faculty of Medicine, Department of Ophthalmology, Samsun, Turkey

ABSTRACT

Orbital myositis is a non-specific inflammatory disease primarily affecting the extraocular muscles. It is most commonly seen in young adults and women and is often unilateral. Periorbital pain, swelling and redness of the eyelid, limitation of eye movements, and diplopia can be seen in patients with this condition. It may be idiopathic or may develop due to secondary diseases such as systemic or infectious causes. Radiological imaging methods such as computed tomography and magnetic resonance imaging are very useful in its differential diagnosis. The response to oral corticosteroid treatment is very good. In this study, we report the clinical and radiological features of a 13-year-old girl diagnosed with orbital myositis, who experienced a complete recovery with steroid treatment.

Keywords: Lateral rectus muscle, magnetic resonance imaging, myositis, steroid

ÖZ

Orbital miyozit, özellikle ekstraoküler kasları etkileyen, spesifik olmayan enflamatuvar bir hastalıktır. Genellikle genç erişkinlerde ve kadınlarda görülür ve çoğunlukla tek taraflıdır. Hastalarda periorbital ağrı, göz kapağının şişmesi ve kızarıklığı, göz hareketlerinde kısıtlılık ve diplopi görülebilir. İdiyopatik olabilir veya sistemik veya enfeksiyöz nedenler gibi sekonder hastalıklara bağlı meydana gelebilir. Bilgisayarlı tomografi ve manyetik rezonans görüntüleme gibi radyolojik görüntüleme yöntemleri ayırıcı tanıda çok yararlıdır. Oral kortikosteroid tedavisine verilen cevap çok iyidir. Biz burada steroid ile tedavi edilen orbital miyozit tanılı 13 yaşında kız çocuğunun klinik ve radyolojik özelliklerini ilgili literature eşliğinde sunmayı amaçladık.

Anahtar Kelimeler: Lateral rektus kası, manyetik rezonans görüntüleme, miyozit, steroid

Introduction

Orbital myositis is an orbital inflammation characterized by an acute onset, unilateral periorbital pain, and diplopia, often involving one or more of the extraocular muscles. Swelling of the eyelid and conjunctival injection are also usually present (1). Orbital myositis can be idiopathic or secondary to any systemic and localized inflammatory disorder. Viral upper respiratory tract infections and inflammatory intestinal diseases can also cause orbital myositis. The condition is very rare in the pediatric age group, especially among infants (2). Diagnosis can usually be made clinically based on the characteristics of pain and signs of inflammation. Imaging methods, particularly magnetic resonance imaging (MRI), are useful for differential diagnoses. The presence of a thickening of the affected muscle, uptake of contrast medium, and high signal intensity on T2-weighted images (WIs) suggests orbital myositis (3). Inflammation is usually unilateral and response to steroid treatment is very good (1). In this article, we report on the case of a 13-year-old girl who was diagnosed with idiopathic orbital myositis through MRI findings after being admitted to the hospital with double vision.

Case Report

A 13-year-old girl was admitted to the hospital with acute onset of diplopia on gazing to the right, with an accompanying headache. She had no previous trauma or symptoms suggesting increased intracranial pathology. She had recently been diagnosed with a viral upper respiratory tract infection. Upon the physical examination, her visual acuity was revealed to be normal in both eyes. In addition, bilateral anterior segment, intraocular pressure, and fundus were normal. The eyes were orthophoric in the primary position, but there was a -1 degree

Address for Correspondence/Yazışma Adresi: Aslı Tanrıvermiş Sayıt MD, Ondokuz Mayıs University Faculty of Medicine, Department of Radiology, Samsun, Turkey
Phone: +90 532 494 90 82 **E-mail:** draslitanrivermissayit@gmail.com **ORCID ID:** orcid.org/0000-0003-2861-156X

Cite this article as/Atıf: Tanrıvermiş Sayıt A, Elmalı M, Güngör İ. Diplopia Due to Orbital Myositis: Diagnosis with Magnetic Resonance Imaging. İstanbul Med J 2019; 20(3): 264-6.

Received/Geliş Tarihi: 27.10.2017
Accepted/Kabul Tarihi: 08.11.2018

restriction to the lateral side in the right eye. Complete blood count, thyroid hormones, and antithyroid antibodies were within normal limits. A contrast enhanced orbital and brain MRI was performed for the differential diagnosis of diplopia. The brain MRI was normal. Also, high signal intensity and thickening in the right lateral rectus muscle and tendon were seen on the T2-WI of orbital MRI (Figure 1). An intensive contrast enhancement was observed in the right lateral rectus muscle and tendon on contrast enhanced T1-WIs (Figure 2a, b).

Based on the clinical, laboratory, and MRI findings, the patient was diagnosed with orbital myositis. We initiated the treatment with oral 64 mg/kg prednisolone per day and continued for one week. Then, the dosage of the drug was gradually reduced. Her pain and gaze paresis disappeared completely after treatment. High T2 signal intensity, thickening, and pathologic contrast enhancement in the right lateral rectus muscle and tendon disappeared from the orbital MRI after the treatment (Figures 3a, b). There was no recurrence after six months.

