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In Memoriam: Professor İ. Nazmi Hoşal Page 177-180

Original Investigations

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Aims and Scope

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is the scientific, peer-reviewed, open-access journal of the Turkish Otorhinolaryngology-Head and Neck Surgery Society since 2001. The journal comprises four issues as March, June, September and December in a volume, and it is published quarterly every year. The journal's publication language is English.

The aim of the journal is to publish qualified original clinical, experimental and basic researches on ear, nose, throat, head and neck diseases and surgery, reviews that contain sufficient amount of source data conveying the experiences of experts in a particular field, case reports, video articles and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

The target audience of the journal includes academic members, specialists, residents and other relevant health care professionals in the field of ear, nose, throat, and head and neck disorders and surgery.

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

Turkish Archives of Otorhinolaryngology is indexed in **PubMed, PubMed Central, Web of Science (Emerging Sources Citation Index), ULAKBIM TR Index, EBSCO, GALE, CINAHL, J-Gate** and **ProQuest.**

Title: The Turkish Archives of Otorhinolaryngology

Official abbreviation: Turk Arch Otorhinolaryngol

E-ISSN: 2667-7474

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.

The Turkish Archives of Otorhinolaryngology's Open Access Policy is based on the rules of Budapest Open Access Initiative (BOAI). 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. 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.

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Abstracting/Indexing Services

Our journal's Abstracting/Indexing services store essential information about articles. In addition, some of our journals' Abstracting/Indexing services archive metadata about the article and electronic versions of the articles.In this way, copies of articles are presented to the scientific

community through these systems as an alternative to journals. This journal's archive has been backed up by PubMed Central (PMC) as from 2015 publications.

Author Self-Archiving Policy

Authors are permitted and encouraged to post their articles on personal and institutional websites after publication (while providing full bibliographic details and a link to the original publication).

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Instructions to Authors

CONTEXT

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is a scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Turkish Otorhinolaryngology Head and Neck Surgery Society, and published quarterly in March, June, September and December. The publication language of the journal is English.

The aim of the journal is to publish qualified original clinical, experimental and basic research on ear, nose, throat, head and neck diseases and surgery, reviews that contain a sufficient amount of source data conveying the experiences of experts in a particular field, case reports and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

EDITORIAL AND PUBLICATION PROCESS

The editorial and publication process of the Turkish Archives of Otorhinolaryngology are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

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 presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

PEER REVIEW PROCESS

Manuscripts submitted to the Turkish Archives of Otorhinolaryngology 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. For more detailed information, please read Ethical Policy page of the Journal.

Preprint

The Turkish Archives of Otorhinolaryngology does not consider preprint publications as prior publications. In other words, authors are allowed to present and discuss their findings on a non-commercial preprint server before submission to a journal.

Authors must provide the journal with the preprint server deposition of their article accompanying its DOI during initial submission. If the article is published in the Turkish Archives of Otorhinolaryngology, it is the responsibility of the authors to update the archived preprint and link it to the published version of the article.

AUTHORSHIP

Each person listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors. The ICMJE recommends that authorship is based on the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

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. Also, the 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.

Author Affiliations

Authors are expected to state the institutions which they affiliated in the time of the study. Their current affiliation can be added to the article as the corresponding address. Change of affiliation requests will not be implemented after submission. The Turkish Archives of Otorhinolaryngology requires corresponding authors to submit a signed and scanned version of the Authorship Contribution Form during the initial submission process 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.

Instructions to Authors

Change of Authorship

The Turkish Archives of Otorhinolaryngology reviews the authorship according to the author's declaration in the Title Page; thus, it is the authors' responsibility to send the final order of the complete author names. Requests in the change of authorship (e.g. removal/addition of the authors, change in the order etc.) after submission are subject to editorial approval. Editorial Board will investigate these kind of cases and act following COPE flowcharts.

Change of authorship requests should be submitted to the Editorial Office with an official letter stating the change's reasons. The letter must be signed by all authors and include their approval on the change in authorship. If the request is approved by the Editorial Board, authors need to submit a new Copyright Agreement Form according to the final order list.

DECLARATION OF INTEREST

The Turkish Archives of Otorhinolaryngology 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. The journal's Editorial Board resolves cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

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Open access is an approach that supports interdisciplinary development and encourages collaboration between different disciplines. Therefore, the Turkish Archives of Otorhinolaryngology contributes to the scientific publishing literature by providing more access to its articles and a more transparent review process.

MATERIAL DISCLAIMER

Statements or opinions expressed in the manuscripts published in the Turkish Archives of Otorhinolaryngology 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 regarding the published content rests with the authors.

SUBMISSION REQUIREMENTS

• Cover Letter,

• ICMJE Conflict of Interest Statement Form for all contributing authors,

• A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged on the title page),

• Abstract divided into appropriate sections,

• Keywords (For indexing purposes, a list of 4–8 keywords in English is essential),

• Article divided into appropriate sections,

• List of references styled according to "journal requirements",

• A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),

• The Copyright Agreement and Acknowledgement of Authorship Form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),

• Upload your title page and forms in the system to the Potential Conflict of Interest category to ensure a blinded review process,

• Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),

• Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles),

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. Authors are required to

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

Instructions to Authors

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports: the CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

Diagnostic accuracy: STARD Guidelines

Non-randomized public behaviour: TREND

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkarchotolaryngol.net. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors 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 Agreement and Acknowledgement of Authorship Form

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 turkarchotolaryngol.net.

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, highest academic degree(s), and ORCID IDs of the author(s),

Grant information and detailed information on the other sources of support,

Name, address, telephone (including the mobile phone number), and e-mail address of the corresponding author,

Acknowledgement of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. 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 four to a maximum of eight 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.

Main Points: All submissions except letters to the editor and clinical images should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

Original Articles: This is the most essential 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 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).

Clinical Trials

Turkish Archives of Otorhinolaryngology adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below:

A clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.

To have their manuscript evaluated in the journal, the author should register their research to a public registry at or before the time of first patient enrollment.

Based on most up to date ICMJE recommendations, the Turkish Archives of Otorhinolaryngology accepts public registries that include a minimum acceptable 24-item trial registration dataset.

Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.

For further details, please check ICMJE Clinical Trial Policy.

Data Sharing

As of 1 January 2019, a data-sharing statement is required for the registration of clinical trials. Authors are required to provide a data

sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual de-identified participant data will be shared

What data, in particular, will be shared

Whether additional, related documents will be available

When the data will be available, and for how long

By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Turkish Archives of Otorhinolaryngology:

Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.

The name of the registry and the registration number should be provided in the Title Page during the initial submission.

Data sharing statement should also be stated on the Title Page even the authors do not plan to share it.

The clinical trial and data sharing policy of the journal will be valid for the articles submitted from 1 January 2021.

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a 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, Tables, Figures, Images, and other media are not included.

Review / Systematic 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. While submitting your Review, please confirm that your manuscript is a systematic review and include a statement that researchers have followed the PRISMA guidelines.

Please check Table 1 for the limitations for Review / Systematic Review Articles.

Video Article: Videos should be up to 30 minutes in duration. The video must include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. Limited number of slides incorporated into video may be included to provide details of patient history, clinical and laboratory findings.

Video articles should include:

1) Copyright Transfer and Author Declaration Statement Form: This form must indicate that "Patients' Informed Consent Statement" is obtained.

2) Title Page

3) **Summary:** Summary should point out critical steps in the surgery up to 500 words. This part was published as an abstract to summarize the significance of the video and surgical techniques. The author(s) may add references if it is required.

5) **Video:** Please upload your video to turkarchotolaryngol.net using online submission system. Accepted video formats are Windows Media Video (WMV), AVI, or MPEG (MPG, MPEG, MP4). High-Definition (HD) video is preferred.

6) "Acknowledgements From" should be uploaded separately.

Preparing video content

In order to provide reviewers with a convenient method of accessing video content online, we have restricted video file types to mp, webM and Ogg format. This allows reviewers to view video content easily from all modern browser types without the inconvenience of downloading plug-ins and video players.

Mp4 is the most common online video format, and there are many converters available that will convert other file types to Mp4.

We can recommend using this free online converter to create a suitable mp4 file.

Video file size is limited to 50 Mbytes, and we suggest reducing file size for quicker upload times using this service Compress Mp4.

Please check Table 1 for the limitations for Video Article.

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 Presentation, 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, 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.

Turkish Archives of Otorhinolaryngology
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Instructions to Authors

Clinical Image: These type of submissions should present a striking image that may challenge and inform readers and contribute to their education. Submissions can include high-quality clinical images, radiology results or surgical images. Please check Table 1 for the limitations for Clinical Images.

Please note that there are author limitations for some article types. Authors should provide a reason for the manuscripts that exceed author limitations. The exception of the articles that are above the author limits is subject to Editorial decision.

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 labelled (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 the 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 shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references. If an ahead-of-print publication is cited, the DOI number should be provided. 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.

Turkish Archives of Otorhinolaryngology does not acknowledge citations to preprints since preprints yet have not passed the reviewers' evaluation process and verified by experts in the field.

Journal Article: Erkul E, Cekin İE, Kurt O, Gungor A, Babayigit MA. Evaluation of patients with unilateral endoscopic sinus surgery. Turk Arch Otorhinolaryngol 2012; 50: 41-5.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach

Table 1. Limitations for each manuscript type

Type of manuscript	Author limit	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	N/A	3500	250 (Structured)	30	6	5 or total of 10 images
Review Article	4	5000	250	50	6	10 or total of 15 images
Systematic Review	N/A	5000	250 (Structured)	50	2	10 or total of 15 images
Video Article	N/A	1500	250 (Structured)	106	2	2
Case Report	6	1000	200	10	No tables	4 or total of 8 images
Letter to the Editor	3	500	No abstract	5	No tables	No media
Clinical Images	3	500	No abstract	5	No tables	3 or total of 7 images

SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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 indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Websites: International Society for Infectious Diseases. ProMed-mail. Accessed February 10, 2016. http://www.promedmail.org/

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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: https://www.cdc.gov/ncidodlEID/cid.html.

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Contents

In Memoriam: Professor İ. Nazmi Hoşal

Obituary

Umut Akyol

Department of Otorhinolaryngology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Prof. Dr. İ. Nazmi Hoşal passed away on the 24th of November 2022, two weeks before his 92nd birthday in his hometown Ankara, Turkey. He was one of the first-generation members who founded and took forward Hacettepe University Medical School into one of the most successful medical schools in Turkey. A strong supporter of audiology, he opened a road for founding modern audiology in our country. The first science of audiology in Turkey was established by Professor Hoşal in 1967 at the Hacettepe University. He trained thousands of medical school students, hundreds of otorhinolaryngology specialists, and treated thousands of patients during his fertile professional life over more than 50 years.

Professor Hoşal was born in İstanbul on 8th December 1930. He completed his high school education in Ankara, at Ankara Gazi High School. He began medical school in Ankara University and after his graduation in 1956 went to the USA. He had his internship at Edgewater Hospital in Chicago, IL. and had completed his Otorhinolaryngology residency in Washington D.C, at the Washington Hospital Center affiliated with the George Washington University School of Medicine and Health Sciences (Figure 1). During his chief residency year in 1960 he achieved the highest number and qualification of surgical procedures among the ENT residents according to American Medical Association (AMA) records. He was then accepted as Assistant Professor by George Sisson at Northwestern University in Chicago. In the meantime he returned to Turkey to complete his obligatory military service.

After returning to Ankara as a young specialist he met Professor Dr. İhsan Doğramacı who was at the time founding an institution at Ankara University, which was later to become first the Hacettepe Medical School and then the Hacettepe University. Professor Doğramacı gathered many young specialists that were trained in the USA and provided them with the means to build their own departments at modern standards as they had learned

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Figure 1. Residency, Washinghton D.C USA

Figure 2. Together with the students, residents and fellows in the developing years of Medical Faculty of Hacettepe University

during their residencies abroad. In this new setting, Professor Hoşal decided not to return to Chicago but stay in Turkey. His most important incentives were to be able to provide state-of-the-art healthcare services and train young people in modern otolaryngology–head and neck surgery (Figure 2, 3). Thanks to the work of Professor Hoşal and his lifetime friends and comrades who have worked with him at the Hacettepe University Medical School from the beginning, Hacettepe University became one of the best modern universities in Turkey along with the Middle East Technical University. Unfortunately, we have lost most of these professors who have jointly built a modern and successful medical school which offers excellent graduate and post-graduate education, nevertheless a modern training hospital which is not inferior to most leading international centers.

Professor Hoşal was one of few living members of these generation. He was especially keen on having international relations. He guided many of us into building good connections with colleagues in Europe and North America. He supported young practitioners to go abroad and visit different clinics where they would interact and work with

Figure 3. Caricature drawn by the late Dr. Nejdet Güçlü

their colleagues. He was the first corresponding member from Turkey in the American Head and Neck Society (AHNS) and the American Laryngological Association (ALA). He was also a co-founder of the European Laryngological Sociey (ELS) representing Turkey.

He lived a long and productive life both as a professor at the Hacettepe University and a physician in his private clinic which he ran for more than 45 years. He retired as professor from the Hacettepe University in 1997, but actively his work in his clinic until age of 89 (Figure 4).

Following a cardiac surgery, he experienced many complications which kept him from working. Until recently, he spent part of his time in his summer house in Bodrum, which he enjoyed a lot, and was socially active on the social media, keeping in touch with his students, friends, and beloved family.

Professor Hoşal was a very caring and loving husband, father and grandfather. He always put his family at the heart of his life along with his profession. He lived 59 happy years with his wife Selma Hoşal, with whom he had two children. He has always been proud of his son, Dr. Şefik Hoşal, who followed on his path and became an otorhinolaryngologist and professor in his own clinic, and his daughter Nazlı Akman who became a successful businesswoman. He spent many a happy days with his four grandchildren (Figure 5).

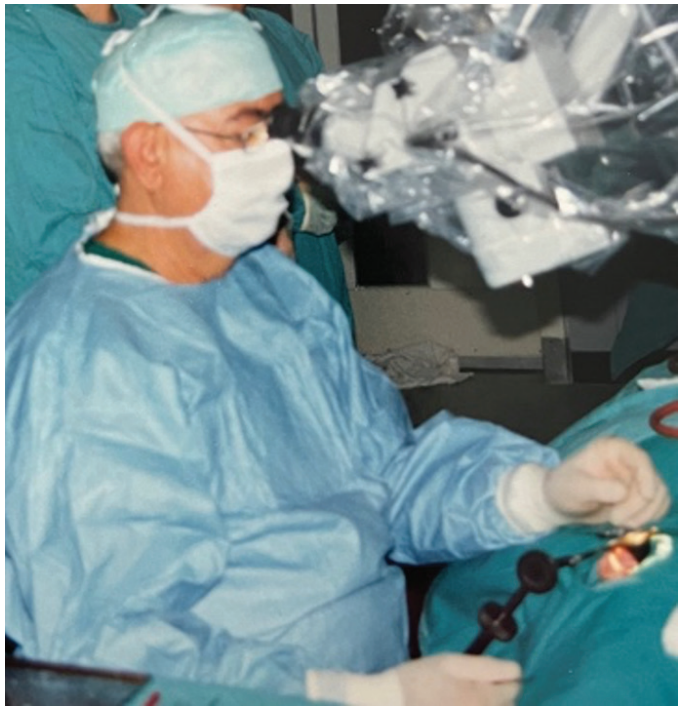

Figure 4. The last stapedectomy performed on the day of retirement at Hacettepe University

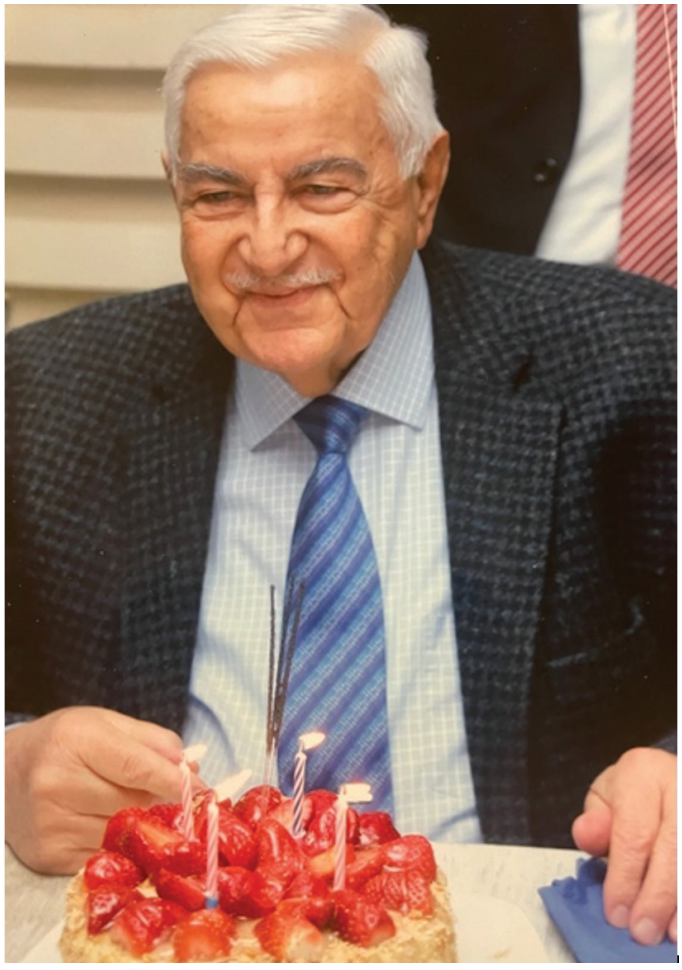

Figure 5. 90th birthday

He liked doing sports in his youth. Bicycling, ice-skating, skiing, judo, spearfishing and horseback riding were some of his passions. He also was a very good sport shooter, but bicycling and horseback riding were his favorites. He was once selected to the Turkish Olympic bicycle team, but his father did not allow him to participate. In his forties he developed great interest in farming, planting, and animals. He had a ranch near Ankara where he raised cows for dairy farming and producing milk. He planted fruits and forest trees, grew vegetables and fruits. This activity helped to reduce his professional stress and tension. Particularly in the summer evenings he came here with his friends relaxed in his swimming pool. He loved horseback riding here and made 20 to 30 km tours across rural Ankara. He spent delightful days in his farm until his mid-eighties.

Professor Hoşal has always been a perfectionist, a meticulous person and wanted his colleagues and students to keep their standards up to a high level. He was the founder and the honorary president of Hacettepe University's ENT Alumni, the first example of clinical alumnae organizations in Turkey. Thanks to the thorough education he fostered, we, alumni members who trained under him or the sister institutions which were later founded by his students following his principles enjoy a special connection. Whenever we get together as alumni, we always end up talking about him, about our days in Hacettepe University and the time we spent with him.

Prof. Hoşal, unlike some of his colleagues at the time and despite their serious criticisms, never kept his professional knowledge and skills to himself, but shared everything he knew with his students and colleagues. He was a pioneer in ORL and undertook many firsts in Turkey including a number of surgical techniques. He had personally taught his students the modern surgical techniques which he had learned in the USA. He performed the first stapes teflon piston operation for otosclerosis, the first modern parotidectomy by preserving facial nerve, the commando procedure in oral cancer in Turkey. He was a strong supporter of radical surgery in head and neck cancer. He pioneered in suprahyoid neck dissection in lower lip cancer and retrosternal mediastinal dissection in subglottic laryngeal cancer. He had an infectious working energy and a tireless passion for his profession. He was one of the few pioneers of his time who brought multi-disciplinary scientific thinking into otorhinolaryngology. All Hacettepe alumni, who trained under his high scientific principles, ethics and professional standards appreciate and cherish the education he has given us to this day.

He indeed was a great man with extraordinary intelligence and memory, willpower, and passion. He was a strong and influential character. He had many close and long-time friends in Ankara where he had spent his early youth, and

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quite active days. All his friends and their families admired and liked him as a brother, uncle, doctor.

He had always been a strong believer and follower of Atatürk, the founder of our Republic, and his modern principles and reforms throughout his lifetime. He always helped the ones in need, created scholarships for students, founded a Prof. Dr. İ. Nazmi Hoşal Foundation for supporting medical and post graduate students.

We will cherish his principles and strive to continue his work.

He will be missed.

Nasal Reactivity After Radiofrequency Ablation of Peripheral Branches of Posterior Nasal Nerve

Original Investigation

Samy Elwany, Ziad Mandour, Ahmed Aly Ibrahim, Remon Bazak

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Abstract

Objective: Transection or ablation of the posterior nasal nerve (TRPN) has been described as an adjunctive tool to reduce the symptoms of intractable allergic rhinitis (AR). The procedure, however, requires surgical skill and carries the risk of bleeding from the sphenopalatine artery. The aim of the present study is to describe radiofrequency ablation of the peripheral branches of the posterior nasal nerves within the inferior turbinates (RAPN) as an effective easier alternative to TRPN.

Methods: The procedure was performed on 24 patients with intractable AR. Nasal reactivity was tested by cold dry air (CDA) provocation before and 12 months after the radiofrequency procedure. Visual analog scale and acoustic rhinometry were used to measure the changes in nasal reactivity subjectively and objectively.

Results: Worsening of nasal symptoms following CDA provocation had significantly decreased after the RAPN procedure. Likewise, postoperative decrease in nasal volumes and minimal cross-sectional areas after CDA provocation were significantly less than the corresponding preoperative values.

Conclusion: RAPN effectively reduces nasal reactivity in patients with AR. The procedure is simple, minimally invasive, and can be performed under local or general anesthesia.

Keywords: Radiofrequency, allergic rhinitis, inferior turbinates, posterior nasal nerve, hyperreactivity

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Introduction

Nasal hyperreactivity (NHR) is defined as an increased sensitivity of the nasal mucosa to commonly encountered environmental stimuli. NHR is an important feature of allergic (AR) and non-allergic (NAR) rhinitis (1). A neurogenic origin is believed to be the culprit behind the development of NHR in AR and NAR patients (2).

Patients with AR usually experience provocation of their symptoms by several non-specific physical stimuli such as sudden change in temperature, smoking, or chemical pollutants (3). Cold dry air

(CDA) is a physiologic, safe, and tolerable stimulus for the nasal mucosa that has been proven to be a good diagnostic tool in non-specific hyperreactivity (4). Braat et al. (5) demonstrated that CDA provocations were superior to nasal histamine provocations in distinguishing AR patients from healthy controls.

Resection of the vidian nerve has been used to reduce hypersecretion and hypersensitivity of the nasal mucosa in patients with intractable AR. A major disadvantage of this procedure are the risks of decreased lacrimation and numbness of the palate. Therefore, vidian neurectomy has been largely replaced with the less invasive endoscopic transnasal resection of the posterior nasal nerve (TRPN) which spares nerve supply to the lacrimal glands and palate (6). Mori et al. (7) reported that submucous inferior turbinate surgery improved nasal breathing as well as nasal symptoms induced by the allergic reaction in patients with AR. Ogawa et al. (8) combined submucous turbinectomy with posterior nasal neurectomy in patients with severe AR and achieved good results.

The peripheral branches of the posterior nasal nerves run within the tissues of the inferior turbinate close to the bony concha (Figure 1). Unintended surgical resection of these branches has been suggested as an explanation of improvement of allergic symptoms following inferior turbinate reduction (8). Based on this report, Kobayashi et al. (9) described the resection of posterior nasal nerves within the inferior turbinates and reported that the effects of the procedure were equivalent to those of conventional TRPN. However, surgical identification of these branches is surgically demanding and may be troublesome or incomplete.

In the presented study, we used radiofrequency coagulation for submucosal ablation of the peripheral branches of the posterior nasal nerves within the inferior turbinate without the need to identify them individually as described by Kobayashi (9). We then used the CDA provocation protocol described by van Gerven et al. (3) to evaluate the effect of the radiofrequency procedure on NHR in patients with intractable AR.

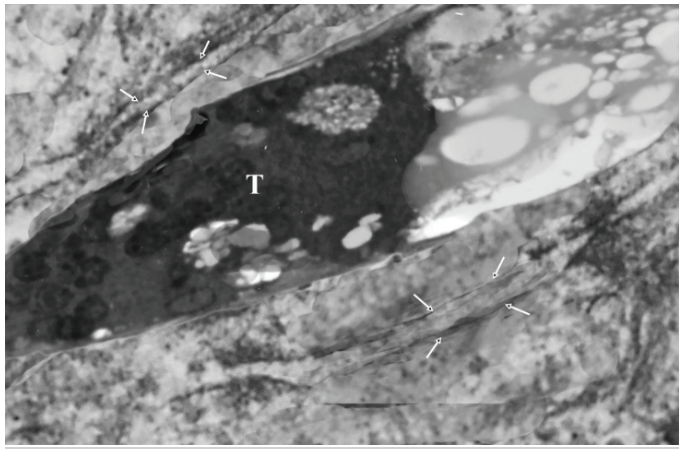

Figure 1. Electron micrograph showing the peripheral nerve fibers of the posterior nasal nerves (arrows) running close to the turbinate bone (T) (x860)

Methods

A sample of 24 patients was set based on sample size calculations assuming 80% power and 5% significance in acoustic rhinometry parameters changes before and after CDA provocation and considering a minimum average reduction of 15%. All patients were between 16 and 42 years of age and had at least two nasal complaints (nasal obstruction, rhinorrhea, or sneezing). All patients had positive skin prick tests, were nonsmokers, and suffered from troublesome intractable AR symptoms for more than five years.

All patients signed the informed consent forms after being informed about the procedure and the CDA provocation test. The consents and the research protocol were approved by the Committee of Medical Ethics of Alexandria University (approval no: 1119-2019, date: January 12, 2019) according to the Helsinki Declaration.

Exclusion criteria included sinonasal infections, severe septal deviation, nasal polyps, previous nasal surgeries, being lost to follow-up, as well as being pregnant or lactating. Local and systemic corticosteroids, antihistamines, or decongestants were stopped one week before every evaluation. Patients who could not stop medications before the tests were also excluded from the study.

Assessment of nasal symptoms by visual analog scale (VAS) and CDA provocation and acoustic rhinometry were performed at the time of the initial evaluation and 12 months after the radiofrequency procedure.

VAS Scale

All patients were requested to mark their nasal symptoms (nasal obstruction, rhinorrhea, and sneezing) on a VAS (0–10 cm) before and 15 minutes after CDA nasal provocation. The same examiner performed all the tests.

Acoustic Rhinometry

Nasal volumes (V1 and V2) and minimal cross-sectional areas (MCA1 and MCA2) were measured by acoustic rhinometry (RhinoScan SRE2000, Interacoustics, Assens, Denmark) in both nasal cavities. The method for performing acoustic rhinometry is well described elsewhere (10, 11).

Data for three rhinometric curves were collected for each nostril. Irregular tracings or discrepant measurements were discarded. Values considered for analysis were an average of three measurements taken from three technically acceptable

curves. All measurements were performed three times and by the same operator.

The following parameters were recorded:

• The volume of the segment located from 10 to 32 mm from the nostril corresponding to the nasal valve region (V1), and the volume of the segment located between 33 and 64 mm from the nostril, corresponding to the turbinate region (V2).

• Minimal cross-sectional area between 0 and 2.3 cm (MCA1) and between 2.3 and 6.4 cm (MCA2).

CDA Provocation

Patients were acclimatized to room temperature (20 °C) for 15 minutes and were exposed to CDA for 15 minutes. The CDA protocol used is described in the study by van Gerven et al. (12). To avoid diurnal variation and intertest error, all provocations were performed in the morning by a single experienced examiner.

Surgical Procedure

All procedures were performed under general anesthesia using an Ellman radiofrequency generator (Surgitron EMC, frequency =3.8 MHz and power =140 watts) and a bipolar straight turbinate handpiece with two parallel 5 cm long needles. We used the COAG setting (partially rectified waves) which diffuses the heat more effectively to the sides. Power setting was 20 watts.

The needles were inserted submucosally in the posterior half of the inferior turbinate and deeply pushed along and close to the medial surface of the turbinate bone toward its posterior end or tail (Figure 2). The average application duration of the radio waves was 5 seconds. The application was stopped once visual blanching of the mucous membrane occurred to limit damage to the overlying mucosa. Typically, three parallel applications were done from superior to inferior. No packing was needed, and all patients were discharged on the same day. The safety profile of the device/procedure was excellent, and there were no safety concerns.

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism software (GraphPad Software, Inc., San Diego, CA. USA). Volume is expressed in cubic centimeters and the results for each group are presented as an average ± standard deviation. The measurements before and after CDA nasal provocation were compared using a paired Student's t-test and a chi-square test. Values of $p<0.05$ were considered significant.

Results

The study included 24 patients (11 male and 13 female) with a mean age of 33.5 years. The baseline demographics and characteristics of the patients are shown in Table 1. The procedure was performed smoothly in all patients and their 6-month postoperative follow-up periods were uneventful. None of the patients reported headache or other significant adverse events in the immediate postoperative period.

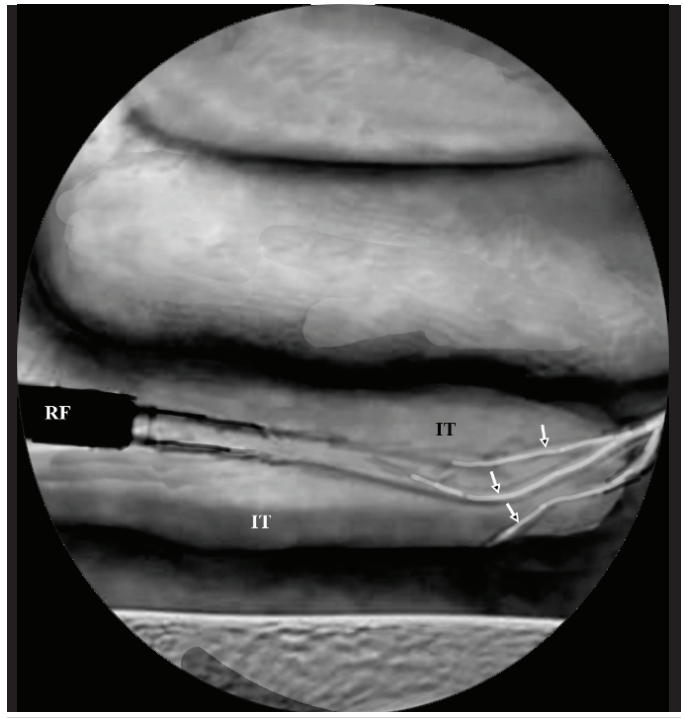

Figure 2. Radiofrequency ablation of the peripheral inferior turbinate branches of the posterior nasal nerves. The needles of the radiofrequency probe (RF) are inserted submucosally to ablate the branches of posterior nasal nerve (arrows) within the inferior turbinate (IT)

Table 1. Baseline demographics and characteristics of patients

Data	**n=24**
Sex	
Male	11
Female	13
Age, years	33.5+/-2.8
Medications used	
Oral antihistamines	24
Nasal steroids	24
Nasal antihistamines	13
Nasal decongestants	24
Oral decongestants	9
Oral steroids	7
Oral leukotriene inhibitors	5
Nasal anticholinergics	1
Previous nasal surgeries	0

N: Number of patients

The patients had significant reductions in mean VAS scores for all nasal symptoms and for total score (Table 2). The mean

total VAS score was reduced by 44.2% (percentage difference) and the drop was statistically significant (p=0.0082). CDA provocation increased the mean total VAS scores by 19.9% before surgery and only 10.5% after surgery (Table 3).

The results of acoustic rhinometry evaluation are presented in Tables 4 and 5. Acoustic rhinometric measurements showed an increase in all studied acoustic rhinometry parameters after the radiofrequency procedure, indicating a wider nasal airway. All acoustic rhinometry parameters decreased after CDA provocation. This drop (% difference) was significantly less after surgery. The preoperative total percentage difference after CDA provocation for MCA1, MCA2, and V1, V2 were 37.0%, 40.0%, and 24.7%, 28.0%, respectively. On the other hand, the postoperative total percentage difference after CDA provocation for the same parameters were 16.2%, 13.1%, and 12.7%, 11.7%, respectively (Figure 3). The differences between preoperative and postoperative values were statistically significant (X^2=5.9, p=0.0292).

Discussion

Resection of posterior nasal nerves has been reported as an effective procedure to treat AR unresponsive to medical therapy. Since the procedure interrupts both of parasympathetic and afferent sensory nerve fibers, it is expected to decrease rhinorrhea, sneezing, as well as nasal reactivity to noxious stimuli.

Ikeda et al. (13) combined inferior turbinoplasty with TRPN and reported satisfactory results in patients with resistant AR and NAR with eosinophilia (NARES). They named the procedure functional inferior turbinosurgery. Likewise, Ogawa et al. (8) used a similar combination of inferior turbinoplasty and TRPN and reported satisfactory results in patients with perennial AR. Mori et al. (7) mentioned that surgically induced damage to peripheral posterior nasal nerve fiber during turbinoplasty might be a major factor in improving allergic symptoms after submucous turbinectomy. Kobayashi et al. (9) compared submucosal resection of peripheral branches of the posterior nasal nerve within the inferior turbinate with classical TRPN and did not find significant difference in the improvement in symptom scores between the two groups, although transection of the posterior nasal nerve near the sphenopalatine foramen denervates a wider area of the nasal mucosa also including part of the middle turbinate. This is most likely due to the dominant role of the inferior turbinate in normal nasal breathing and reactivity (14, 15).

Nevertheless, submucosal selective identification of all peripheral posterior nasal nerves branches within the inferior turbinate can be surgically demanding, and some branches may be frequently missed. In the presented study, we used the radiofrequency probe to coagulate the inferior turbinate tissue where the peripheral posterior nasal nerves branches normally pass submucosally close to the bony concha obviating the need for individual identification of the branches. Although TRPN denervates a wider area of the nasal mucosa, it is a more surgically demanding procedure that typically requires general anesthesia, and often the exposure and the coagulation of the sphenopalatine artery. Also, some of the branches arising through separate foramina may be missed. On the other hand, the radiofrequency ablation of the peripheral branches of the posterior nasal nerves within the inferior turbinates (RAPN) procedure is a short procedure that is technically easy, minimally invasive, and can be performed under local or general anesthesia. Furthermore, there is practically no risk of postoperative hemorrhage as may occur from the sphenopalatine artery during TRPN. RAPN delivers results comparable to TRPN and can also be combined with complete radiofrequency turbinoplasty if needed.