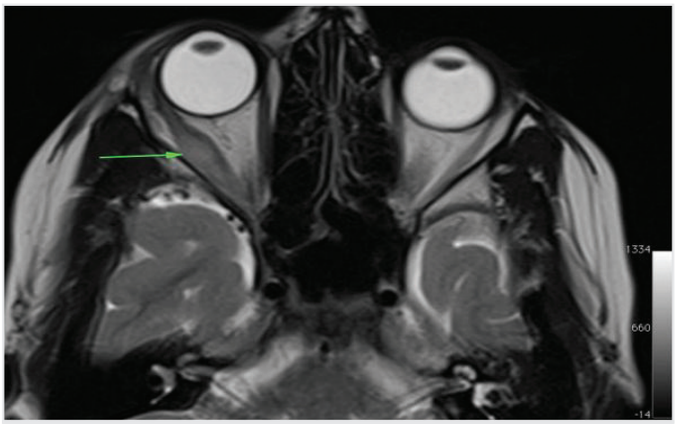
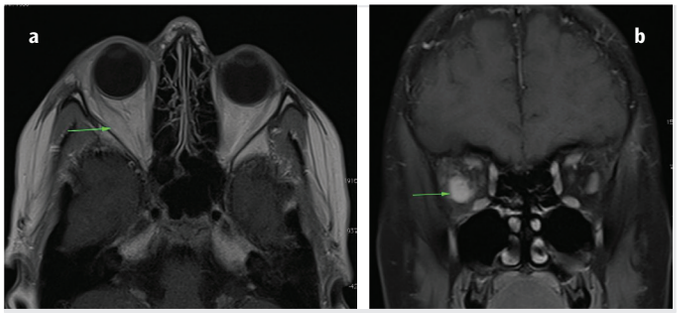
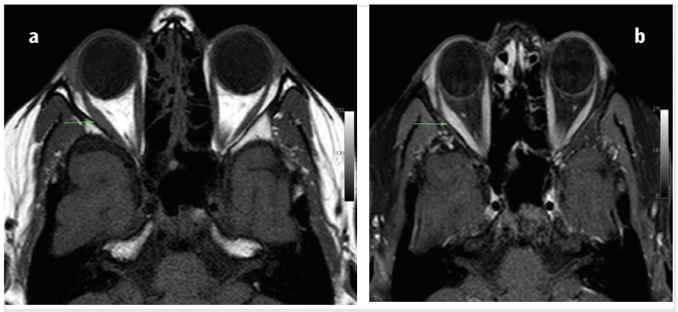


Figure 1. Axial T2-weighted image shows thickening and high signal intensity in the right lateral rectus muscle (arrow)



Figures 2a, b. Contrast-enhanced axial a) and coronal fat-suppressed b) T1-weighted images show mild-to-significant contrast enhancement of the enlarged right lateral rectus muscle (arrow)



Figures 3a, b. Axial T2-weighted image (WI) a) shows no abnormal signal intensity in the right lateral rectus muscle. b) Also, there was no abnormal contrast enhancement in the right lateral rectus muscle on contrast-enhanced axial fat-suppressed T1-WI

Verbal informed consent was obtained from the patient who participated in this case study.

Discussion

The most common diseases of the orbits are thyroid orbitopathy, lymphoproliferative diseases, and orbital myositis (2). Orbital myositis is an inflammatory disease of the extraocular muscles that is most commonly seen in young and middle-aged people. The characteristic clinical triad include periorbital pain, diplopia, and signs of inflammation, such as conjunctival injections or swelling. Concurrent pain is present in >95% of all cases (1). The most common presentation is that of unilateral single muscle involvement though multiple or bilateral involvement can also be seen (4). Superior, lateral, and medial rectus muscles are equally involved frequently, and recurrence occurs in 56% of cases (5,6).

Although the etiology of the condition is not completely known, infectious and autoimmune-related factors are thought to play a role. Cases of autoimmune-related orbital myositis are associated with diseases including giant cell myocarditis, Crohn disease, systemic lupus erythematosus, rheumatoid arthritis, and linear scleroderma. Also, spirochetotic (Lyme disease) (7), viral (herpes zoster virus) (8), and bacterial infections (group A streptococcal pharyngitis) (9) can cause orbital myositis.

A diagnosis of orbital myositis is usually made via physical examination. Laboratory tests, such as complete blood count, hepatic and renal function tests, erythrocyte sedimentation rate, C-reactive protein levels, thyroid function tests, and various antibodies, can also be performed (2). The differential diagnosis of orbital myositis includes the following: infections (viral infections, orbital cellulitis, orbital abscess), inflammatory reaction (trauma, foreign body, bisphosphonate-related reaction, and postvaccinal reaction), Tolosa-Hunt syndrome, thyroid ophthalmopathy, vasculitis, systemic lupus erythematosus, sarcoidosis, inflammatory bowel disease, neoplasm, arteriovenous fistulas, and malformations (2). Orbital myositis should be distinguished primarily from thyroid orbitopathy. Thyroid function tests and thyroid ultrasonography can be performed for the differential diagnosis. Moreover, imaging methods such as computed tomography (CT) and MRI are also very useful. Thyroid orbitopathies are usually bilateral (85%) and rarely unilateral (10-30%) (10). CT and MRI reveal enlarged muscle bellies and thickened tendons in orbital myositis. By contrast, thyroid orbitopathy only involves the extraocular muscles and not their tendons (4). Furthermore, normal thyroid function tests and negative antithyroid antibodies exclude thyroid orbitopathy.

Spontaneous remission may occur without treatment in orbital myositis. Also, the response to systemic steroid treatment is very good (1). Steroid therapy reduces the risk of muscle fibrosis and recurrence, however, relapse or recurrent inflammation may occur despite the treatment with steroids (11). Multiple muscle involvement, male gender, eyelid retraction, and lack of response to systemic corticosteroids are

associated with recurrent orbital myositis (12). Low-dose external beam radiation therapy or immunosuppressive agents may be used in cases with multiple recurrences and steroid-resistance (4). Our case responded well to steroid treatment and the lateral rectus muscle was completely normal in the control MRI performed after two months.

Conclusion

Orbital myositis is an inflammatory disease of the extraocular muscles that is most commonly seen in young and middle-aged people. Orbital myositis should be differentiated from infections, inflammatory reactions, Tolosa-Hunt syndrome, thyroid orbitopathies, vasculitis, and neoplasms. The response to systemic steroid treatment is very good. In addition, steroid therapy reduces the risk of muscle fibrosis and recurrence.

Informed Consent: Verbal informed consent was obtained from the patient who participated in this case study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.T.S., M.E., İ.G.; Design - A.T.S., M.E., İ.G.; Supervision - A.T.S., M.E., İ.G.; Resources - A.T.S., İ.G.; Materials - A.T.S., M.E.; Data Collection and/or Processing - A.T.S., İ.G.; Analysis and/ or Interpretation - A.T.S., İ.G.; Literature Search - A.T.S.; Writing Manuscript - A.T.S., İ.G.; Critical Review - A.T.S., M.E., İ.G.

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

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

References

1. Fischer M, Kempkes U, Haage P, Isenmann S. Recurrent orbital myositis mimicking sixth nerve palsy: diagnosis with MR imaging. AJNR Am J Neuroradiol 2010; 31: 275-6.
2. Önder O, Bilgin RR, Köşkderelioğlu A, Gedizlioğlu M. Orbital myositis: evaluating five new cases regarding clinical and radiological features. Noro Psikiyatr Ars 2016; 53: 173-7.
3. Yan J, Wu P. Idiopathic orbital myositis. J Craniofac Surg 2014; 25: 884-7.
4. Court JH, Janicek D. Acute unilateral isolated ptosis. BMJ Case Rep 2015: 2015.
5. Dubey A, Eidsness R, Koul R. Idiopathic orbital myositis and review of literature. The Internet Journal of Ophthalmology and Visual Science 2009; 8: 1-5.
6. Mombaerts I, Koornneef L. Current status in the treatment of orbital myositis. Ophthalmology 1997; 104: 402-8.
7. Seidenberg KB, Leib ML. Orbital myositis with Lyme disease. Am J Ophthalmol 1990; 109: 13-6.
8. Kawasaki A, Borruat FX. An unusual presentation of Herpes zoster ophthalmicus: orbital myositis preceding vesicular eruption. Am J Ophthalmol 2003; 136: 574-5.
9. Alshaikh M, Kakakios AM, Kemp AS. Orbital myositis following streptococcal pharyngitis. J Paediatr Child Health 2008; 44: 233-4.
10. Chakor RT, Santhosh NS. Painless orbital myositis. Ann Indian Acad Neurol 2012; 15: 224-6.
11. Jacobs D, Galetta S. Diagnosis and management of orbital pseudotumour. Curr Opin Ophthalmol 2002; 13: 347-51.
12. Mannor G, Rose GE, Moseley IF, Wright JE. Outcome of orbital myositis: clinical features associated with recurrence. Ophthalmology 1997; 104: 409-14.

İstanbul Med J 2019; 20(3): 267-9
DOI: 10.4274/imj.galenos.2018.82956

Pneumomediastinum due to Penetrating Neck Injury: A Case Report

Penetran Boyun Yaralanmasına Bağlı Pnömomediastin: Bir Olgu Sunumu

Kasım Turgut[1], Abdullah Algın[2], Hasan Öğünç Apaydın[3]

[1]Adıyaman University Training and Research Hospital, Clinic of Emergency Medicine, Adıyaman, Turkey
[2]Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[3]Adıyaman University Training and Research Hospital, Clinic of Pediatric Surgery, Adıyaman, Turkey

ABSTRACT

Penetrating neck injuries are rarely encountered, but have a highly mortal course because of the presence of many vital organs in this small region. We reported a tracheal rupture and pneumomediastinum case which occurred due to the penetration of a sharp piece of wood to the neck. The hemodynamically stable patient was evaluated by radiologic and endoscopic procedures and the pneumomediastinum and tracheal defect were found. The tracheal defect was left to heal spontaneously, the laceration was repaired cutaneously and the antibiotherapy was started. The patient recovered and was discharged from the clinic after 10-day follow-up. The unstable patients with active hemorrhages must undergo surgical exploration without any delays, but interventions must be initially avoided in stable patients as in our case. The wide spectrum antibiotics should be started in traumatic pneumomediastinum cases to prevent the development of mediastinitis.

Keywords: Neck injury, pneumomediastinum, tracheal rupture

ÖZ

Penetran boyun yaralanmaları nadir görülür. Ancak bu küçük bölgede birçok hayati organın varlığı nedeniyle oldukça mortal seyretmektedir. Hemodinamik olarak stabil bir hastanın boyununa keskin bir odun parçasının girmesi sonucu radyolojik ve endoskopik ileri görüntüleme yöntemleriyle tespit edilen trakeal rüptür ve pnömomediastinum olgusu raporlamaktayız. Trakeal defekt sekonder iyileşmeye bırakıldı. Lazerle deri alanı onarıldı ve antibiyoterapi başlanan hasta şifa ile taburcu edildi. Unstabil kanayan hastalarda cerrahi eksplorasyon temeldir. Ancak olgumuzda olduğu gibi stabil hastalarda girişimler ilk planda düşünülmemelidir. Mediastinit komplikasyonunu engellemek için geniş spektrumlu antibiyotik başlanmalıdır.

Anahtar Kelimeler: Boyun yaralanması, pnömomediastinum, trakeal delinme

Introduction

Penetrating trauma to the head-neck commonly occurs secondary to stab and gunshot wounds and accounts for 5-10% of all trauma cases that are admitted to the emergency departments (ED) (1). The mortality rate reaches 10% in penetrating neck injuries, which are especially accompanied by massive hemorrhages due to vascular damage (2). Tracheal injury may occur if a wound track crosses the trachea. Pneumomediastinum, subcutaneous emphysema, and paratracheal air can be found in tracheal injury cases (1). The accumulation of air in the mediastinum, spontaneously or post traumatic, is known as pneumomediastinum. Increased alveolar pressure or weak lung parenchyma may result in alveolar rupture and the emerged air moves and accumulates in the mediastinum. This process is the main mechanism of pneumomedistinum and is called as the "Macklin effect". In addition to this, pneumomediastinum rarely occurs due to post traumatic leakage of air from air containing mediastinal organs, such as trachea, esophagus, and larynx (3).