Table 2. Preoperative and postoperative VAS scores and acoustic rhinometry parameters without CDA provocation

Parameter	Preoperative	Postoperative	p-value
VAS score	28.95	18.47	0.0082*
MCA1 cm^2	0.32	0.40	0.1216
MCA2 cm^2	0.36	0.57	0.0241*
V1 cm^3	1.59	2.00	0.1302
V2 cm^3	2.85	4.16	0.0027*

*p<0.05 is considered statistically significant. VAS: Visual analog scale, CDA: Cold dry air, MCA: Minimal cross-sectional area, V: Nasal volume

Table 3. Comparison of preoperative and postoperative VAS scores before and after CDA provocation

	Preoperative Mean (SD)		Postoperative Mean (SD)	
	Before CDA	After CDA	Before CDA	After CDA
Itching	6.22 (1.71)	8.1 (1.08)	5.43 (0.98)	4.83(1.10)
Sneezing	7.13 (1.23)	9.19 (1.12)	4.61 (1.03)	5.90 (1.21)
Rhinorrhea	7.45 (1.62)	9.20 (1.03)	5.01(1.06)	6.00 (1.43)
Nasal obstruction	8.15 (0.98)	8.89 (1.65)	3.42 (0.89)	3.79 (0.94)
Total nasal score	28.95	35.38	18.47	20.52
% difference (total)	19.9		10.5	

VAS: Visual analog scale, CDA: Cold dry air, SD: Standard deviation

Table 4. Comparison of preoperative and postoperative MCA1 and MCA2 values before and after CDA provocation

	MCA1					
	Preoperative (cm²) mean (SD)			Postoperative (cm²) mean (SD)		
Group	Right	Left	Total	Right	Left	Total
Before CDA provocation	0.35 (0.11)	0.29 (0.18)	0.32 (0.12)	0.43 (0.14)	0.37 (0.13)	0.40 (0.11)
After CDA provocation	0.24 (0.15)	0.20 (0.12)	0.22 (0.17)	0.36 (0.11)	0.32 (0.15)	0.34 (0.18)
		% difference			% difference	
	37.2	34.7	37.0	15.0	11.7	16.2
	MCA2					
	Preoperative (cm²) mean (SD)			Postoperative (cm²) mean (SD)		
Group	Right	Left	Total	Right	Left	Total
Before CDA provocation	0.38 (0.21)	0.34 (0.19)	0.36 0.18)	0.58 (0.22)	0.59 (0.12)	0.57 (0.16)
After CDA provocation	0.25 (0.15)	0.23 (0.16)	0.24 (0.16)	0.49 (0.17)	0.51 (0.15)	0.50 (0.11)
		% difference			% difference	
	41.2	38.5	40.0	16.8	14.5	13.1

MCA: Minimal cross-sectional area, CDA: Cold dry air, SD: Standard deviation

Table 5. Comparison of preoperative and postoperative V1 and V2 values before and after CDA provocation

	V1		
	Preoperative mean (SD)		
	Before CDA	After CDA	% difference
V1 (cm³) right	1.58 (0.31)	1.26 (0.31)	22.5
V1 (cm³) left	1.60 (0.56)	1.22 (0.51)	26.9
V1 (cm³) total	1.59 (0.41)	1.24 (0.39)	24.7
	Postoperative mean (SD)		
	Before CDA	After CDA	
V1 (cm³) right	2.01 (0.54)	1.75 (0.41)	13.8
V1 (cm³) left	1.99 (0.34)	1.78 (0.32)	11.1
V1 (cm³) total	2.0 (0.39)	1.76 (0.36)	12.7
	V2		
	Preoperative		
	Before CDA	After CDA	% difference
V2 (cm³) right	2.59 (0.91)	1.95 (0.51)	28.1
V2 (cm³) left	3.11 (0.67)	2.34 (0.61)	28.2
V2 (cm³) total	2.85 (0.59)	2.15 (0.63)	28.0
	Postoperative		
	Before CDA	After CDA	
V2 (cm³) right	4.10 (0.71)	3.71 (0.51)	9.9
V2 (cm³) left	4.22 (8.68)	3.69 (0.62)	13.4
V2 (cm³) total	4.16 (0.57)	3.70 (0.60)	11.7

V: Nasal volume, CDA: Cold dry air, SD: Standard deviation

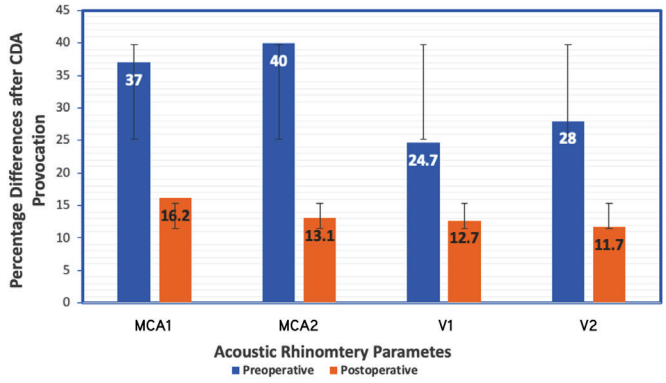

Figure 3. CDA-induced changes (percentage difference) before and after RAPN procedure. The drop of all parameters was significantly less 12 months after the procedure ($p<0.05$)
CDA: Cold dry air, RAPN: Radiofrequency ablation of the peripheral inferior turbinate branches of the posterior nasal nerves, MCA: Minimal cross-sectional area, V: Nasal volume

The results of our study demonstrated a significant and clinically noticeable reduction in symptom severity from the minimally invasive radiofrequency procedure. Patients' VAS scores were significantly decreased at 12 months postoperatively. A more important observation is the reduction of the nasal mucosal response. Radiofrequency submucous coagulation of the inferior turbinate tissues has been frequently used to reduce the size of the turbinates in patients with AR and NAR. The procedure reduces the size of the turbinate, by scar formation, resulting in improvement of nasal breathing while preserving the mucociliary mechanism of the turbinate. It also decreases the number of nasal glands and vessels, and therefore has also been thought reduce rhinorrhea and congestion (9, 16-20). Ablation of the peripheral branches of posterior nasal nerves within the inferior turbinate, as described above, further reduces nasal reactivity and sneezing in these patients.

The limitations of this study include the lack of a control arm, and the 12-month follow-up period. While the study showed that RAPN effectively reduced nasal reactivity and

improved nasal symptoms in patients with AR, further research is needed to establish its durability and long-term outcomes.

Conclusion

In this study, ablation of the peripheral branches of the posterior nasal nerve has proved to be a safe and efficient technique for reducing nasal reactivity and improving the symptoms of patients with AR unresponsive to medical therapy. The procedure is minimally invasive, easy to perform, and well tolerated by patients. Although this is a preliminary short-term study, the results of the study suggest that RAPN can be one of the treatment options for intractable AR. Further research is required to test the durability of the results.

Ethics Committee Approval: The consents and the research protocol were approved by the Committee of Medical Ethics of Alexandria University (approval no: 1119-2019, date: January 12, 2019) according to the Helsinki Declaration.

Informed Consent: All patients signed the informed consent forms after being informed about the procedure and the CDA provocation test.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Concept: S.E., Design: S.E., Data Collection and/or Processing: Z.M., A.A.I., R.B., Analysis and/or Interpretation: S.E., A.A.I., Literature Search: Z.M., Writing: S.E., R.B.

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

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Main Points

- Interruption of the autonomic supply to the nasal mucosa has been used to improve the symptoms in patients with allergic rhinitis.
- The peripheral branches of the posterior nasal nerve run within the inferior turbinate close to the bony concha.
- Ablation of these branches with radiofrequency energy effectively reduced nasal reactivity and improved the symptoms in the patients.
- The procedure is short, safe, minimally invasive, and much easier to perform than transection of the posterior nasal nerve at the sphenopalatine foramen (TRPN), with comparable results. RAPN can also be performed as an office procedure under local anesthesia.

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Evaluation of the Effect of Musical Perception Activities on Speech Perception in Adult Cochlear Implant Users

Original Investigation

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Abstract

Objective: This study aimed to evaluate clinical musical perception, analyze the relationship between speech recognition and music perception, and investigate the effects of a three-month musical perception activities on these parameters in adult cochlear implant (CI) users with post-lingual hearing loss.

Methods: Free-field hearing and speech tests in a quiet environment, the Turkish matrix test, and the Turkish version of the clinical assessment of musical perception test were performed on 18 adult unilateral CI users before and after the three-month music training. Results were compared with those of 18 healthy controls.

Results: Prior to the musical perception activities, word recognition scores, Turkish matrix test results, and 500, 1000, and 6000 Hz free-field hearing thresholds were significantly correlated with the clinical assessment of musical perception test scores in the CI group ($p<0.047$). Timbre recognition scores ($p=0.019$) had improved significantly in the CI group after the three-month musical perception activities. On the other hand, timbre recognition scores had significantly affected the Turkish matrix test results (R^2adjusted=0.56).

Conclusion: Our study showed that speech perception in noise and clinical musical perception measurements affected each other in CI users. The inclusion of musical perception activities to support an auditory rehabilitation program may contribute to increased speech recognition skills in noise.

Keywords: Cochlear implantation, speech perception, music, pitch discrimination, timbre perception

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Introduction

Cochlear implants (CI) transmit acoustic signals to the cochlea and the central auditory system by transforming the signals into electrical stimuli. Like other devices developed to compensate for hearing loss, CI are primarily designed to convey speech sounds comfortably

and effectively to the listener. Many factors affect the level of benefit obtained from CI in individuals with post-lingual hearing loss (1). Despite significant advances in speech perception, fundamental aspects of music perception remain a challenge for most CI recipients.

Music can be divided into several basic components: rhythm, pitch, melody, and timbre. It has been previously reported that CI users typically exhibited good rhythm perception but have poorer perception of pitch, melody, and timbre (2). Many tests have been described in the literature that measure the ability of CI recipients to perceive music (3). The University of Washington clinical assessment of music perception test (CAMP) was developed in 2009, and subsequently, the Turkish cross-cultural adaptation of the CAMP test was devised (4-6). The CAMP test evaluates pitch direction discrimination thresholds (PDD, dB) and standard errors for 262, 330, and 392 Hz base frequencies; melody recognition (MR, %); and timbre recognition (TR, %) scores. CAMP results of post-lingual adult CI recipients have been reported in previous studies (4, 7, 8). Pitch, timbre, and melody perception are high-level skills that reflect peripheral and central auditory system performance (8). Thus, the evaluation of such competencies in CI users can provide essential data regarding auditory reorganization after implantation. A significant relationship between musical perception and speech recognition has been reported in the literature (2, 9). This relationship reveals that better frequency resolution required for melody perception is also an important factor for speech recognition, especially in noise (10). Similarly, other studies have shown positive correlation between pitch perception and speech comprehension in noise (11, 12). It has been suggested that this could be due to the inability of CI users to distinguish between stimulus and noise because of pitch detection inadequacies (11). It has also been stated that a lack of musical perception could be due to a similar mechanism (13). Moreover, the findings of these previous studies suggest that musical perception activities (MPA) in CI users improved recognition of consonants in fluctuant noise, speech perception in noise, familiar MR, timbre identification, and musical pitch perception (12, 14, 15). MPA was also reported to lead to significant improvements in the perception of music and speech when applied for 45 minutes a day for three to five weeks (16).

While the relationship between speech recognition and musical perception in different populations have been evaluated in previous studies, this relationship, and the effect of MPA on speech recognition have not yet been studied in Turkish adult CI users. Therefore, in our study we aimed to evaluate clinical musical perception, analyze the relationship between speech recognition and musical perception in quiet and noise in comparison to healthy controls, and investigate the effects of three-month MPA on these parameters in adult monaural CI users with post-lingual hearing loss.

Methods

Ethical approval was obtained from the Göztepe Training and Research Hospital, Clinical Researches Ethics Committee (date: 10.04.2018, decision no: 2018/0092). In addition, this study was supported by the scientific research projects committee of the university (T_GAP_2019_1510).

Participants

Adult volunteers were recruited for the study. Eighteen post-lingually deafened unilateral CI users and 18 healthy adults were enrolled. CI users that met the following inclusion criteria were included in the CI group: aged 18–65 years at the time of testing, severe to profound post-lingual hearing loss, at least one year of unilateral CI use, normal auditory nerve and cochlear anatomy, mental competency to perform audiological and musical perception tests, no physical or psychological illness that could affect participation in the test, and ability to communicate verbally. Thirteen subjects had Opus2 sound processor (MedEl, Innsbruck, Austria) and used fine structure processing coding strategies; three subjects had Nucleus 6 processor, and one had a Kanso sound processor (Cochlear, North Sydney, Australia), both with advanced combination encoder coding strategies; and one subject had a Neuro 2 sound processor (Oticon Medical, Vallauris, France) with adaptive processing strategies. None of the CI users had formal musical education nor were they professional musicians; the participants were questioned regarding their usual music listening habits, and none listened to music regularly. Written informed consent was obtained from all participants.

Testing Procedure

Free-field behavioral hearing thresholds for 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz were obtained with frequency-modulated stimuli presented at a distance of 1 m and 0º azimuth using a Madsen Astera audiometer (Otometrics, Natus Medical, Denmark). Initially, the averages of the hearing thresholds were calculated for 500, 1000, 2000, and 4000 Hz. Then, speech detection thresholds (SDT), word recognition scores (WRS), and the most comfortable levels (MCL) in quiet were determined with the same setting. Next, the Turkish matrix test (TURMatrix), adapted for the Turkish language by Zokoll et al. (17) was performed to evaluate speech perception in noise performance of the patients in free field (Oldenburg Measurement Applications, HörTech, Oldenburg, Germany).

TURMatrix is a Turkish adaptive speech perception in noise test used to determine the threshold for speech recognition in the ±1 dB range. TURMatrix uses syntactically fixed sentences comprising five words: name, number, adjective, object, and verb. The test lists are randomly selected from a 50-word inventory, and 20 sentences are created using these words. Patients were asked to listen carefully and repeat the sentence in the presence of background noise. For each sentence, words known by the

listeners were selected from the computer screen by the examiner. The scores were calculated as signal-to-noise threshold levels (dBSNR), where the listeners could correctly repeat more than 50% of the words. Speech stimuli were presented from 0˚, and continuous 65 dBSPL bubble noise was presented from 180˚ azimuth (18). Before the test, all subjects performed a training session (17). In case of fatigue, all subjects were allowed short breaks.

Finally, the Turkish version of the clinical assessment of music perception test (CAMP-TR) evaluated CI recipients' pitch, timbre, and melody perception skills (5). The CAMP-TR test consists of three subtests that evaluate PDD, MR, and TR. CAMP-TR tests were conducted in a sound-treated double-walled room with a custom MATLAB (The MathWorks Inc., USA) program on a computer connected to a Madsen Astera audiometer (Otometrics, Natus Medical, Denmark) with a sound field presentation level of 65 dB-A. All stimuli were delivered through a JBL control one loudspeaker (JBL, Harman International, USA) positioned at 0˚ azimuth and 0˚ elevation at 1 m distance from the subjects. CAMP-TR testing was carried out following the procedure previously described by Nimmons et al. (19) and Yüksel and Çiprut (6).

After completing the first evaluation protocol, as daily MPA, participants were given a list of the instruments (Turkish saz, piano, guitar, violin, trumpet, flute, clarinet, and saxophone) and YouTube addresses of the melodies of CAMP-TR test (Appendix). Patients were free to choose the YouTube addresses where they would listen to the instruments in the CAMP-TR test. Patients were asked to listen to the melodies from the YouTube addresses (Appendix). The songs in the melody list were selected from the melodies in the MR subtest of the CAMP-TR test. There were no predetermined acoustic targets. Care was taken to ensure that the selected songs were not polyphonic or symphonic. Support was obtained from the family members of those participants who had insufficient internet usage skills. The patients were given a music listening diary and were asked to listen to the melodies and the instruments for 45 minutes per day (either in one go or in three 15-minute sessions) and mark their listening on the checklist. The MPA period continued for three months, and then the CI group was reevaluated with the same testing protocol, and the results were analyzed.

Statistical Analysis

The power of this study was calculated based on a reference study using G* Power version 3.1.9.2 (6). Assuming a medium effect size value of 0.50, a total of 36 participants were estimated to be sufficient with 80% power at a 95% confidence level. Distribution of the data was analyzed using the Shapiro–Wilk test. As the data distribution was not normal, nonparametric tests were performed for statistical analyses. Continuous data median, minimum and maximum values, and frequencies of categoric data were calculated. In addition, to analyze the significance of differences between independent and related groups before and after the three-month MPA, Mann–Whitney U and Wilcoxon signed-rank tests were performed. Relationships between the continuous variables were analyzed by calculating the Spearman's correlation coefficients. Multiple regression analysis was done to study the relationships between parameters in the CI group. Four multiple regression models were created to analyze the relationship between the CI group findings. The first model evaluated the effect of independent variables of pitch, melody, and timbre discrimination percentages on the TURMatrix test signal-to-noise ratios dependent variable. The second model evaluated the effect of the average of free-field hearing thresholds, SDT, WRS and most comfortable loudness levels independent variables on TURMatrix test signal-to-noise ratios dependent variable. The third model evaluated how the independent variables of the averages of free-field hearing thresholds, SDT, and most comfortable loudness levels affected the dependent variable of the WRS. The fourth model evaluated how much the independent variables of 250–8000 Hz free field hearing thresholds affected the WRS dependent variable. Statistical analysis was performed using SPSS 21.0 (SPSS Inc., IBM, New York, USA). A p-value less than 0.05 was considered significant for all tests.

Results

The study included 36 participants, namely, 13 males (72.2%) and 5 females (27.8%) in the CI group, and 11 males (61.1%) and 7 females (38.9%) in the control group. Of the participants in the CI group, 11 (61.1%) had CI in the right ear and 7 (38.9%) in the left ear. The median age was 31 years in the CI group, with a minimum of 19 and a maximum of 65 years. In the control group, the median age was 34 years, with a minimum of 22 and a maximum of 65 years. There was no significant age difference between the groups (p=0.924). The median duration of CI usage was 45.5 months, with a minimum of 12 and a maximum of 192 months, and the duration until implantation (time from diagnosis of hearing loss to cochlear implantation, patients used hearing aid/s unilaterally or bilaterally) was 32 years with a minimum of 15 and a maximum of 59 years (Table 1). The CI group's free-field hearing and speech test results in quiet were significantly worse than those of the control group (p<0.001) (Table 2). TURMatrix, PDD, MR, and TR scores were also significantly lower in the CI group than in the controls (p<0.001) (Table 3). It was determined that the TR scores (p=0.019) improved significantly in the CI group after three months of MPA (Tables 2, 3).