In this paper, it was aimed to present a pneumomediastinum case resulting from tracheal rupture that occurred after falling on a sharp piece of wood in a construction area.

Case Report

A 8-year-old boy patient was admitted to the emergency service with penetrating neck injury that occurred due to falling on a sharp piece of wood while he was running around a construction zone. He had chest pain and dyspnea at admission. The physical examination of

Address for Correspondence/Yazışma Adresi: Abdullah Algın MD, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
Phone: +90 216 216 10 15 **E-mail:** dralgin@hotmail.com **ORCID ID:** orcid.org/0000-0002-9016-9701

Cite this article as/Atıf: Turgut K, Algın A, Apaydın HÖ. Pneumomediastinum due to Penetrating Neck Injury: A Case Report. İstanbul Med J 2019; 20(3): 267-9.

Received/Geliş Tarihi: 09.10.2018
Accepted/Kabul Tarihi: 08.11.2018

the patient revealed a 3 cm laceration on the anterior of neck, below the thyroid gland, and air passage was also detected on that hole (Figure 1). Additionally, swelling and crepitation were found on the chest, neck and face up to the right eye. His initial vital signs were as follows: temperature: 37.2 °C, heart rate: 85 beats per minute, blood pressure: 105/60 mmHg, respiratory rate: 24 breaths per minute, and O_2 saturation: 96%.

In the emergency room, the patient was firstly monitored for hemodynamics, started oxygen via mask, and applied dressing on the laceration. Then, two large-bore vascular lines were opened, blood samples were taken, and saline infusion was started. No active bleeding was observed and the patient was hemodynamically stable. Computed tomography (CT) of the neck and thorax, which confirmed tracheal rupture, pneumomediastinum and subcutaneous emphysema, was performed (Figures 2,3). Also, the pediatric surgeon and ear nose throat (ENT) physician examined the patient. The nasolaryngoscopy, which was performed by ENT doctor, showed the tracheal defect, too. The first dose of antibiotics (Cefazolin and Ornidazole) was administered in ED because of the high risk of mediastinitis. The first laboratory analyses revealed the following results: 15.4 103/mL leucocytes, 11.3 g/dL hemoglobin, and 34.1% hematocrit.

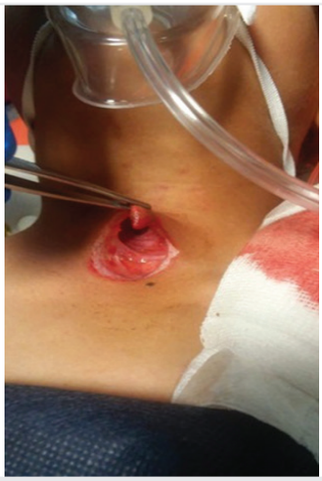


Figure 1. The 3 cm laceration and air-hissing hole on the anterior of neck

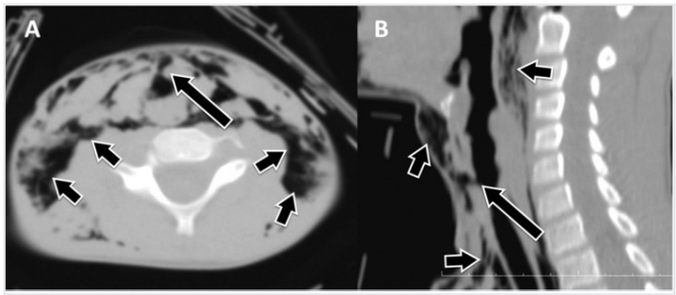


Figure 2. Axial (A) and sagittal (B) series of neck computed tomography. The tracheal defect (long arrow) and subcutaneous emphysema (short arrows) are seen

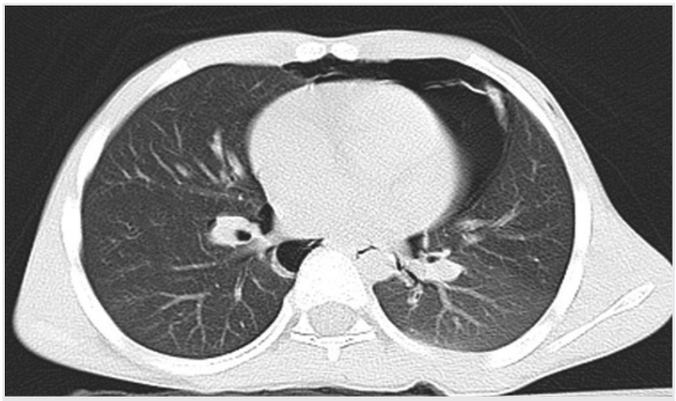


Figure 3. Pneumomediastinum image on axial series of thoracic computed tomography

In the intensive care unit, the oral feeding was stopped due to the suspicion of esophageal injury and the antibiotherapy (vancomycin and meropenem) and humidified oxygen were continued. On the second day, the ENT physician performed laryngoscopy under general anesthesia and determined a minor defect on the anterior of trachea. The cutaneous laceration was sutured and no intervention was done on the tracheal tear, by leaving for spontaneous healing. Pediatric surgeon performed esophagoscopy at the same session and no esophageal damage was confirmed. On the third day, the patient was still stable and had no new complaints, so oral feeding with liquids was started and he was taken into the pediatric surgery clinic. He was followed up in the clinic by performing routine chest graphics and wound care for ten days until being discharged. At the 3-month follow-up, the patient had no sequelae from his injury and the last chest radiography confirmed no pneumomediastinum. Written informed consent from the patient and approval from the hospital were obtained for presenting this case report.