Four multiple regression models were created to analyze the relationship between the CI group findings (Table 4). The first model evaluated the effects of independent variables (pitch, melody, and timbre discrimination percentages before MPA) on the dependent variable (TURMatrix test signal-to-noise ratios before MPA). As a result of the analysis, a significant regression

model could be formed [F(8,9)=3.697, p=0.034] and it was found that 56% of the variance in the dependent variable (R^2adjusted =0.559) was affected by the independent variables. The timbre perception negatively and significantly affected the signal-to-noise ratios [β=-0.568, t(9)=-3.264, p=0.01, pr^2=0.542]. It was determined that other independent variables did not affect the dependent variable significantly. The second model evaluated the effects of the independent variables (averages of free-field hearing thresholds, SDT, WRS and most comfortable loudness levels after MPA) on the dependent variable (TURMatrix test signal-to-noise ratios after MPA). As a result of the analysis, a significant regression model could be established [F(4,12)=7.907, p=0.002], and it was found that 63% of the variance in the dependent variable (R^2adjusted =0.633) was affected by the independent variables. Accordingly, the WRS [β=-0.855, t(12)=-4.228, p=0.001, pr^2=0.599] have negative and significant effects on the TURMatrix test signal-to-noise ratios. It was determined that other independent variables did not affect the dependent variable significantly. The third model evaluated how much the independent variables of the averages of free-field hearing thresholds, SDT, and most comfortable loudness levels (before MPA) affected the dependent variable of WRS (before MPA). As a result of the analysis, a significant regression model could be created [F(3,14)=4.802, p=0.017] and it was found that 40% of the variance in the dependent variable (R^2adjusted =0.402) was affected by the independent variables. Accordingly, the most comfortable loudness levels affected the WRS negatively and significantly [β=-0.545, t(12)=-2.331, p=0.035, pr^2=0.279]. It was found that other independent variables did not affect the dependent variable significantly. The fourth model evaluated how much the independent variables of 250–8000 Hz free field hearing thresholds (after MPA) affected the dependent variable of WRS (after MPA). As a result of the analysis, a significant regression model could be created [F(7,9)=3.368, p=0.047] and it was found that 51% of the variance in the dependent variable (R^2adjusted =0.509) was affected by the independent variables. Accordingly, 250 Hz [β=-0.885, t(9)=-2.402, p=0.04, pr^2=0.391] and 6000 Hz free-field hearing thresholds [β=-1.136, t(9)=-2.285, p=0.048, pr^2=0.367] affected the WRS negatively and significantly. It was determined that other independent variables did not affect the dependent variable significantly.

Table 1. Demographics of study and control groups

	CI group	Controls
n	13 males 5 females	11 males 7 females
Age (years)	31 (min: 19, max: 65)	34 (min: 22, max: 65)
Duration of CI use (months)	45.5 (min: 12, max: 192)	-
Duration until implantation (years)	32 (min: 15, max: 59)	-
CI ear	11 right ears, 7 left ears	

CI: Cochlear implant, min: Minimum, max: Maximum

Relationships between the test parameters before the MPA were analyzed with Spearman's correlation coefficients (Tables 5-7, Figure 1). Accordingly, before MPAs were held, WRS, MCL, TURMatrix (dBSNR), and the 500, 1000, and 6000 Hz free-field hearing thresholds were significantly correlated with the CAMP-TR scores in the CI group (p>0.047). Before the MPA, the 1000 Hz free-field hearing

Table 2. Free-field hearing and speech tests findings in quiet, and comparisons of CI group and controls

Test parameters	Pre-tests of CI group			Post-tests of CI group			Controls			Controls versus post-tests of CI group (Mann–Whitney U)		Pre versus post-tests of CI group (Wilcoxon signed-ranks)	
	Median	Min	Max	Median	Min	Max	Median	Min	Max	p	z	p	z
250 Hz	30	20	60	30	20	60	10	0	15	<0.001	-5.094	0.414	-0.816
500 Hz	35	25	55	35	25	55	7.5	0	15	<0.001	-5.101	1	0.000
1000 Hz	35	25	50	35	25	50	7.5	0	20	<0.001	-5.089	0.518	-0.647
2000 Hz	35	10	45	35	10	45	5	0	15	<0.001	-4.893	0.234	-1.190
4000 Hz	32.5	10	45	30	10	50	5	5	20	<0.001	-4.94	0.276	-1.089
6000 Hz	35	20	50	35	20	55	10	0	20	<0.001	-5.08	0.071	-1.807
8000 Hz	35	25	60	40	25	65	7.5	0	25	<0.001	-5.043	0.197	-1.289
Averages of 500–4000 Hz (dB)	34	18	48	32	18	50	8	2	18	<0.001	-5.049	0.553	-0.594
Speech detection thresholds (dB)	37.5	25	60	35	25	55	15	5	25	<0.001	-5.033	0.317	-1
Word recognition scores (%)	48	4	80	44	4	80	96	92	100	<0.001	-5.104	0.071	-1.983

Pre: Before musical perception activities, Post: After musical perception activities, CI: Cochlear implant, min: Minimum, max: Maximum

Table 3. Results of Turkish Matrix and Turkish version of clinical assessment of music perception tests in CI group and controls

Test parameters	Pre-tests of CI group			Post-tests of CI group			Controls			Controls versus post-tests of CI group (Mann–Whitney U)		Pre versus post-tests of CI group (Wilcoxon signed- ranks)	
	Median	Min	Max	Median	Min	Max	Median	Min	Max	p	z	p	z
TurMatrix (dBSNR)	22.5	4	23	22.5	4.8	25	-3.45	-7.7	2.8	<0.001	-5.059	0.286	-1.067
Pitch discrimination (262 Hz-thresholds)	5.28	0.94	11.94	5.28	2.72	11.94	2.41	0.78	11	<0.001	-3.516	0.646	-0.459
Pitch discrimination (262 Hz-standard errors)	1.34	0.07	3.54	2.01	0.07	4.42	0.55	0.07	2.14	0.007	-2.658	0.328	-0.978
Pitch discrimination (330 Hz-thresholds)	6.77	1.72	11.5	7.11	0.83	11.56	2	0.72	11.5	<0.001	-3.518	0.248	-1.156
Pitch discrimination (330 Hz-standard errors)	1.85	0	4.14	1.29	0	3.5	0.34	0.14	2.69	0.057	-1.899	0.79	-0.267
Pitch discrimination (391 Hz-thresholds)	3.91	1	11.39	4.22	1.28	11.56	0.88	0.61	1.78	<0.001	-4.792	0.683	-0.408
Pitch discrimination (391 Hz-standard errors)	1.68	0.07	4.26	1.6	0.07	4.26	0.28	0.07	1.18	0.001	-3.221	0.173	-1.364
Melody recognition (%)	6.94	0	55.56	8.33	0	55.56	76.39	12.5	91.67	<0.001	-4.548	0.496	-0.680
Timbre recognition (%)	10.41	4.17	45.83	16.67	4.17	50	77.08	12.5	95.83	<0.001	-4.634	0.019	-2.346

Pre: Before musical perception activities, Post: After musical perception activities, CI: Cochlear implant, min: Minimum, max: Maximum, TURMatrix: Turkish matrix test

thresholds were significantly correlated with the duration of CI use (p=0.04). TURMatrix showed a significant relationship with the 500 Hz free-field hearing thresholds (p=0.022), SDT (p=0.035), WRS (p<0.001), MR (p=0.03), and PDD standard errors (p<0.032) (Table 5). After the MPA, the TURMatrix was significantly correlated with the 250 and 500 Hz free-field hearing thresholds, post-WRS, post-TR, and post-MR scores (p<0.04). PDD scores were correlated with the pre-WRS, pre-TURMatrix, and post-1000–6000 Hz free-field hearing thresholds (p<0.049). TR scores were correlated with pre-WRS, post-1000, and 6000 Hz free-field hearing thresholds and post-WRS (p<0.027). MR scores were significantly correlated with age, the duration before CI, the 500 Hz free-field hearing thresholds, and post-MCL (p<0.0049) (Table 6). In the control group, age was significantly correlated with SDT, MCL, TURMatrix, and TR (p<0.049). TURMatrix exhibited a relationship with speech audiometry parameters and 391 Hz PDD scores (p<0.037) (Table 7). PDD and MR scores showed significant correlation with 1000 and 4000 Hz free-field hearing thresholds (p<0.049), and TR scores also exhibited relationships with 6000 and 8000 Hz thresholds (p<0.038) (Table 7). Parameters that present change in correlation before and after MPA in the CI group.

Discussion

In the literature, tests such as speech recognition in quiet or noisy environments, hearing thresholds measurements, and analysis of changes in temporal auditory processing have been used to evaluate auditory performance after CI (8, 19-22). Perceptions of pitch, timbre, and melody are high-level skills, which can reflect the performance of the peripheral and central auditory systems (8, 9, 13, 23). Therefore, the assessment of such abilities in patients can provide significant data regarding auditory reorganization after cochlear implantation.

CAMP findings of adult CI users have been previously reported. Kang et al. (4) reported the PDD score averages of post-lingual adult CI recipients as 2.9±2.7, 3.4±3.1, and 2.5±2.5 for 262, 330, and 392 Hz base frequencies, respectively, and MR and TR as 25.1±22.2% and 45.3±16.2%, respectively. The best performance in the PDD scores was seen at 391 Hz base frequency, while the worst was at 330 Hz. Similarly, the base frequencies that presented the best and worst performances in our study were 391 and 330 Hz, respectively. In another study, Jung et al. (7) reported PDD score averages of 2.7±1.7 st, 4.4±4.2 st, and 8.1±3.0 st for 262, 330, and 391 Hz base frequencies, respectively, and MR and TR as 21.1±21.7% and 25.7±8.5%, respectively. Drennan et al. (8) reported PDD score averages as 3.15 st, 2.59 st, and 3.11 st for 262, 330, and 392 Hz base frequencies, and MR and TR were 26.2 and 43.2%, respectively. The CAMP results reported by other researchers are better than those obtained in our study. This may be related to differences in CI use (monaural, binaural, or bimodal), sample size, duration of CI use, and heterogeneous musical background.

Table 4. Summary of the multiple regression models

Models	Dependent variable	Independent variables	Adjusted R square	df1	df2	F	Sig.	Independent variables affect dependent variable	Beta	t(df2)	Sig.	pr^2
1	TurMatrix (S/N) ratios (before musical perception activities)	262, 330 and 391 Hz pitch perception thresholds, melody, and timbre discrimination percentages (before musical perception activities)	0.559	8	9	3.697	0.034	Timbre discrimination percentages	-0.568	-3.264	0.01	0.542
2	TurMatrix (S/N) ratios (after musical perception activities)	Average of free-field hearing thresholds, speech detection thresholds, word recognition scores and most comfortable loudness levels (after musical perception activities)	0.633	4	12	7.907	0.002	Word recognition scores	-0.855	-4.228	0.001	0.599
3	Word recognition scores (before musical perception activities)	Averages of free-field hearing thresholds, speech detection thresholds, and most comfortable loudness levels	0.402	3	14	4.802	0.017	Most comfortable loudness levels	-0.545	-2.331	0.035	0.279
4	Word recognition scores (after musical perception activities)	250–8000 Hz free field hearing thresholds (after musical perception activities)	0.509	7	9	3.368	0.047	250 Hz free field hearing thresholds	-0.885	-2.402	0.04	0.391
								6000 Hz free field hearing thresholds	-1.136	-2.285	0.048	0.367

TURMatrix: Turkish matrix test

Table 5. Correlation coefficients between test parameters before musical perception activities in CI group

	Spearman's correlation coefficients	Duration of implantation	Pre-TURMatrix	Pre-PDD thresholds			Pre-PDD standard errors			Pre-TR	Pre-MR
				262 Hz	330 Hz	391 Hz	262 Hz	330 Hz	391 Hz		
Pre 500 Hz	r	-	0.537*	-	-	0.473*	-	-	-	-	-0.582*
	p	-	0.022	-	-	0.047	-	-	-	-	0.011
Pre 1000 Hz	r	-0.487*	-	-	-	-	-	-	-	-	-0.551*
	p	0.04	-	-	-	-	-	-	-	-	0.022
Pre 6000 Hz	r	-	-	-	-	-	-	-	-	0.503*	-
	p	-	-	-	-	-	-	-	-	0.033	-
Pre SDT	r	-	-0.498*	-	-	-	-	-	-	-	-
	p	-	0.035	-	-	-	-	-	-	-	-
Pre WRS	r	-	-0.742**	-	-0.471*	-	-	-	-	-	0.525*
	p	-	<0.001	-	0.049	-	-	-	-	-	0.025
Pre MCL	r	-	-	-	0.544*	-	-	-	-	-	-0.603**
	p	-	-	-	0.02	-	-	-	-	-	0.008
Pre-TURMatrix	r	-	-	-	-	-	-	0.509*	0.586*	-	-0.512*
	p	-	-	-	-	-	-	0.031	0.011	-	0.03

*Moderate correlation, **Strong correlation, Pre: Before musical perception activities, SDT: Speech detection thresholds, WRS: Word recognition scores, PDD: Pitch direction discrimination, TR: Timbre recognition, MR: Melody recognition, MCL: Most comfortable level, CI: Cochlear implant, CAMP-TR: The Turkish version of clinical assessment of music perception test, TURMatrix: Turkish matrix test

Table 6. Correlation coefficients between test parameters after musical perception activities in CI group

	Spearman's correlation coefficients	Post-PDD thresholds			Post-TR	Post-MR	Post-WRS	Post-TURMatrix
		262 Hz	330 Hz	391 Hz				
Age	r	-	-	-	-	-0.551*	-	-
	p	-	-	-	-	0.022	-	-
The duration before CI	r	-	-	-	-	-0.486*	-	-
	p	-	-	-	-	0.048	-	-
Pre WRS	r	0.484*	-	-	0.553*	-	-	-
	p	0.019	-	-	0.021	-	-	-
Pre TURMatrix	r	-	-	0.568*	-	-	-	-
	p	-	-	0.014	-	-	-	-
Post 250 Hz	r	-	-	-	-	-	-0.634*	0.553*
	p	-	-	-	-	-	0.006	0.021
Post 500 Hz	r	-	-	-	-	-0.589*	-0.597*	0.612*
	p	-	-	-	-	0.013	0.011	0.009
Post 1000 Hz	r	0.571*	-	-	-0.538*	-	-0.588*	-
	p	0.004	-	-	0.026	-	0.013	-
Post 2000 Hz	r	-0.561*	-	-	-	-	-	-
	p	0.019	-	-	-	-	-	-
Post 4000 Hz	r	-0.715**	-	-	-	-	-	-
	p	0.001	-	-	-	-	-	-
Post 6000 Hz	r	-0.528*	-	0.512*	-0.543*	-	-0.498*	-
	p	0.029	-	0.036	0.024	-	0.042	-
Post averages of 500–4000 Hz (dB)	r	-0.486*	0.521*	-	-	-	-	-
	p	0.048	0.032	-	-	-	-	-
Post WRS	r	-	-	-	0.589*	-	-	-0.812**
	p	-	-	-	0.013	-	-	<0.001
Post MCL	r	-	-	-	-	-0.583*	-	-
	p	-	-	-	-	0.014	-	-
Post-TURMatrix	r	-	-	-	-0.505*	-0.505*	-0.812**	1
	p	-	-	-	0.039	0.039	<0.001	1

*Moderate correlation, **Strong correlation, Pre: Before musical perception activities, Post: After musical perception activities, WRS: Word recognition scores, PDD: Pitch direction discrimination, TR: Timbre recognition, MR: Melody recognition, MCL: Most comfortable level, CI: Cochlear implant, CAMP-TR: The Turkish version of clinical assessment of music perception test, TURMatrix: Turkish matrix test

In the literature, the definition given for pitch discrimination ranges from the ability to hear a semitone difference up to a difference of two octaves. The ability to hear rhythm and duration in CI users is close to normal. Timbre perception is generally poor, but about two-thirds of listeners can identify instruments in a closed set. CI recipients typically have poor melody perception but are supported by rhythm and lyrics. Without rhythm or lyrics, only about a third of those with implant can identify common melodies in a closed set. Correlations were found between the ability to perceive music and speech perception in noisy environments. Therefore, improving music perception may provide further clinical benefits (21).

MR was reported as the most challenging parameter of musical perception for patients with CI, as the melody's frequency range affected CI MR, with higher frequency ranges producing better performances (10). Also in our study, MR was the test that patients had the most difficulty with. However, 500 Hz free-field hearing thresholds of both pre- and post-music training showed significant correlation with MR. Higher frequency hearing thresholds with CI did not show significant relationship with MR.

Positive correlation was reported in the literature between low-frequency hearing and pitch recognition, while negative correlation was observed between high-frequency hearing and pitch recognition (24). Similarly, in our study, 500 Hz free-field hearing thresholds were positively correlated with 391 Hz PDD thresholds, and 2, 4, and 6 kHz free-field hearing thresholds were negatively correlated with 262 Hz PDD thresholds.

Table 7. The correlation coefficients between test parameters in controls

	Spearman's correlation coefficients	SDT	MCL	TURMatrix	PDD thresholds			PDD standard errors			TR	MR
					262 Hz	330 Hz	391 Hz	262 Hz	330 Hz	391 Hz		
Age	r	0.559*	0.559*	0.604**	-	-	-	-	-	-	-0.469*	-
	p	0.016	0.016	0.008	-	-	-	-	-	-	0.049	-
1000 Hz	r	0.494*	-	-	-	-	-	-	-	0.473*	-	-0.582*
	p	0.037	-	-	-	-	-	-	-	0.048	-	0.011
4000 Hz	r	-	-	-	-	-	-	-	0.528*	-	-	-0.520*
	p	-	-	-	-	-	-	-	0.024	-	-	0.027
6000 Hz	r	-	-	-	-	-	-	-	-	-	-0.494*	-
	p	-	-	-	-	-	-	-	-	-	0.037	-
8000 Hz	r	-	-	-	-	-	-	-	-	-	-0.588*	-
	p	-	-	-	-	-	-	-	-	-	0.01	-
SDT	r	1	-	-0.623*	-	-	-	-	-	-	-	-
	p	1	-	0.006	-	-	-	-	-	-	-	-
WRS	r	-	-	-0.496*	-	-	-	-	-	-	-	-
	p	-	-	0.036	-	-	-	-	-	-	-	-
MCL	r	-	1	0.623**	-	-	-	-	-	-	-	-
	p	-	1	0.006	-	-	-	-	-	-	-	-
TURMatrix	r	-	-	1	-	-	0.568*	-	-	0.508*	-	-
	p	-	-	1	-	-	0.014	-	-	0.031	-	-

*Moderate correlation, **Strong correlation, SDT: Speech detection thresholds, WRS: Word recognition scores, PDD: Pitch direction discrimination, TR: Timbre recognition, MR: Melody recognition, MCL: Most comfortable level, CI: Cochlear implant, TURMatrix: Turkish matrix test

It has been stated that PDD, MR, and TR were significantly associated with word recognition and speech perception in noise (2, 4, 7, 10, 25). In our study, WRS correlated with 330 Hz PDD thresholds and MR scores before the MPA. In addition, TURMatrix dBSNR thresholds also showed significant correlation with 330 and 391 Hz PDD standard errors and MR scores. Following MPA, WRS showed correlation with TR scores, and TURMatrix dBSNR thresholds showed significant correlation with 391Hz PDD thresholds, TR, and MR scores.

Gfeller et al. (10) reported weak correlation between hearing loss history and pitch perception but found that hearing loss and implant duration had a significant effect on speech perception. In their study, the authors found negative correlation between the duration of implant use and pitch perception, while in another study, Gfeller et al. (9) described a weak relationship between the duration of CI use and musical pitch perception. In contrast, Jung et al. (7) reported no relationship between age, the duration of deafness or CI use, and musical perception, whereas Drennan et al. (8) reported negative correlation between age and timbre and weak correlation between melody perception and CI use. In our study, the ages of patients showed significantly negative correlation with MR scores. Also, the duration before CI showed significantly negative correlation with MR scores. It is estimated that the short duration of hearing aid usage, and the cochlear implantation as early as possible, may positively affect the MR ability.

Lo et al. (26) found that while six weeks of melodic listening training improved pitch perception, temporal processing, and consonant recognition in quiet in CI users, such training did not change speech recognition in noise. Another study found that one month of audiobook and music listening training improved pitch and timbre perception in adult CI users (15). Petersen et al. (27) suggested that music education and music listening studies, when started in the early postoperative period, were effective in improving speech perception; however, this effect might also be related to implant adaptation. There are also studies reporting that consonant recognition and perception of prosody improved after music education, but speech recognition in noise were not affected (28). Our study included patients who had been using CI for at least one year to eliminate the adaptation factor. After three months of MPA, we found that the TR scores (p=0.019) had improved significantly. However, WRS in quiet and speech recognition in noise remained unchanged.

The potential of CI speech processing strategies to affect music perception has also been evaluated in the literature. For example, it has been shown that the harmonic single sideband encoder strategy had potential advantages over continuous interleaved sampling or similar strategies in conveying timbre cues to CI recipients by encoding

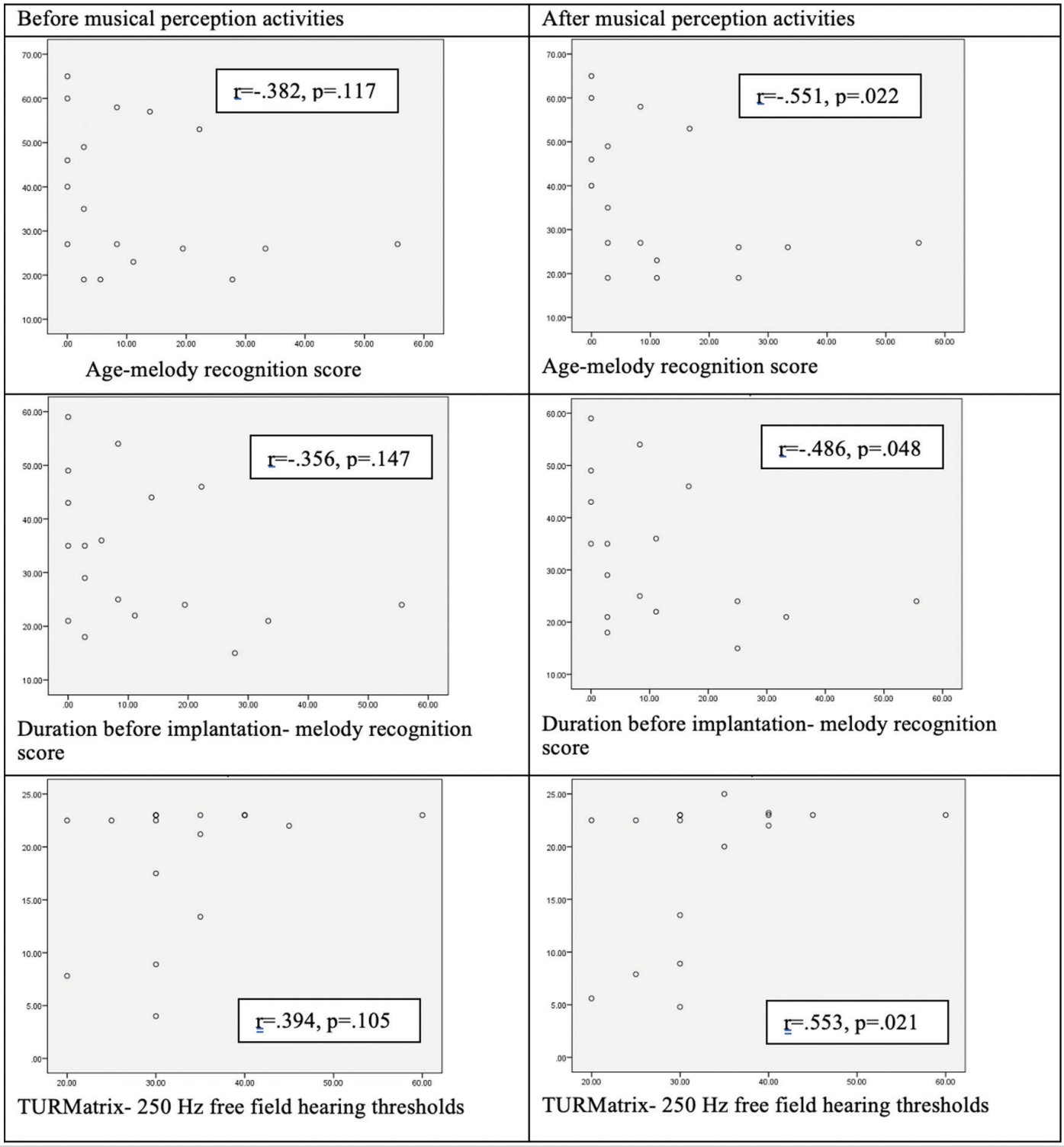

Figure 1. Parameters that present change in correlation before and after musical perception activities in the cochlear implant group
TURMatrix: Turkish matrix test

harmonic and temporal fine structure information (29). Further, Parkinson et al. (30) compared the MR and TR results of traditional electrical stimulus and electro-acoustic (hybrid) stimulus systems in CI recipients. Their results showed that hybrid system CI recipients performed better in MR, probably because of better low-frequency perception with acoustic stimuli. There were, however, no differences in the timbre discrimination test. Unfortunately, in our study, the sample size was insufficient to compare different speech processors or strategies.

The multiple regression analysis showed that the ability to perceive timbre, one of the clinical music perception parameters, affected speech recognition abilities in noise. This finding is not valid for the WRS in silence. This result strengthens the idea that music perception should be improved to increase speech recognition skills in CI users in their natural habitat.

The low number of subjects, the socio-cultural heterogeneity of the patients, the fact that patients living in a different city could not effectively continue their auditory rehabilitation programs after cochlear implantation, and that the patients, in general, did not have the habit of listening to music were the limitations of our study. In this study, MPA continued for three months. However, it is predicted that musical perceptional activities that started immediately after cochlear implantation and lasted longer could enable more significant changes in audiological evaluation parameters.

Conclusion

The inclusion of MPA to support an auditory rehabilitation program may contribute to increased speech recognition skills in noise. It is estimated that the increase in longitudinal studies evaluating musical perception in CI users would contribute to the literature.

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Göztepe Training and Research Hospital, Clinical Research Ethics Committee (date: 10.04.2018, decision no: 2018/0092).

Informed Consent: Written informed consent was obtained from all participants.

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Authorship Contributions

Concept: B.M., M.T.T., M.Y., M.T.K., Design: B.M., M.T.T., M.T.K., Data Collection and/or Processing: B.M., M.T.T., Analysis and/or Interpretation: B.M., M.T.T., Literature Search: B.M., M.T.T., M.Y., Writing: B.M., M.T.T., M.Y., M.T.K.

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Main Points

- The ability to speech recognition in noise increases as the ability to timbre recognition increases.
- The ability to speech recognition in noise improves as melody recognition improves.
- Melody recognition skills show negative relationship with age of patients.

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Appendix

1. https://www.youtube.com/watch?v=sJ_uiWLe4CE Arı Vız
2. https://www.youtube.com/watch?v=Dywhwm4Gstk Mutlu yıllar sana
3. https://www.youtube.com/watch?v=h_mokaAf6Nc&t=11s Benim annem güzel annem
4. https://www.youtube.com/watch?v=SbSaRT7x85I Yağmur yağıyor
5. https://www.youtube.com/watch?v=Fm-_tlLWv4A Dağ başını duman almış
6. https://www.youtube.com/watch?v=sJ4Ze3BcPk4 Baş parmağım neredesin
7. https://www.youtube.com/watch?v=njlgzg8nctM Bak postacı geliyor
8. https://www.youtube.com/watch?v=I5P4WCF5gWY Daha dün annemizin
9. https://www.youtube.com/watch?v=zfUEAK9tJ0M Mini bir kuş
10. https://www.youtube.com/watch?v=MnCQyemsFPA Küçük kurbağa
11. https://www.youtube.com/watch?v=kaGYK9RCfoI Kırmızı balık
11. https://www.youtube.com/watch?v=7WYDeCdIRQ8 Baltalar elimizde

Investigation of the Relationship Between BPPV with Anxiety, Sleep Quality and Falls

Original Investigation

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Abstract

Objective: To investigate the effects of dizziness on sleep quality and psychological status in patients with benign paroxysmal positional vertigo (BPPV) and to evaluate its relationship with falls.

Methods: A Demographic Data Form, a Visual Vertigo Analog Scale, the Falls Efficacy Scale - International (FES-I), the Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Index (PSQI) were administered in 102 individuals diagnosed with BPPV by videonystagmography test. The same scales were applied to 75 healthy volunteers as the control group, and the two groups were compared. The BPPV group was divided into two groups as posterior canal and lateral canal BPPV. These two groups were compared among themselves and with the control group.

Results: A statistically significant difference was found between the BPPV and control groups, the lateral canal BPPV and posterior canal BPPV groups, the lateral canal BPPV and control groups, and the posterior canal BPPV and control groups in terms of total scores of the PSQI, the FES-I, and the HADS ($p<0.001$). In the regression model, the FES-I score was fully explained by the PSQI and HADS scores ($p<0.001$).

Conclusion: BPPV significantly affects sleep quality, psychological state, and the risk of fall. The negative effects of BPPV restrict daily living activities, affect the prognosis of the disease, and increase the risk of falling. Considering that psychiatric issues and sleep problems increase the risk of falling in individuals with BPPV, counseling services on this issue would reduce the incidence of falls and related injuries.

Keywords: Benign paroxysmal positional vertigo, anxiety, sleep quality, falls

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Introduction

Dizziness caused by changes in head position was defined by Barany (1) as a syndrome of acute onset and short duration. It was named as benign paroxysmal positional vertigo (BPPV) by Dix and Hallpike (2). BPPV is a sudden-onset, short-term, peripheral vestibular

disease triggered by angular changes in head position relative to gravity, and it is characterized by rotational dizziness and positional nystagmus. BPPV occurs due to the movement of otoconia detached from the utricular macula into the semicircular canals (SSCs) (3). BPPV is seen as canalithiasis, cupulolithiasis, or rarely as canalithiasis jam. According to the canalithiasis theory, otoliths float in SSCs, whereas according to the cupulolithiasis theory, otoliths are attached to the cupula. Canalithiasis occurs when otoliths are rarely blocked in the canal or cupula. While nystagmus is observed in the SSC plane, which is affected by otoliths, it causes severe dizziness that limits the daily living activities of individuals (4). The separation mechanism of otoconia from the macula is usually idiopathic. In addition, head trauma, Meniere's disease, post-operative vestibular neuronitis, sudden sensorineural hearing loss, and migraine are among the secondary causes of BPPV (5).

BPPV is the most common cause of dizziness with a lifetime prevalence of 2.4%. Its prevalence is higher in women than in men, and its incidence increases with age (6). Dizziness due to BPPV is usually triggered when the patient is getting in/out of bed, turning right/left in bed, or tilting the head back or forward (3). Dizziness caused by BPPV and occurring with the angular changes of the head negatively affects the sleep quality (7), triggers anxiety and depression (8), and increases the risk of falls, especially in older individuals (9). Dizziness experienced by BPPV patients due to the angular changes of the head during sleep may awake the patient (3). Wang et al. (7) conducted a study in recurrent BPPV patients and reported that sleep quality was low, and low sleep quality was an independent factor causing BPPV. Kim et al. (10) reported that the sleep quality of individuals with vertigo was negatively affected. Ertugrul and Soylemez (11) reported that the sleep quality of BPPV patients was lower than the healthy controls. In studies evaluating the psychological state of patients with dizziness and imbalance, it has been observed that there is a significant relationship between dizziness and anxiety and depression. Ferrari et al. (8) reported that anxiety and depression are common in BPPV patients, and that psychological problems are more common in female BPPV patients. Dizziness increases the risk of falling, especially in the elderly. Fall-related accidents may cause serious injury and death (9). The aim of this study was to investigate the effects of dizziness in BPPV on sleep quality and psychological state of the patients and to evaluate its relationship with falls.

Methods

Research Design

In this study, a prospective cross-sectional analytical study design was used to obtain information about the relationship between BPPV with anxiety, sleep quality and falling.

Participants

The study was carried out prospectively between February 2021 and July 2021 at the Audiology Unit of the Department of Otorhinolaryngology, İnönü University Turgut Özal Medical Center. The sample of this study was calculated via a power analysis. According to the calculation made using the G*power 3.1 program, the sample size was determined as 176, with an effect size of 0.50, a margin of error of 0.05, a confidence level of 0.95, and a population representation of 0.95 (12). The study group consisted of 102 people who were diagnosed with BPPV by the Dix-Hallpike and Head Roll tests on the Videonystagmography device. The study also included 75 healthy controls. The study group was divided into 4 groups as lateral canal canalolithiasis (n=29), lateral canal cupulolithiasis (n=22), posterior canal canalolithiasis (n=30), and posterior canal cupulolithiasis (n=21). One hundred and two patients with a history of BPPV attack and 75 healthy individuals were included in the study. Exclusion criteria were the presence of communication barrier, chronic disease, previously diagnosed balance problems, and other otological-neurootological diseases. To exclude other vestibular system pathologies, spontaneous nystagmus, cerebellar tests, and walking tests were performed after taking a detailed anamnesis. The Visual Vertigo Analog Scale (VVAS) was used to evaluate the severity of dizziness in patients with diagnosed BPPV before the reposition maneuver. Then, the Demographic Data Form, the Falls Efficacy Scale- International (FES-I), the Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Index (PSQI) were administered face-to-face.

Data Collection Tools

Falls Efficacy Scale- International

It is a self-report scale about the level of anxiety about falling during activities of daily living. The scale consists of 16 questions. The total score ranges from 16–64. The cut-off point for the Turkish version of the scale was determined as 24 (13).

Hospital Anxiety and Depression Scale

It was developed to evaluate anxiety and depression in patients. The scale is used not to diagnose, but to quickly identify anxiety and depression in patients with physical illnesses and in those presented to primary health care. The scale includes a total of 14 items: Seven items about anxiety (odd-numbered questions) and seven items about depression (even-numbered questions). Responses are scored on a four-point Likert scale between zero and three. The lowest score that patients can get from each subscale is zero, and the highest score is 21. The cut-off points of the Turkish version of the scale were determined as 10 for the anxiety subscale and seven for the depression subscale (14).

Pittsburgh Sleep Quality Index

It was developed to evaluate the sleep quality and disorder of patients in the last month. The scale consists of 24 items, of which 19 are self-report questions and five are questions that partners/roommates answer based on their observations. The total score ranges from zero to 21. A total score greater than five indicates "poor sleep quality" (15).

Statistical Analysis

Data analysis was made with the SPSS (Statistical Program in Social Sciences) 25. The Kolmogorov–Smirnov test was used to check whether the data included in the study fit the normal distribution. The significance level (p) for comparison tests was set as 0.05. Since the data showed normal distribution, a significance test (t-test) and the ANOVA test were used for the difference between two means. To determine the groups with difference as a result of the ANOVA test, the Duncan's multiple comparison (post-hoc) test was used because homogeneity of variance was established. The Cronbach α coefficient was used to conduct the reliability analysis of the scales. Multicollinearity [variance inflation values (VIF)] Analysis was performed to ensure that there was no relationship between independent variables (factor sub-dimensions). Multivariate regression analysis was used to explain the relationships between a dependent variable and two or more independent variables with a mathematical equation. Since the variables included in the study showed normal distribution, the Spearman–Pearson correlation coefficient was used.

Ethical Principles

The approval for the study was obtained from the İnönü University Health Sciences Institute's Non-Interventional Clinical Research Ethics Committee (decision number: 2021/1458, date: 05.01.2021) and consent was obtained from all patients participating in the study.

Results

A total of 177 participants were included in the study: 29 (14.4%) in the lateral canal canalithiasis group, 22 (12.4%) in the lateral canal cupulolithiasis group, 30 (16.9%) in the posterior canal canalithiasis group, and 21 (11.9%) were in the posterior canal cupulolithiasis group, and 75 (42.4%) were in the control group. There was no statistically significant difference between the groups according to age and gender of the participants (p=0.211, p=0.242). A statistically significant difference was found between the groups according to VAS scores (p=0.001) (Table 1).

A statistically significant difference was found between the patient and control groups according to the total scores of the PSQI, HADS, and FES-I scales (p<0.001, Table 2).