Discussion

Pneumomediastinum, which has a high mortality rate unless diagnosed on time, was described firstly by Laënnec in a chest trauma patient. Trauma is responsible for 80% of all pneumomediastinum cases and penetrating trauma is seen more rarely than blunt traumas. Generally, it occurs by the moving of air in the lungs to the mediastinum, but in penetrating traumas, air may come outside of the body or from the trachea in the case of tracheobronchial injuries (3). The main complaints of pneumomediastinum patients include chest pain, dyspnea, hoarseness, and foreign body sensation in the throat. Additionally, subcutaneous emphysema on the chest, neck and face may be seen by movement of free air (4). Tracheobronchial injuries rarely occur in traumas to the neck and chest. In such cases, pneumomediastinum, soft tissues injury signs (swelling and ecchymosis), and subcutaneous emphysema may be seen. (5) Fortunately, the incidence of tracheobronchial injuries in children are much lower than in adults due to the shorter neck, larger mandible, and greater pliability of cartilages (6). In our report, the child fell down on a sharp piece of wood while he was running in a construction zone that had no security cordon and had a penetrating injury on the anterior of his neck. There was a 3 cm laceration with air hissing on the injury site and the patient suffered from chest pain and dyspnea.

The diagnostic tests for penetrating neck injuries include radiographics, endoscopic studies, ultrasound (US), CT, and magnetic resonance imaging (MRI). The common roentgen is the first diagnostic tool in

patients with chest pain and dyspnea, but it has a high false negativity rate in pneumomediastinum cases. The US is not the ideal diagnostic technique because of the subcutaneous air that prevents the evaluation of vital structures. The MRI requires a lot of time to perform and the metallic foreign bodies on injury site can preclude the patient from entering the MRI suite. On the other hand, the CT is the ideal diagnostic modality to confirm pneumomediastinum, tracheal injury, paratracheal air, and subcutaneous emphysema. If the patient has no need for urgent surgery, the gold standard diagnostic tool is the CT angiography. Nasolaryngoscopy, bronchoscopy and esophagoscopy can be used to evaluate the aerodigestive organs. The patient should immediately undergo surgical exploration without performing any diagnostic modality if the patient is hemodynamically unstable with active bleeding or any air leakage (1,3). In this report, our patient was stable and had no active bleeding, so CT of the neck and thorax was performed. Tracheal injury, pneumomediastinum, and subcutaneous emphysema were found on CT. The ENT physician performed also nasolaryngoscopy and confirmed the tracheal tear on the anterior wall.

Penetrating neck injuries should undergo surgical exploration without losing time if the patient is hemodynamically unstable with expanding hematoma, frothing/hissing of air, subcutaneous emphysema, hoarseness, and dysphonia signs. However, several diagnostic procedures such as CT, US and endoscopies can be used to avoid unnecessary surgery in stable patients (7). Conservative management consisting of observation, humidified oxygen and antibiotherapy is adequate in hemodynamically stable pneumomediastinum cases that have no aerodigestive tract injuries, but tracheostomy or primary repair may be required in patients with tracheobronchial injuries (5). Antibiotics are not recommended in patients with spontaneous pneumomediastinum, and also, no infection cases secondary to spontaneous pneumomediastinum have been reported in the literature. In cases of traumatic pneumomediastinum and in cases having high risk of mediastinitis, the broad spectrum antibiotics should be administered (3). In our case, the patient had no active hemorrhage and he was hemodynamically stable. The laceration on the anterior neck was cleaned and sutured primarily. No intervention was done to the tracheal tear and it was left to heal spontaneously. An antibiotic was started because of the high risk of mediastinitis.

Conclusions

In penetrating neck traumas, tracheobronchial injuries are seen rarely and we should be careful mostly for vascular injuries with massive hemorrhages (5). The vital findings of patients should be recorded at admission to evaluate the hemodynamics quickly. The surgical exploration must be performed in unstable patients with active bleeding. The stable patients must be comprehensively evaluated by diagnostic studies to avoid unnecessary surgical interventions because the surgical exploration may not be necessary in these patients, even in the presence of a tracheal injury as in our case. Additionally, the adequate measures should be taken around the construction zones to avoid such accidents.

Informed Consent: Written informed consent from the patient and approval from the hospital were obtained for presenting this case report.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - A.A.; Design - K.T.; Supervision - K.T.; Data Collection and/or Processing - A.A.; Analysis and/ or Interpretation - K.T.; Literature Search - H.Ö.A.; Writing Manuscript - K.T.; Critical Review - H.Ö.A.

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

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

References

1. Saito N, Hito R, Burke PA, Sakai O. Imaging of penetrating injuries of the head and neck: current practice at a level I trauma center in the United States. Keio J Med 2014; 63: 23-33.
2. Wang Y, Sun Y, Zhou T, Liu GH, Zhang XM, Yue JX, et al. Penetrating neck trauma caused by a rebar: A case report. Medicine (Baltimore) 2018; 97: e0468.
3. Kornmann VN, van Ravesteyn LM, Reif HM, Sallevelt PE, Krol RM. Unique case of pneumomediastinum due to penetrating injury to the mediastinum. BMJ Case Rep 2015: 2015.
4. Kara H, Uyar HG, Degirmenci S, Bayir A, Oncel M, Ak A. Dyspnoea and chest pain as the presenting symptoms of pneumomediastinum: two cases and a review of the literature. Cardiovasc J Afr 2015; 26 :1-4.
5. Sogut O, Cevik M, Boleken ME, Kaya H, Dokuzoglu MA. Pneumomediastinum and subcutaneous emphysema due to blunt neck injury: a case report and review of the literature. J Pak Med Assoc 2011; 61: 702-4.
6. Kuniyoshi Y, Kamura A, Yasuda S, Tashiro M, Toriyabe Y. Laryngeal injury and pneumomediastinum due to minor blunt neck trauma: case report. J Emerg Med 2017; 52:145-8.
7. Cruvinel Neto J, Dedivitis RA. Prognostic factors of penetrating neck trauma. Braz J Otorhinolaryngol 2011; 77: 121-4.