A statistically significant difference was found between the lateral canal BPPV, posterior canal BPPV, and control groups according to the total scores of the PSQI, HADS, and FES-I scales (p<0.001, Table 3). The Duncan Multiple Comparison test was performed, as the variance homogeneity condition was met, to determine which groups differed in all scores. As a result of the test, a significant difference was found in the total scores of the PSQI, FES-I, and depression between the lateral and posterior canal BPPV, between the lateral canal BPPV and the control group, and between the posterior canal BPPV and the control group (p<0.001). Also, a statistically significant difference was found between the lateral canal BPPV and the control group, and between the posterior canal BPPV and the control group in the total scores of the anxiety (p<0.001). However, no statistically

Table 1. Distribution of demographic variables between groups

Variables			Lateral canal canalolithiasis	Lateral canal cupulolithiasis[2]	Posterior canal canalolithiasis[3]	Posterior canal cupulolithiasis[4]	Control group[5]	Total	χ^2 value
Sex	Female	n	20	15	18	12	36	101	0.242[a]
		%	69.0%	68.2%	60.0%	57.1%	48.0%	57.1%	
	Male	n	9	7	12	9	39	76	
		%	31.0%	31.8%	40.0%	42.9%	52.0%	42.9%	
Total %		n	29	22	30	21	75	177	
		%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
Variables			**Lateral canal canalolithiasis [1]**	**Lateral canal cupulolithiasis [2]**	**Posterior canal canalolithiasis [3]**	**Posterior canal cupulolithiasis [4]**	**Control group [5]**		**p-value**
Age	Mean ± SD		45.66±11.04	46.64±14.32	45.23±12.69	40.14±11.24	38.92±10.15		0.211
	M (min-max)		47 (25–71)	45.5 (23–74)	44 (25–77)	40 (20–58)	39 (19–58)		
VAS	Mean ± SD		7.86±1.53	9±1.63	8.27±1.78	8.52±1.17	0±0		0.001[b*] (1–2, 1–5, 2–5, 3–5, 4–5)
	M (min-max)		8 (5–10)	10 (5–10)	8.5 (3–10)	9 (6–10)	0 (0–0)		

n: Number, %: Percentage, SD: Standard deviation, M: Median, [a]: χ^2 test p-value, [b]: Kruskal–Wallis test p-value, *p<0.05; there is a statistically significant difference between groups
[1]Lateral canal canalolithiasis, [2]Lateral canal cupulolithiasis, [3]Posterior canal canalolithiasis, [4]Posterior canal cupulolithiasis, [5]Control group

Table 2. Comparison of patient and control groups according to total scores obtained from the scales

Scales/ dimensions	Group	Mean ± SD	Test value	p-value
PSQI	Patient	11.81±4.93	16.564	<0.001*
	Control	3.59±0.77		
Depression	Patient	8.6±4.38	19.557	<0.001*
	Control	0.09±0.29		
Anxiety	Patient	11.3±4.67	24.082	<0.001*
	Control	0.12±0.37		
FES-I	Patient	40.63±11.45	34.969	<0.001*
	Control	0.75±1.09		
VVAS	Patient	8.36±1.59	-	-
	Control	0±0	45.317[a]	<0.001*

PSQI: Pittsburgh Sleep Quality Index, Falls Efficacy Scale- International (FES-I), VVAS: Visual Vertigo Analog Scale, SD: Standard deviation, [a]Significance test (t-test) value of the difference between two means, *p<0.05 there is a statistically significant difference between groups

Table 3. Comparison of lateral, posterior, and control groups according to total scores obtained from the scales

Scales/ dimensions	Group	Mean ± SD	Test value	p-value
PSQI	Lateral	13.8±4.93	137,954	<0.001*
	Posterior	9.82±4.1		
	Control	3.59±0.77		
Depression	Lateral	9.63±4.45	153,357	<0.001*
	Posterior	7.57±4.09		
	Control	0.09±0.29		
Anxiety	Lateral	12.12±4.71	221,905	<0.001*
	Posterior	10.49±4.53		
	Control	0.12±0.37		
FES-I	Lateral	43.94±10.93	498,026	<0.001*
	Posterior	37.31±11.08		
	Control	0.75±1.09		
VVAS	Lateral	8.35±1.66	1020,97[b]	<0.001*
	Posterior	8.37±1.55		
	Control	0±0		

PSQI: Pittsburgh Sleep Quality Index, Falls Efficacy Scale- International (FES-I), VVAS: Visual Vertigo Analog Scale, SD: Standard deviation, [b]ANOVA test F-value, *p<0.05 there is a statistically significant difference between groups

significant difference was found between lateral canal BPPV and posterior canal BPPV (p>0.05).

In both patient and control groups, multiple linear regression analysis was performed in the model in which the FES-I score was the dependent variable, and the PSQI, depression, and anxiety scores were independent variables. Analysis was continued as there was no multicollinearity between independent variables (VIF <10, Table 4). Analysis results are given in Table 4.

For the patient group, the model established to test that the FES-I score, which is the dependent variable, is explained by the independent variables PSQI, Depression, and Anxiety scores was found to be significant as a whole (F=12.729, p_2<0.001, Table 4). It was calculated that 25.8% (R^2= 0.258) of the participants' FES-I scores were explained by their PSQI and anxiety scores.

In the multiple linear regression model created for the study, PSQI and anxiety scores, independent variables scores, and the coefficient were found to have a statistically significant effect on the fall scale score (p_1=0.004, p_1=0.035, p_1=0.001, Table 4). A 1-unit change in the PSQI score results in a positive 0.619-unit (β_1) change on the total FES-I score; and, a 1-unit change in the anxiety score causes a positive 0.615-unit (1) change on the total FES-I score. The effect of the PSQI score on the FES-I score is greater than the anxiety score. It was determined that the depression score did not have a statistically significant effect on the FES-I score (p_1=0.169, Table 4).

For the control group, the model established to test that the dependent variable FES-I score was explained by the independent variables PSQI, depression, and anxiety scores was not found to be significant as a whole (F=1.823, p_2=151, Table 4). In the control group, the FES-I score was not statistically explained by the PSQI, depression, and anxiety scores.

Discussion

Dizziness caused by BPPV due to the angular changes of the head negatively affects sleep quality (7, 10), triggers anxiety and depression (8), and increases the risk of falling, especially in elderly individuals (9). The aim of this study was to investigate the effects of dizziness occurring in BPPV on sleep quality and psychological status of patients and to evaluate its relationship with falls.

An analysis of the demographic data of the patient group showed that, similar to the literature, the mean age was approximately between 45 and 50 years, and female patients were more than male patients (16). Ogun et al. (17) stated that BPPV is more common in women due to hormonal fluctuations associated with menopause and low estrogen levels.

In the present study, the VVAS scores, by which dizziness was assessed, were statistically higher in the patient group. In addition, the lateral canal cupulolithiasis score of the patient group was higher than that of the lateral canal canalithiasis score, and the posterior canal cupulolithiasis score was also higher than the posterior canal canalithiasis score. The higher VVAS scores of the patients with cupulolithiasis than those with canalithiasis were attributed to the longer duration of nystagmus and dizziness (18).

Table 4. Results of multiple linear regression modeling of the relationship between FES-I and PSQI, depression, and anxiety scores

Group	Variables		β_1	t-test	p_1-value	R^2	F-test	p_2-value
Patient	Fall	Coefficient	22.651	**7.226**	**0.001***	0.258	12.729	**<0.001****
		PSQI	0.619	**2.947**	**0.004***			
		Depression	0.433	1.384	0.169			
		Anxiety	0.615	**2.138**	**0.035***			
Control	Fall	Coefficient	1.877	3.016	0.004	0.032	1.823	0.151
		PSQI	-0.299	-1.806	0.075			
		Depression	0.149	0.346	0.731			
		Anxiety	-0.592	-1.688	0.096			

PSQI: Pittsburgh Sleep Quality Index, Falls Efficacy Scale- International (FES-I), dependent variable: fall score; Independent variables: PSQI, Depression and Anxiety scores; β_1: non-standardized regression coefficients; *p_1<0.05: t-test result for the significance of the regression coefficients; VIF: Variance inflation values; R^2: Explanatory coefficient; **p_2<0.05: F-test result for the significance of the model

It is stated that vestibular dysfunction may cause many emotional disorders. It is particularly associated with particular emotional disorders such as anxiety and depression (8). Contrary to this approach, there are also opinions that emotional disorders may cause balance disorders (19). In addition, psychological factors may negatively affect the treatment of balance disorders and delay the process (20). In a study in which patients with BPPV were examined psychologically, it was stated that 40.94% of the patients had anxiety symptoms, 41.73% had depression symptoms, and 33.07% had both symptoms (21). Additionally, Ferrari et al. (8) reported mild to moderate depression in 21.7% of the BPPV patients, and Magliulo et al. (22) reported that 29.2% of the BPPV patients had clinical anxiety. In the present study, the statistically higher scores of the patient group on anxiety and depression scales compared to the control group supports the relationship between dizziness and emotional disorders. It is stated that there are important connections between neuroanatomical regions and neurotransmitters in the vestibular system and pathways associated with emotional states (23). In addition, there are functional connections between the anatomical and neurovestibular system and the structures involved in the pathogenesis of panic disorder. These links support the relationship between vestibular disorders and some psychiatric disorders (24).

Most patients with BPPV experience severe dizziness when lying down, turning in bed, and getting out of bed (25). Patients may experience stress due to vertigo attacks occurring with postural changes while lying in bed. Stress makes it difficult to fall asleep and stay asleep, causing insomnia. In the literature, it is noted that head positions during sleep are associated with BPPV and that inappropriate head positions may trigger sleep disorders. It was reported that there was a higher rate of recurrence in patients who slept in a position towards the affected side in the treated patient group after the reposition maneuver (26). Although there are many studies examining the relationship between BPPV and sleep position, there are limited studies examining the relationship between BPPV and sleep quality (11). Wang et al. (7) found that the sleep quality of patients with recurrent BPPV was worse than those with non-recurrent BPPV. Korres et al. (25) reported that there was a correlation between dizziness and sleep quality in 75.9% of the patients with BPPV. Ertugrul and Soylemez (11) also stated that the sleep quality of the patients with BPPV was significantly worse than that of healthy individuals (11). In our study, the fact that the sleep quality of the patients with BPPV was worse than that of healthy individuals and that their quality of life was negatively affected, which is similar to the literature.

Accidents and environmental factors are among the most common causes of falls, which are followed by dizziness, balance disorder, and mobility difficulties. Vestibular pathologies that may cause dizziness and balance disorders significantly increase the risk of falling (27). The unpredictability and physical symptoms of vertigo attacks significantly limit the movements of individuals during activities of daily living. BPPV patients in particular are frequently exposed to unpredictable and sudden-onset dizziness. Therefore, during symptomatic attacks, most patients avoid daily activities such as going out alone, doing housework, and driving (28). Balatsouras et al. (29) stated that BPPV increases the risk of falls and related injuries in the elderly. It is also stated that the prevalence of falls is 78% in elderly patients with BPPV, and 32%–42% of patients over the age of 70 experience fall at least once a year (30). The elderly make restrictions in their routine daily activities due to their tendency to fall (29). Choosing a sedentary lifestyle or avoiding movement as much as possible in their daily lives seriously affects the treatment process and quality of life. von Brevern et al. (6) stated that 86% of the patients with BPPV restricted their daily activities. Denkinger et al. (31) also highlighted that patients with BPPV may experience falls due to head movement or unpredictable dizziness, and injuries related to these falls. Based on the present results, the risk of falling in patients with BPPV is higher than that of healthy individuals, which is similar to the literature. In

addition, patients with vertigo had a lower walking speed than healthy individuals. The reason for this may be the fear of falling, which slows them down to prevent accidents.

In the present study, the PSQI, FES-I, and depression scale scores of the patients with lateral canal BPPV were higher than those with posterior canal BPPV and the control groups. More stimulation of the lateral SSC plane during head movements in the lying position shows that they experience vertigo attacks more frequently and their quality of life is more adversely affected. We think that these findings may be related to the worse subjective evaluations of the patients with lateral canal BPPV compared to posterior canal BPPV and control groups.

The multiple linear regression analysis model performed in our study shows that insomnia and anxiety increase the risk of falling. Examining the relationship between insomnia, psychiatric problems, and falls in patients with BPPV is important regarding the prognosis of the disease and the risk of fall. In the literature, it is noted that patients with recurrent BPPV have more psychiatric problems and that these psychiatric problems may also affect sleep (7). It is also stated that sleep disorder may cause various psychiatric and physical health problems (32). There are also studies showing that sleep disorders may cause vestibular problems (7). In addition, it is stated that the quality of life of patients with BPPV improves after treatment. Similar to our study, Sklare et al. (33) stated that when acute and episodic vertigo attacks are accompanied by emotional disorders, the fear of fall may increase and cause panic attacks. Consistent with the findings of our study, the relationship between emotional disorders and fall is highlighted. An increase in balance loss is observed as BPPV brings along psychiatric problems and insomnia. Therefore, the risk of falling increases depending on these factors.

Conclusion

Evaluation of patients with BPPV in terms of psychiatric problems, insomnia, and falls provides important information about both the immediate effect of the disease and its prognosis. Evaluation of patients in terms of psychiatric and sleep disorders is also important regarding their treatment, as it will affect the prognosis of BPPV and risk of falling. Identifying patients experiencing these problems and directing them to the psychiatry outpatient clinics will contribute to the prognosis of the disease. In addition, considering that psychiatric problems and sleep problems increase the risk of falling, we think that counseling on this subject will reduce the rates of falls and related injuries.

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Main Points

- Benign paroxysmal positional vertigo (BPPV) negatively affects the sleep quality of patients.
- There is a relationship between BPPV and psychological disorders.
- BPPV increases the risk of falling.
- Variations of BPPV affect differently sleep quality, anxiety, depression, and the risk of falling.

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The Importance of Prostate-Specific Membrane Antigen Expression in Salivary Gland Tumors

Original Investigation

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Objective: Prostate-specific membrane antigen (PSMA) is a cell membrane protein expressed by prostate tissues. It is not prostate specific and is also expressed by some non-prostatic solid neoplasms. Our study aimed to investigate the potential role of PSMA in salivary gland tumors.

Methods: The present study was designed to retrospectively analyze our cases that presented with salivary gland tumors. The files of 105 patients were reviewed and their paraffin embedded blocks were retrieved from the pathology department. Immunohistochemical examination and staining were done using PSMA antibody. Tumor tissue PSMA immunohistochemical staining was scored semi-quantitatively with the modified quartile approach. Negative staining was scored 0, >0% and ≤25% tissue expression was considered weak (score 1), >25% and ≤50% tissue expression was considered mild (score 2), >50% and ≤75% tissue expression was considered moderate (score 3), and >75% tissue expression was considered strong (score 4).

Results: Eighty-eight patients (55 males, 33 females) were included in the study. Forty-eight patients had pleomorphic adenoma (PA), 35 had Warthin's tumor (WT), two had mucoepidermoid carcinoma, two had adenoid cystic carcinoma, and one had squamous cell carcinoma. There was statistically significant difference in terms of PSMA expression between PA and WT (p=0.003). PSMA expression was high in PA and absent in WT.

Conclusion: PSMA is a potential source of inspiration for future studies on the development of novel diagnostic and theranostic investigations of salivary gland tumors. Prospective studies targeting intratumoral PSMA in salivary gland tumors should be planned.

Keywords: Prostate-specific membrane antigen, immunohistochemistry, salivary glands, pleomorphic adenoma

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Introduction

Prostate-specific membrane antigen (PSMA) is a cell membrane protein expressed by prostate cells. However, PSMA can also be physiologically expressed by other cells such as the small intestinal, renal tubular, salivary glands, and astrocytes (1, 2). PSMA is significantly overexpressed in prostate cancer but is also expressed in the neo-vasculature of certain non-prostatic solid tumors (1, 3). Klein Nulent et al. (4) reported that adenoid cystic carcinoma (AdCC) of the head and neck salivary gland showed PSMA expression on immunohistochemistry. PSMA overexpression may have important implications for PSMA targeted imaging and new potential for non-invasive therapy strategies.

The primary treatment for salivary gland tumors is surgery. However, some benign and malignant salivary gland tumors have the potential for local recurrence. Treatment of these recurrent neoplasms are challenging. Especially, there is no standard treatment for the local recurrence of pleomorphic adenoma (PA). Another challenge in surgical treatment is that the operation can be risky due to senility and comorbid diseases in some patients (5).

Expressions of new molecules can pave the way to new imaging and/or treatment modalities. In this way, PSMA seems to be a promising and distinctive target for this purpose. In our study, we analyzed PSMA staining pattern in salivary gland tumors.

Methods

One-hundred-and-five patients that were operated on for salivary gland tumors in our clinic between January 2010 and January 2021 were analyzed. The paraffin blocks of 88 out of the 105 patients were suitable for PSMA staining and immunohistochemical examination. The Clinical Research Ethics Committee of the Süleyman Demirel University Faculty of Medicine approved our study protocol (decision no: 18/254, approval date: 11.09.2020). Informed consent was not obtained from the individuals since the study was designed retrospectively.

After the records of all patients' files were reviewed and the paraffin embedded blocks were acquired from the pathology department, immunohistochemical examination and staining were done using PSMA antibody.

Tissue Samples

All formalin-fixed paraffin blocks were sectioned in 4-5 µm and Hematoxylin-Eosin-stained slides obtained from the archive were re-read to visualize gross morphology. Appropriate blocks were selected as the tissue block most representative of the tumor. All cases were signed out according to the 4th Edition of the World Health Organization Classification of Head and Neck Tumours (5). Reporting was performed according to the protocol for the examination of specimens from patients with carcinomas of the major salivary glands of The College of American Pathologists which comprises the 8th edition TNM Classification System of the American Joint Committee on Cancer (6).

Immunohistochemistry Applications

A clinically validated PSMA antibody was applied to the blocks representing tumor morphology. PSMA antibody was prepared according to the instructions of the manufacturer, as shown in the datasheet. We used the automatized sample preparation and staining system Dako Omnis. The tissue samples were cut from the formalin-fixed paraffin-embedded blocks and transferred to 4-µm thickness adhesive-coated slides that were assembled with prostate tissue samples as the control positive antibody. For antigen retrieval, tissues were incubated with Envision-FLEX (Carpinteria, CA, USA), high PH solution for 30 minutes at 97 °C and then rinsed with wash buffer for two minutes. After the antigen retrieval step, PSMA antibody incubation was performed for 20 minutes. Then the slides were rinsed with wash buffer for two minutes. Subsequently, Envision-FLEX peroxidase-blocking solution was applied for three minutes; then the slides were again rinsed for two minutes. Before the 20-minute Envision-FLEX/HRP incubation step, slides were incubated with Envision-FLEX mouse linker for crisped staining for 10 minutes, followed by two times two minutes washing steps. Envision substrate working solution was incubated as chromogen for five minutes, and the 2-minute washing cycle was done two times. Finally, hematoxylin was applied for counterstaining for three minutes.

Immunohistochemical Staining

The slides were blindly interpreted by one pathologist experienced in surgical pathology. The slides were examined under a light microscope, and the case was accepted as positive for any cytoplasmic staining and membrane staining. PSMA immunohistochemical stained slides were scored for the percentage of positive tumor cells (4).

The non-tumoral tissue around the tumor showed a diffusely positive and faint reaction therefore these areas (expression between 1-10%) were scored as negative (score 0). Tumor tissue PSMA immunohistochemical staining was scored semi-quantitatively with the modified quartile approach (7, 8). Negative staining was scored 0, >0% and ≤25% tissue expression was considered weak (score 1), >25 and ≤50% tissue expression was considered mild (score 2), >50 and ≤75% tissue expression was considered moderate (score 3), and >75% tissue expression was considered strong (score 4). The immunohistochemical staining intensity of tumor epithelium was gradually increased from score 1 to score 4 (Figure 1).

Statistical Analysis

The data were transferred to SPSS v.23.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Prior to analysis, controls were made to see whether there were any data entry errors and whether the parameters were within the expected range. Normality assumptions of continuous variables were examined with the Shapiro-Wilk test. Mean and standard deviation were given in the descriptive statistics of continuous variables, and frequency (n) and percentage (%) values were given in the definition of categorical variables. In the comparisons of three or more groups, the Kruskal-Wallis test was used when the data did not show normal distribution. Relationships between categorical variables were examined with the chi-square test, and $p<0.05$ was accepted as the level of significance in all analyses.

Results

Eighty-eight patients (55 males, 33 females) were included in this study. The ages of patients ranged from 13 to 82 years (mean, 49.50±16.77 years). Forty-eight patients had PA, 35 had Warthin's tumor (WT), two had mucoepidermoid carcinoma (MEC), two had AdCC, and one had squamous cell carcinoma (SCC). Gender, tumor side, type of surgery, and local recurrence data of the patients are shown in Table 1. PSMA expression in tumor epithelium is shown in Table 2. There was statistically significant difference in PSMA expression between PA and WT (p=0.003). We observed that PSMA expression was higher in PA than in other tumors (Table 1). There was no PSMA expression in the tumor epithelium of WT. Local recurrence was detected in three patients with PA and in one patient with AdCC. PSMA expression was score 1 in one of the three patients with recurrent PA and score 2 in the other two. There were no differences between the PSMA expression of these three patients and the non-recurrent 45 patients. There was no statistically significant relationship between PSMA and local recurrence (p=0.193).

Discussion

PSMA is a potential and promising molecule that can be used in the imaging and staging of some malignant tumors, the molecular characterization of tumors, the molecular

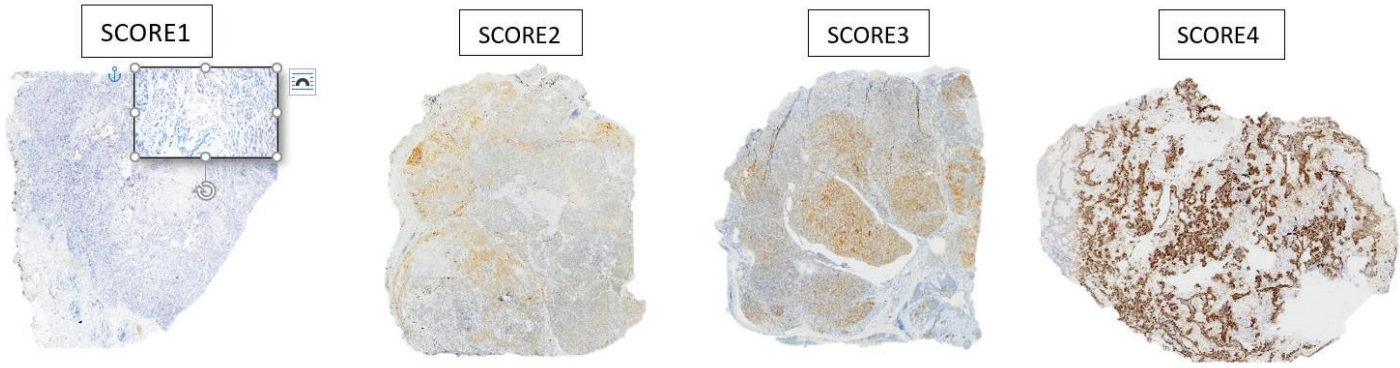

Figure 1. Tissue PSMA expression pattern as depicted
PSMA: Prostate-specific membrane antigen

Table 1. Gender, tumor side, type of surgery, and local recurrence data of the patients

		PA	WT	MEC	SCC	AdCC	
				n (%)			p-value
Gender	Male	23 (26.1)	31 (35.2)	0 (0.0)	0 (0.0)	1 (1.1)	**<0.001**
	Female	25 (28.4)	4 (4.5)	2 (2.3)	1 (1.1)	1 (1.1)	
Side	Right	28 (31.8)	13 (14.8)	2 (2.3)	1 (1.1)	0 (0.0)	0.150
	Left	20 (22.7)	21 (23.9)	0 (0.0)	0 (0.0)	2 (2.3)	
	Bilateral	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Surgery	Superficial	42 (47.7)	35 (39.8)	0 (0.0)	0 (0.0)	0 (0.0)	**<0.001**
	Total	4 (4.5)	0 (0.0)	2 (2.3)	1 (1.1)	2 (2.3)	
	Submandibular gland excision	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Recurrence	No	45 (51.1)	35 (39.8)	2 (2.3)	1 (1.1)	1 (1.1)	0.12
	Yes	3 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	

AdCC: Adenoid cystic carcinoma, MEC: Mucoepidermoid carcinoma, n: Number of patients, PA: Pleomorphic adenoma, SCC: Squamous cell carcinoma, WT: Warthin's tumor

Table 2. PSMA expression scores of the patients in tumor epithelium

		PA	WT	MEC	SCC	AdCC	
				n (%)			p-value
Expression	Negative	7 (8.0)	35 (39.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.003*
	Score 1	10 (11.4)	0 (0.0)	2 (2.3)	1 (1.1)	1 (1.1)	
	Score 2	17 (19.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Score 3	13 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Score 4	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	

AdCC: Adenoid cystic carcinoma, MEC: Mucoepidermoid carcinoma, n: Number of patients, PA: Pleomorphic adenoma, SCC: Squamous cell carcinoma, WT: Warthin's tumor, PSMA: Prostate-specific membrane antigen

*Statistically significant difference between Warthin's tumor and Pleomorfic adenoma.

characterization of neovascularization and PSMA-targeted radioligand therapy (2). Positron emission tomography (PET) imaging and targeted radioligand therapies with PSMA ligands are widely used in prostate cancer. However, PSMA is not specific to the prostate tissue or prostate cancer. PSMA overexpression has also been detected in some malignancies other than prostate cancer (1, 3). This entity gives PSMA a promising and important role for targeted imaging and new treatment strategies for other malignancies.

Klein Nulent et al. (4) analyzed the value of PSMA-11-PET/computed tomography (CT) for AdCC of the salivary gland in nine patients. They concluded that PSMA PET/CT was able to detect and visualize local recurrent and distant metastatic AdCC. PSMA imaging of neoplasms other than prostate cancer generally originates from the neovascular tissues, but the authors observed that AdCC cells expressed PSMA. They also found that both PSMA PET/CT and immunohistochemistry were positive in all patients' tumor tissues (4).

Although PSMA expression is detected in some non-prostatic tumors and salivary glands (physiologically), there are few studies that investigated PSMA in salivary gland tumors other than AdCC (1, 3). In our study we investigated 88 patients with different salivary gland tumors. Forty-eight patients had PA, 35 had WT, two had MEC, two had AdCC, and one had SCC; and the difference in PSMA expression was statistically significant among the tumor types. We observed that PSMA expression was higher in PA than in other tumors. WT had no PSMA expression in tumor cells. Grade 1 expression was detected in all MEC and SCC specimens. One specimen had Grade 1 and one had Grade 4 PSMA expression in AdCC (Table 1).

Salivary gland tumors are rare neoplasms of the head and neck and are commonly found in the parotid gland. The primary treatment for these tumors is surgery. However, some benign and malignant salivary gland neoplasms have the potential for local recurrence. Treatment of these recurrent salivary gland tumors is also very challenging. Another problem for surgical treatment is that the operation can be risky due to senility and comorbid diseases in some patients. In PSMA-PET using current 68Ga- and 18F-tracers, salivary glands are the second organ with the strongest tracer accumulation (9). Reliable with the comparable distribution of therapeutic PSMA radioligands as 177Lu-PSMA-617, salivary glands are exposed to the most elevated dosages and are considered the basic organs in PSMA radionuclide treatment (10). Exposure to high dose makes salivary gland tumors a very suitable potential treatment target for radioligand therapy. It can be predicted that this targeted therapy will be even more effective in tumors with high PSMA expression. In most tumors PSMA is found within the tumor-associated endothelium, and not on cancer cell membrane. This may lead to an enlarged interval between the radiation emitter and the tumor cell that would likely reduce the possibility of an emitted electron to influence a neoplastic cell (11). But we observed that in PA, MEC, AdCC and SCC PSMA was detected on the cell membrane. Therefore, the possibility of reduced influence of radiation due to enlarged interval between the radiation emitter and the tumor cell did not exist in PSMA positive tumors in our study. We believe that, because of these properties, salivary gland tumors would be quite suitable for PSMA-targeted radioligand therapies.

PA is the most common salivary gland neoplasm. Although a benign neoplasm, it has a potential for malignant transformation, and its rates for transformation were reported between one and 23% (12). PA has a tendency for local recurrence, with rates ranging from two to 45% (13). There is no standard treatment for recurrent PA. Treatment options are re-excision and radiotherapy. They both have disadvantages and side effects. With repeated excision, further recurrence rates have increased up to 50% and the risk of morbidity, especially facial nerve dysfunction, is also increased (14). In addition, the scar tissue that develops with repeated surgeries makes the dissection of the tumor more difficult. Thus, the possibility of facial nerve injury increases. Radiotherapy may have negative impact on the recovery of facial nerve injury and increase the risk of malignant transformation and secondary malignancies (15). In our study, we observed that PSMA expression was high in PA. We believe that this may open a window of opportunity for a new treatment strategy (radioligand therapy) for PA.

In a study by Nishida et al. (16) on the immunohistochemical reactivity of PSMA in salivary gland tumors the researchers performed immunohistochemistry for PSMA in 55 salivary gland tumors comprising 10 PAs, 10 WTs, nine basal cell adenomas, nine AdCCs, nine MECs, and eight salivary duct carcinomas. They found that 87% of the tumors were PSMA-positive. The positive ratios for PA and WT were the highest (100%) followed by those for basal cell adenoma, AdCC, and MEC (89%, 89%, and 78%, respectively). They observed that PA showed multifocal positive staining, while all WTs showed a diffusely positive, faint reaction (16). These results may seem different from our results, especially in immunohistochemical reactivity of WT; however, this difference is due to the use of different PSMA immunohistochemical staining scoring. Nishida et al. (16) used intensity scoring, population scoring and the product of the intensity score and population score. We used a scoring system positive for any cytoplasmic staining and membrane staining. In our study, the non-tumoral tissue around the tumor showed a diffusely positive and faint reaction therefore these areas were scored as negative (score 0). WT and normal peritumoral salivary gland tissue differentiation was weak. Therefore, PSMA expression in the tumor epithelium of WT was considered as score 0. This finding is in fact consistent with the finding reported by Nishida et al. (16) that WT showed a diffusely positive, faint reaction. While the number of benign tumor cases were much higher in our study, the number of malignant tumor cases were slightly higher in the referred study. For this reason, we believe that our study will provide additional and complementary contributions to the literature.

The limitations of our study are its small number of patients, especially in malignant tumors, and its retrospective design. Another important limitation is that our patients did not have PSMA-PET results that we could compare with our immunohistochemical results. Further studies are needed to resolve these limitations.

Tan et al. (17) concluded in their review that there was a potential role of PSMA-PET as a diagnostic tool, especially when conventional imaging is inconclusive or does not correlate with clinical findings. They also indicated that the use of PSMA ligand had the potential to be a form of theranostics whereby it can be used as a diagnostic and therapeutic tool in the management of salivary gland tumors (17). These comments are quite consistent with our results and conclusions.

Conclusion

PSMA expression in tumor epithelium was detected in PA, MEC, AdCC and SCC. Prospective studies should be planned targeting intratumoral PSMA in benign and malign salivary gland tumors. PSMA-targeted modalities may be future diagnostic and therapeutic methods.

Ethics Committee Approval: The Clinical Research Ethics Committee of the Süleyman Demirel University Faculty of Medicine approved our study protocol (decision no: 18/254, approval date: 11.09.2020).

Informed Consent: Informed consent was not obtained from the individuals since the study was designed retrospectively.

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Authorship Contributions

Concept: M.E.S., H.Y., Design: M.E.S., H.Y., Data Collection and/or Processing: M.E.S., Y.Ç.K., O.E., S.S., Analysis and/or Interpretation: Y.Ç.K., O.E., Literature Search: M.E.S., H.Y., Y.Ç.K., O.E., S.S., Writing: M.E.S., H.Y.

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Main Points

- Prostate-specific membrane antigen (PSMA) is significantly overexpressed in prostate cancer but is also expressed in the neo-vasculature of certain non-prostatic solid tumors.
- There are few studies investigating PSMA in salivary gland tumors other than adenoid cystic carcinoma.
- PSMA expression in tumor epithelium was identified in pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma and squamous cell carcinoma.
- We observed that PSMA expression was higher in pleomorphic adenoma than in other tumors and there was no PSMA expression in the tumor epithelium of Warthin's tumor.
- PSMA-targeted approaches may become important diagnostic and therapeutic modalities in the future, especially for recurrent pleomorphic adenoma.

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Factors Affecting Permanent Sensorineural Hearing Loss and Bone Conduction in Patients After Receiving Radiotherapy to the Head and Neck Region

Original Investigation

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Abstract

Objective: This study aimed to investigate the factors affecting permanent sensorineural hearing loss (SNHL) and causing changes in bone conduction (BC) thresholds over time in patients after receiving radiotherapy (RT) or chemoradiotherapy (CRT) to the head and neck region.

Methods: A total of 63 patients with irradiated HNC that were admitted to the Radiation Oncology Department between 2011 and 2018 were included in the study. All patients were assessed with pure tone audiometry at eight different time points (first before RT and last five years after completion of RT). A chi-square test was used to analyze the variables that affected permanent SNHL occurrence. Repeated measure analysis of variance was conducted to investigate the factors affecting change in the BC threshold at pure-tone average (0.5–2 kHz) and the air conduction (AC) threshold at 4 and 6 kHz frequencies over time.

Results: Median follow-up was 52 months (range, 12–110 months). SNHL was found in 18 (14%) of the 126 ears. According to the receiver operating characteristic analysis, the cut-off values of cochlear D_{mean} and D_{max} radiation doses were 40 Gy [p=0.017, area under the curve (AUC): 0.676] and 45 Gy (p=0.008, AUC: 0.695). D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} (≤45 Gy vs. >45 Gy) cochlear doses and age (≤40 vs. >40 years) were determined as factors affecting SNHL in the chi-square test. Repeated measures showed that BC thresholds between 0.5–2 kHz and AC thresholds at 4 and 6 kHz increased over time. Age (≤40 vs. >40 years), treatment of head and neck cancer (RT vs. CRT), cisplatin use, and D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} cochlear dose (≤45 Gy vs. >45 Gy) were important factors affecting the course of BC threshold over time.

Conclusion: D_{mean} and D_{max} cochlear doses and age were found to be associated with permanent SNHL. Conduction thresholds worsened over time at all frequencies, and this trend was affected by cochlear doses, age, CRT, and cisplatin use.

Keywords: Head and neck cancer, radiotherapy, chemoradiotherapy, side effect, hearing loss, radiation dose

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Introduction

Radiotherapy (RT) is a treatment method frequently used in head and neck cancers (HNC) and brain tumors. In HNC patients RT or chemoradiotherapy (CRT) can be definitive or adjuvant, and typically given in high doses. Many critical organs such as the medulla spinalis, the cochlea, the brain stem, the optic nerves, and the optic chiasm are located within the area targeted by RT. The side effects of RT in these organs can be observed in the early and late periods.

RT can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL). CHL, originating in the outer and middle ear, is usually observed in early periods of RT and temporary, while SNHL can be seen as a late and irreversible side effect of fractional RT. SNHL is probably caused by the changes induced by radiation in the retrocochlear component or the cochlea of the auditory system (1, 2). Schuknecht and Karmody (3) reported marked changes in soft tissue, stria vascularis degeneration, and spiral ligament and basilar membrane atrophy after RT.

Leach (4) found that the outer hair cells were destroyed, and atrophy developed in the eighth cranial nerve. Moretti (5) reported extensive degeneration of the outer hair cells in the Corti organ in guinea pigs after radiation to the inner ear. Furthermore, in postmortem studies of the human temporal bone, destruction of the Corti organ, atrophy of the audiovestibular nerve, loss of outer hair cells, loss of spiral ganglion cells, atrophy of the stria vascularis, changes in the nerve vessels, the macula of the utricle, and the cristae of the semicircular canals were observed after radiation (4-6).