İstanbul Med J 2019; 20(3): 270-2
DOI: 10.4274/imj.galenso.2018.16779

A Case of Femoral Neuropathy Secondary to Iliopsoas Hematoma Due to Warfarin Intoxication

Warfarin İntoksikasyonuna Bağlı İliopsoas Hematomuna Sekonder Femoral Nöropati Olgusu

Köksal Sarıhan, Hasan Ali Gilan, Akın Erdal

Atatürk University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Erzurum, Turkey

ABSTRACT

Warfarin is a widely used drug in patients with a high risk of thromboembolism in cardiovascular diseases. Serious complications can be encountered as a result of high side effect profile and narrow therapeutic window. Iliopsoas hematoma and secondary femoral neuropathy are among the complications that may be encountered. The patient was admitted to the hematology clinic because of warfarin intoxication. Paresis was observed in the right lower extremity during follow-up. Iliopsoas hematoma was detected in the imaging study and electrophysiological study revealed femoral nerve neuropathy. After the diagnosis, conservative treatment and rehabilitation program was initiated immediately. In this article, a case of femoral nerve neuropathy following iliopsoas hematoma due to warfarin intoxication was presented.

Keywords: Femoral neuropathy, hematoma, intoxication, warfarin

ÖZ

Warfarin, kardiyovasküler hastalıklarda tromboemboli riski yüksek olan gruplarda yaygın olarak kullanılan bir ilaçtır. Yan etki profilinin yüksek olması ve terapötik pencerenin darlığı sonucu ciddi komplikasyonlarla karşılaşılabilmektedir. İliopsoas hematomu ve buna sekonder femoral nöropati karşılaşılabilecek komplikasyonlardan biridir.

Hasta warfarin intoksikasyonu nedeni ile hematoloji servisine yatırılmış, izlemi esnasında sağ alt ekstremitede kas gücü kaybı gelişmiştir. Hastanın görüntüleme çalışmasında iliopsoas hematomu görülmüştür. Elektrofizyolojik çalışmasında ise femoral sinir nöropatisi saptanmıştır. Hastaya tanı konduktan sonra ivedilikle konservatif tedavi ve rehabilitasyon programı başlanmıştır. Bu yazıda warfarin intoksikasyonu nedeniyle gelişen iliopsoas hematomu sonrası oluşan femoral sinir nöropatisi olgusu takdim edilmiştir.

Anahtar Kelimeler: Femoral nöropati, hematom, intoksikasyon, warfarin

Introduction

Femoral neuropathy, which is one of the lower extremity neuropathies, is not a common condition and is mostly due to diabetic amyotrophy. Femoral nerve neuropathies are not common because the femoral nerve is located in the pelvis and in the anterior part of the thigh. Hip and pelvic fractures, compression due to mass lesions, birth complications, abdominal and pelvic lymphedema, blunt trauma, femoral artery interventions such as coronary angiography, hip replacement surgery, abdominal and pelvic surgery, femoral lymph node biopsy can be the cause of femoral nerve neuropathy (1,2). Prolonged lithotomy position may also be a cause of femoral neuropathy (2). Bleeding disorders or anticoagulant therapies can also cause retroperitoneal hematoma and may cause compression on the femoral nerve (3,4). Retroperitoneal hemorrhages and hematomas that cause compression on the femoral nerve can cause a wide range of symptoms, from mild inguinal pain to death. Therefore, early diagnosis and treatment are important in reducing morbidity and mortality (5,6). Femoral neuropathy caused by iliac hematoma is characterized by reduced muscle strength in knee extensors and hip flexors, and diminished patellar reflex (5). Hypoesthesia in the anteromedial aspect of the thigh is generally detected on the sensory examination (5). In this article, a case with iliopsoas hematoma and secondary femoral neuropathy following warfarin intoxication, and who was enrolled to a rehabilitation program will be discussed in the light of the literature.

Case Report

An 87-year-old male patient was admitted to the general surgery clinic with a complaint of right-sided inguinal pain and bruising of the back and legs for 10 days. He was transferred to the hematology clinic with

Address for Correspondence/Yazışma Adresi: Köksal Sarıhan MD, Atatürk University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Erzurum, Turkey
Phone: +90 536 890 14 34 **E-mail:** koksalsarihan@hotmail.com **ORCID ID:** orcid.org/0000-0002-5010-4591

Cite this article as/Atıf: Sarıhan K, Gilan HA, Erdal A. A Case of Femoral Neuropathy Secondary to Iliopsoas Hematoma Due to Warfarin Intoxication. İstanbul Med J 2019; 20(3): 270-2.

Received/Geliş Tarihi: 13.07.2018
Accepted/Kabul Tarihi: 24.09.2018

a preliminary diagnosis of warfarin intoxication. He had previously undergone aortic valve replacement and surgery for bladder cancer, and was diagnosed with chronic renal failure. He was taking warfarin irregularly. In laboratory tests, international normalized ratio (INR) was 4.5 and hemoglobin was 9.2. His warfarin treatment was stopped. The patient was started on 2x0.6 cc enoxaparin. Due to the presence of pain in the inguinal region and signs of femoral nerve injury, he was consulted to physical medicine and rehabilitation (PMR) clinic and magnetic resonance imaging (MRI) was performed with a prediagnosis of iliopsoas hematoma. The MRI result was reported as "approximately 78x65x114 mm mass lesion suggestive of hematoma in the right iliacus muscle area, centrally hypointense and peripherally hyperintense on T1-weighted images (T1-WI), having heterogeneous intensity on T2-WI, restricted diffusion on diffusion-WI, no prominent contrast enhancement on post-contrast images" (Figures). The patient was consulted with the general surgery clinic. Surgical intervention was not considered because the hematoma was only in the muscular plane, there was no history of trauma and the patient's general condition was good. He was followed-up with medical treatment. Vitamin K and fresh frozen plasma were administered for hemorrhage. He was consulted again to PMR clinic for diagnosis and rehabilitation program. On his physical examination, hip movements were painful, hip flexor muscle strength was 2/5, hip abductor muscle strength was 2/5 and muscle strength of knee extensors was 2/5. The patellar reflex was hypoactive. Electromyography (EMG) was requested with a preliminary diagnosis of femoral nerve neuropathy. Femoral nerve neuropathy was detected in EMG. Isometric-isotonic strengthening exercises for hip flexors and knee flexors were started 3x20 times a day, for a total of 20 sessions during the patient's hospital stay. Following muscle strength increase tracking, rehabilitation program including progressive resistance strengthening exercises and balance training was initiated. The patient was consulted to the algology clinic because of pain, and tramadol and pregabalin treatment was started. In the follow-up, femoral nerve examination revealed clinical improvement with medical treatment and exercise. On his physical examination, hip movements were minimally painful, hip flexor muscle strength was 4/5, hip abductor muscle strength was 4/5 and muscle strength of knee extensors was 4/5. Patellar reflex was evaluated as normoactive. The patient's initial visual analogue scale score was 8 and decreased to 3 in the post-treatment period. The patient was discharged with 2x0.6 cc enoxaparin treatment and home exercise program recommendations. In the control examination, after the resolution of psoas hematoma in imaging and improvement in his complaints, warfarin treatment was initiated with the recommendations of the hematology and cardiology clinics.

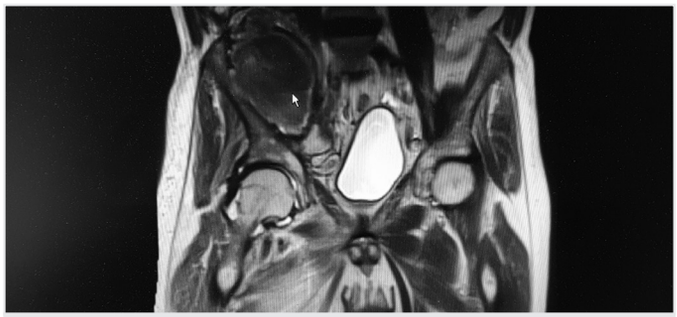


Figure 1. Hematoma on T2-weighted images sequence in coronal plane

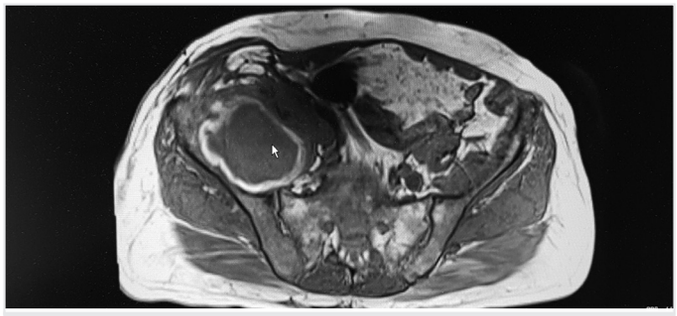


Figure 2. Hematoma on T1-weighted images sequence in axial plane

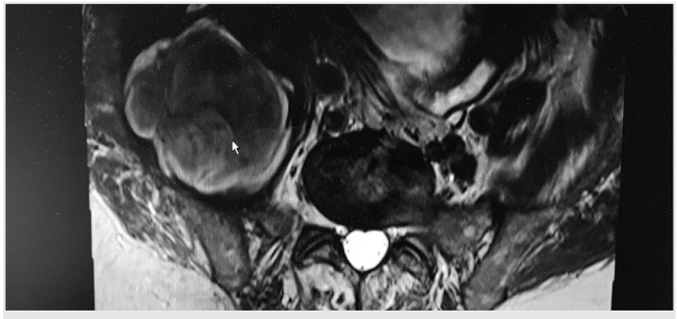


Figure 3. Hematoma on T2-weighted images sequence in axial plane

Written and oral informed consents were obtained from the patient and presented.

Discussion

Femoral nerve is a mixed motor and sensory nerve, which is the largest branch of lumbar plexus. It originates from L2, L3, and L4 nerves and lies anterior to the psoas muscle. This level is at the upper margin of L5 vertebra. The nerve runs from here through the iliac and psoas muscles until it passes under the inguinal ligament. It passes under the inguinal ligament with the femoral artery and vein, and is divided into motor and sensory branches. The motor branch of the femoral nerve innervates the iliopsoas muscle, the pectineus muscle, the quadriceps femoris and the sartorius. The sensory branch innervates the medial part of the thigh and the medial part of the leg (1).

Hemorrhagic complications in anticoagulant therapy are potential complications. The most dangerous complications are seen in the intracranial and retroperitoneal regions. The risk of hemorrhage is directly proportional to the INR level. Major hemorrhagic complications increase significantly when INR is more than 3. The INR value was 4.5 in our patient and he was in the high-risk group for hemorrhagic complications.

Retroperitoneal hemorrhages mostly present with anemia, back pain, thigh pain, paresthetic complaints or shock due to massive bleeding. In the cases, the femoral nerve is most likely to be compressed and the associated symptoms occur (3).

Iliopsoas hematoma is a rare disease and is associated with high mortality. Although mortal, most of the cases are expected to recover within the first year. Although hemorrhage due to warfarin intoxication is usually seen in the early years of drug initiation, iliacus muscle

hematoma developed after long-term use of warfarin in our case.

Iliopsoas hematoma usually manifests with sudden onset of inguinal, hip, thigh or low back pain. In the differential diagnosis, ureteric stones, aortic dissection, hip pathologies, and radiculopathies originating from lumbar region should be considered first (3). The femoral nerve can be compressed everywhere during the course of the nerve, but the region where the femoral nerve is most vulnerable to injury is in the iliacus muscle compartment. Most of the femoral nerve neuropathies develop due to hematomas or rupture of iliacus or iliopsoas muscles resulting from traumas in the iliopsoas compartment. Femoral neuropathy caused by iliacus hematoma is characterized by reduced muscle strength in knee extensors and hip flexors, and diminished or absent patellar reflex. Hip flexion is affected in proximal level lesions, while hip flexion is preserved in lesions at the level of inguinal ligament and the problem is more related to knee extension. On the sensory examination, the sensation on the inner face of the leg and thigh is generally lost or decreased (6). Also, the leg cannot be held straight and the patient may fall due to knee flexion while walking.

The most commonly used imaging methods for the diagnosis of iliopsoas hematoma are ultrasonography (USG), MRI and computed tomography (CT). While USG is in the second place due to its inability to show deep tissues effectively, MRI should be considered in the first place with its ability to show retroperitoneal hemorrhage and provide effective differential diagnosis. CT can be effective in determining the localization of the hemorrhage in the acute period and in patients in whom MRI cannot be performed (6). In the follow-up of retroperitoneal hemorrhage and hematomas, MRI is one step ahead. EMG is a useful technique for the diagnosis of femoral neuropathy and the exclusion of other nerve pathologies. In addition, the severity of femoral nerve involvement and regeneration in the recovery period can also be determined by EMG. Bilateral femoral nerve motor and saphenous nerve sensory measurements are performed. Impulses are repeated above and below the inguinal ligament. Because of the clinical improvement in our patient, no control EMG was required.

Although the femoral nerve is large in size, it is difficult to detect femoral nerve in MRI. While it can be detected on coronal images in the inguinal region, it is difficult to detect it in the thigh region due to its small size. Intrapelvic femoral nerve injury should be considered when signal changes compatible with denervation are detected in the iliopsoas muscle (6).

The treatment can be conservative, transarterial embolization or surgery. Surgical decompression should be considered in trauma patients and in patients with large hematomas and neurological progression. Surgical decompression in the early period may accelerate recovery. The patients may not benefit from surgery if the surgery is delayed in patients with increased hematoma volume or progressive neurological deterioration. Conservative treatment approach should be considered in patients with coagulation disorder and prolonged coagulation due to drugs (7). In conservative treatment, bed rest is recommended and analgesic is given to the patient. Open surgery or percutaneous surgical techniques can be used. In one study, it was shown that paralysis persisted with conservative treatment where recovery was faster with surgery (4). However, there was no significant difference in prognosis between conservative and surgical treatment in some studies (8). In a review, it was reported that the complications of surgical treatment in femoral nerve neuropathy could lead to very serious consequences and that conservative methods should be tried firstly in treatment (9). Recently, successful cases have been reported by percutaneous transcatheter arterial embolization of the responsible artery (10). Patients should be included in the rehabilitation program, regardless of the treatment approach. Patients should start electrotherapy and exercise program in the rehabilitation program (5). EMG biofeedback and electrical stimulation can also be used in rehabilitation programs.

Conclusion

In patients with femoral neuropathy findings and bleeding diathesis or anticoagulant use, iliopsoas muscle hematoma should be considered in all cases. After being treated conservatively or surgically, patients should be included in the rehabilitation program. Regardless of the etiology and treatment, all patients should be included in the early rehabilitation program to maintain muscle mass and patient functionality.

Informed Consent: Written and oral informed consents were obtained from the patient and presented.

Peer-review: External and internal peer-reviewed.

Author Contributions: Concept - K.S.; Design - K.S.; Supervision - A.E.; Resources - H.A.G.; Materials - H.A.G.; Data Collection and/or Processing - K.S.; Analysis and/ or Interpretation - A.E.; Literature Search - K.S.; Writing Manuscript - K.S.; Critical Review - H.A.G., A.E.

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

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

References

1. Moore AE, Stringer MD. Iatrogenic femoral nerve injury: a systematic review. Surg Radiol Anat 2011; 33: 649-58.
2. Al-Ajmi A, Rousseff RT, Khuraibet AJ. Iatrogenic femoral neuropathy: two cases and literature update. J Clin Neuromuscul Dis 2010; 12: 66-75.
3. Rao RK, Basappa G, Jayaprakash H. Iliopsoas haematoma presenting with femoral neuropathy during anticoagulation therapy with warfarin. International Journal of Innovative Research in Medical Science 2018; 3: 1644-5.
4. Sako T, Yokoyama Y, Hasegawa K, Tsuge S, Kazumasa N, Wada A, et al. Femoral nerve pulsy due to iliopsoas muscle hematoma: a mini literature review. Open Journal of Orthopedics 2017; 7: 375-81.
5. Küçükşen S, Gezer İA, Cingöz HT, Sallı A. Warfarin tedavisi sırasında geç dönemde oluşan iliopsoas hematomuna bağlı femoral nöropati olgusu. J PMR Sci 2012; 15: 53-6.
6. Giuliani G, Poppi M, Acciarri N, Forti A. CT scan and surgical treatment of traumatic iliacus hematoma with femoral neuropathy: case-Report. J Trauma 1990; 30: 229-31.
7. Weiss JM, Tolo V. Femoral nerve palsy following iliacus hematoma. Orthopedics 2008; 31: 178.
8. Merrick HW, Zeis J, Woldenberg LS. Percutaneous decompression for femoral neuropathy secondary to heparin-induced retroperitoneal hematoma: case report and review of literature. Am Surg 1991; 57: 706-11.
9. Muratlı K, Araç Ş. Entrapment neuropathies around the hip. TOTBİD Dergisi 2015; 14: 572-9.
10. Wada Y, Yanagihara C, Nishimura Y. Bilateral iliopsoas hematomas complicating anticoagulant therapy. Intern Med 2005; 44: 641-3.