In the treatment of HNC, the use of cisplatin-based chemotherapy, simultaneously with RT, is also quite common. In animal experiments, cisplatin has been shown to cause injury to the outer hair cells in the Corti organ and in marginal cells in the stria vascularis (7-10). Cisplatin, like RT, causes irreversible SNHL, but unlike RT, usually starts acutely and occurs bilaterally (9-10).

The best way to protect patients from hearing loss due to RT to the head and neck region is to exclude the cochlea or retrocochlear region from the planned target region. In the past, it was not possible to exclude the cochlea from the target region, especially in nasopharyngeal and parotid cancers, but thanks to the technological advancements, normal tissues can be preserved completely or partially by three-dimensional (3D) contouring. Particularly with the availability of the intensity modulated radiotherapy (IMRT) technique it became possible to better preserve the cochlea and the retrocochlear region.

This study aimed to investigate possible factors causing SNHL and the changes in BC over time in patients who received RT or CRT to head and neck region.

Methods

This study was conducted at the Department of Radiation Oncology at Sivas Cumhuriyet University Hospital in Turkey, in accordance with the principles of the Declaration of Helsinki following the approval of Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2017-11/22, date: 8.11.2017). All patients provided written consent for the use of their information. A total of 118 patients (n=236 ears) with irradiated HNC that were admitted to the Radiation Oncology Department between 2011 and 2018 were included in the study. However, 55 patients were excluded because of insufficient data (e.g., without regular audiological tests, with short follow-up, etc.). Patients with tumor invasion into the external ear pathway, the middle ear, or the inner ear, 70 decibel (dB) or worse bone conduction (BC) thresholds, recurrent disease; a history of previous RT, and those who had used ototoxic drugs, had not completed RT, or were followed-up for less than twelve months were excluded from the study. Eventually, the data of 63 patients were analyzed. Each ear was evaluated independently for radiation doses and hearing status.

RT Techniques and Dose Fractionation

In all patients RT was administered using contrast-enhanced computed tomography (CT) or positron emission tomography-CT. Axial CT images were taken from the top of the head to the lower neck with patients in treatment position. In all cases slice thickness was 3 mm and the cochlea was contoured on the bone window of the CT. Figure 1 shows the contouring of the cochlea on CT (on the bone window) and T2-weighted magnetic resonance imaging.

RT was administered using a linear accelerator device (Varian Clinac DHX, Varian Medical Systems, Inc., Palo Alto, CA, USA) or TomoTherapy (Accuray, USA). The 3D-conformal radiation therapy (3D-CRT) planning was done using the Varian Eclipse treatment planning (Varian Medical Systems,

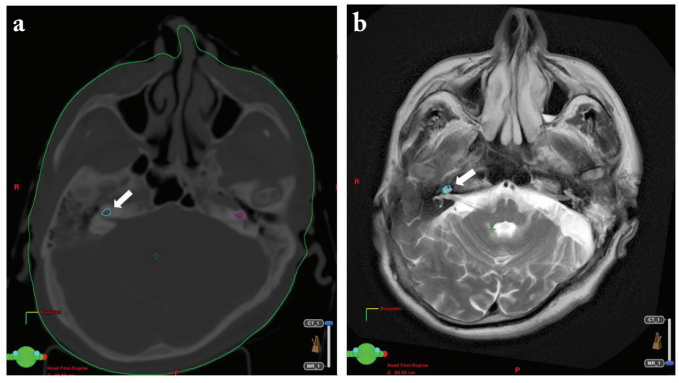

Figure 1. Contour of the cochlea on computed tomography and T2-weighted magnetic resonance imaging. a. The contour of the cochlea on computed tomography (white arrow). b. The contour of the cochlea on T2-weighted magnetic resonance imaging (white arrow)

Inc., Palo Alto, CA, USA), taking into account tissue inhomogeneity during dose calculation. IMRT planning was done using the TomoTherapy Planning Workstation (TomoTherapy Inc., Madison, WI, USA). RT was given with 6 MV photons on both devices. RT was prescribed to a total dose of 46–70 Gy at 1.8–2 Gy per fraction with 5 fractions per week.

Chemotherapy

Patients with locally advanced HNC received concurrent platinum-based chemotherapy (cisplatin 40 mg/m^2 were given every week during the radiation course). Induction CT and adjuvant CT were given with DCF protocol (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 and 5FU at 750 mg/m^2/day for five days every three weeks).

Audiological Evaluation

Pre- and post-RT audiological evaluations were done in the otolaryngology department of the same institution. Hearing data of all patients were obtained using an AC-40 Interacoustics Clinic Audiometer (Interacoustics, Assen, Denmark) at baseline (the start RT; T_1), completion of RT (T_2), six months after completion of RT (T_3), one year after completion of RT (T_4), two years after completion of RT (T_5), three years after completion of RT (T_6), four years after completion of RT (T_7) and five years after completion of RT (T_8) and retrieved from the audiological evaluation form of each patient.

All patients underwent a standard evaluation using pure-tone audiometry. This test was performed in a standardized, soundproofed and shielded room. Pure-tone thresholds were obtained for air conduction (AC) at 0.25–6 kHz and for BC at 0.5–2 kHz measured in the dB hearing level, respectively.

An increase in BC threshold of least 10 dB from baseline was considered significant (11). Permanent hearing loss was defined as a difference greater than 10 dB in hearing level results between two consecutive hearing threshold measurements done six months apart (11). Hearing levels of the left and the right ears were analyzed separately in each patient.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (IBM Corp. Armonk, NY, USA). Medians and frequencies were calculated for patient demographics. In RT techniques, the Mann–Whitney U test was used to compare the median of D_{mean} and D_{max} cochlear doses.

Receiver operating characteristic (ROC) analysis was used to determine the cut-off values of the cochlear D_{mean} dose and the cochlear D_{max} dose that affected hearing.

A chi-square test was used to analyze the variables that affected permanent SNHL occurrence. Repeated measures analysis of variance was conducted to investigate the factors (age, treatment of HNCs, use of cisplatin, D_{mean} and D_{max} cochlear doses) affecting change in the BC threshold at pure-tone average (0.5–2 kHz) and the AC threshold at 4 and 6 kHz frequencies over time. P values ≤0.05 were accepted as statistically significant.

Results

Demographic Features

The study group consisted of 51 (81%) male and 12 (19%) female patients. Their median age at the time of their cancer diagnosis was 52 years (range, 16–75 years). Fifteen (24%) of the patients were ≤40 years old, and 48 (76%) were >40 years old. Nineteen (30%) had at least one comorbid disease.

Ranked in order of frequency, the cancer classifications were head and neck (n=51, 81%) and central nervous system (n=12, 19%). Regions of head and neck tumors were nasopharynx (NPC) in 26 (41%) patients, oral cavity/oropharynx in 11 (18%), larynx/hypopharyngeal in 10 (16%), and salivary gland in 4 (6%) patients. The 12 brain tumors (18%, 24 ears) were: grade 1-2.

Staging of the HNCs were: stage I in 2 (4%) patients, stage II 11 (22%), stage III in 23 (45%), and stage IVA in 15 (29%) patients. Brain tumors were not staged.

Treatments

Surgical treatment was performed in 25 (40%) patients. A total of 17 (27%) patients were treated with postoperative RT, six (10%) patients with definitive RT, and a total of 40 patients (63%) were treated with concurrent CRT, seven (11%) patients with postoperative CRT, and 33 (52%) patients with definitive CRT. Induction chemotherapy was administered to five (8%) patients, and 16 (25%) patients received adjuvant chemotherapy.

The median treatment RT dose was 70 Gy (range, 46–70.2 Gy). From January 2011 to June 2015, a total of 37 (59%) patients (74 ears) were treated with 3D-CRT. From June 2015 to December 2018, 26 (41%) patients (52 ears) were treated with IMRT.

Median D_{mean} cochlear dose was 23.13 Gy (range, 0.52–71.60 Gy) and median D_{max} cochlear dose was 32.9 Gy (range, 0.58–74.80 Gy). Median D_{max} cochlear dose was 36.77 Gy (range, 0.58–73.67 Gy) in 3D-CRT and 26.95 Gy (range, 1.16–74.80) in IMRT (p=0.931). Median D_{median} cochlear dose was 32.48 Gy (range, 0.52–71.58) in 3D-CRT and 18.01 Gy (range, 1.14–71.60 Gy) in IMRT (p=0.886).

The median dose of cumulative cisplatin in all treatments (induction, adjuvant and simultaneously) was 435 mg (range, 200–980 mg).

Audiological Results

The median clinical follow-up was 52 months (range, 12–110 months). Permanent SNHL was observed in 18 (14%) of the 126 ears.

According to the ROC analysis, the cut-off values of cochlear D_{mean} and D_{max} radiation doses were 40 Gy (p=0.017, AUC: 0.676, range, 0.532–0.820) and 45 Gy (p=0.008, AUC: 0.695, range, 0.553–0.838), respectively (Figures 2, 3). The cut-off value was not found for the cisplatin dose.

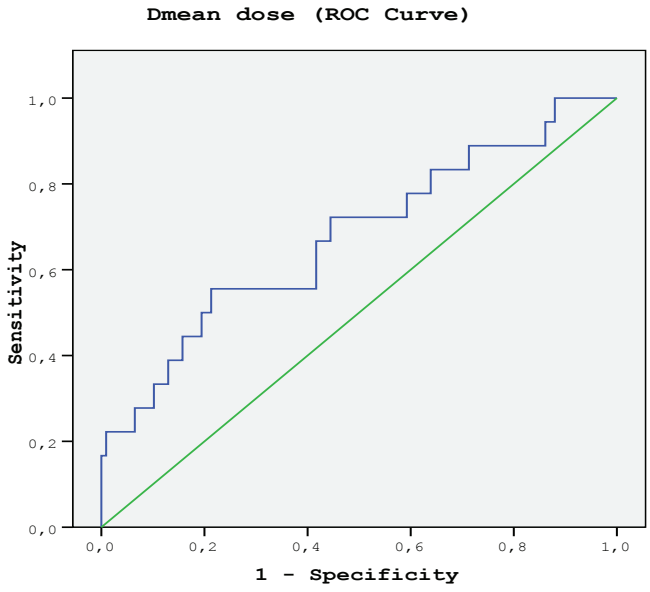

Figure 2. ROC analysis of D_{mean} radiation dose of cochlea
ROC: Receiver operating characteristic

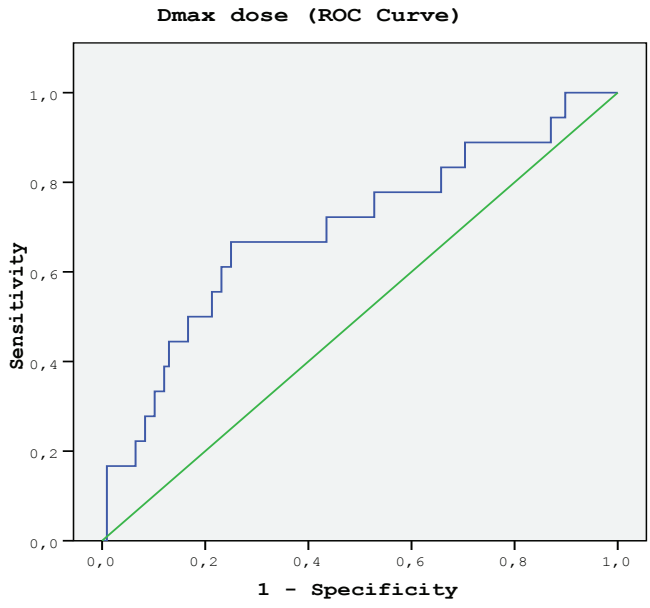

Figure 3. ROC analysis of D_{max} radiation dose of cochlea
ROC: Receiver operating characteristic

The chi-square test showed D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} (≤45 Gy vs. >45 Gy) cochlear dose and age (≤40 vs. >40 years) as factors affecting permanent SNHL. Gender, comorbidity, the localization of the disease (HNC vs. brain tumors), treatment of HNC (RT vs. CRT) and use of cisplatin, RT technique (3D-CRT vs. IMRT) and BC threshold at diagnosis (≤20 vs. >20 dB) did not affect the rate of SNHL (p>0.05). Table 1 shows the factors affecting permanent SNHL rates.

Table 1. Factors affecting the rate of permanent sensorineural hearing loss

Chi-square test	All ears n (%)	SNHL absent n=108 (86%)	SNHL present n=18 (14%)	p-value
D_{mean} cochlear dose				
≤40 Gy	93 (74)	85 (91)	8 (9)	0.004
>40 Gy	33 (26)	23 (70)	10 (30)	
D_{max} cochlear dose				
≤45 Gy	90 (71)	83 (92)	7 (8)	0.002
>45 Gy	36 (29)	25 (69)	11 (31)	
Gender				
Female	24 (19)	19 (79)	5 (21)	0.236
Male	102 (81)	89 (87)	13 (13)	
Age				
≤40 years	30 (24)	30 (100)	- (0)	0.005
>40 years	96 (76)	78 (81)	18 (19)	
Comorbidity				
No	89 (71)	75 (84)	14 (16)	0.339
Yes	37 (29)	33 (89)	4 (11)	
Localization of the disease				
HNC	102 (81)	86 (84)	16 (16)	0.286
Brain tumors	24 (19)	22 (92)	2 (8)	
Treatment of HNC				
RT	22 (22)	19 (86)	3 (14)	0.531
CRT	80 (78)	67 (84)	13 (16)	
RT techniques				
3D-CRT	74 (59)	64 (87)	10 (13)	0.481
IMRT	52 (41)	44 (85)	8 (15)	
Use of cisplatin				
No	46 (36)	41 (89)	5 (11)	0.290
Yes	80 (64)	67 (84)	13 (16)	
Cumulative dose of cisplatin				
≤435 mg	44 (55)	40 (60)	4 (31)	0.053
>435 mg	36 (45)	27 (40)	9 (69)	
BC threshold at diagnosis				
≤20 dB	106 (84)	91 (84)	15 (83)	0.575
>20 dB	20 (16)	17 (16)	3 (17)	

n: Number of ears, SNHL: Sensorineural hearing loss, HNC: Head and neck cancers, 3D-CRT: Three-dimensional conformal radiation therapy, RT: Radiotherapy, IMRT: Intensity modulated radiotherapy

In repeat measurements, it was observed that BC thresholds at 0.5–2 kHz and AC thresholds at 4 and 6 kHz increased over time. Table 2 shows that BC thresholds at 0.5–2 kHz and AC thresholds at 4 kHz and 6 kHz increased over time. Age (≤40 vs. >40 years), treatment of HNC (RT vs. CRT), use of cisplatin, and D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} cochlear dose (≤45 Gy vs. >45 Gy) were important factors affecting the course of BC threshold over time. Table 3 shows the average BC threshold of these variables. Gender, comorbidity, the localization of the disease (HNC vs. brain tumors), and BC threshold at diagnosis (≤20 vs. >20 dB) did not affect the course of BC threshold over time (p>0.05).

Discussion

RT-induced ear toxicity is related to the anatomical location of the ear in the irradiation field. Radiation-induced ear toxicity can lead to a wide range of conditions from otitis media to SNHL. Similarly, the incidences of toxicity are also very different. Therefore, it is important to know the incidence and the factors causing permanent SNHL.

In their study, Wang et al. (12) analyzed 395 ears of 220 NPC patients who were followed-up for a median of 36 months (3–120 months) after completion of RT. The researchers found that 13.7% of the ears had an increase of at least 30 dB in BC threshold at low frequencies and 46.2% at 4 kHz. Bhandare et al. (13) retrospectively investigated ototoxicity in 325 patients who received RT for HNC between 1964 and 2000 and recorded 15.1% SNHL at low frequencies. Yilmaz et al. (14) reported a median loss of 22.6 dB at a rate of 47% at any frequency of BC threshold one year after the completion of RT in 19 HNC patients. Oh et al. (11) found that in 24 NPC patients who underwent CRT, SNHL was 44% at 4 kHz and 17% at low frequencies 40 months after completion of RT. The SNHL due to a retro-cochlea (cochlea nerve) damage may occur, although, this was relatively rare compared to the cochlea damage (15). Kwong et al. (16) reported that the patients with NPC (n=132) had 24.2% permanent SNHL in a median 30-month follow-up after completion of RT.

In our study, we investigated the factors affecting the occurrence of SNHL at low frequencies, and similarly

Table 2. Changes in bone conduction threshold at 0.5–2 kHz and air conduction thresholds at 4 and 6 kHz over time

Conduction thresholds	T_1 n=126	T_2 n=126	T_3 n=126	T_4 n=126	T_5 n=86	T_6 n=78	T_7 n=58	T_8 n=58	p-value
Bone (0.5–2 kHz)	15±7	15±6	16±6	16±16	16±16	18±17	18±17	19±19	0.005
Air (4 kHz)	35±23	37±24	38±22	41±22	44±23	46±23	48±25	48±25	<0.001
Air (6 kHz)	37±24	40±26	41±24	42±23	46±26	51±24	54±23	58±25	<0.001

T_1: Start of RT, T_2: Completion RT, T_3: Six months after completion of RT, T_4: One year after completion of RT, T_5: Two years after completion of RT, T_6: Three years after completion of RT, T_7: Four years after completion RT, T_8: Five years after completion of RT, n: Number of ears, RT: Radiotherapy

Table 3. Effects of age, treatment of head and neck cancers, use of cisplatin, D_{mean} and D_{max} cochlear doses on bone conduction threshold over time

	T_1 n=126	T_2 n=126	T_3 n=126	T_4 n=126	T_5 n=86	T_6 n=78	T_7 n=58	T_8 n=58	p-value
Age									
<40	11±12	11±13	12±13	12±13	13±14	13±14	14±15	16±17	0.002
≥40	44±14	43±13	43±13	43±13	43±11	46±10	46±16	40±21	
Treatment[1]									
RT	6±4	7±5	8±4	9±4	7±4	9±5	11±6	10±6	0.048
CRT	18±18	18±18	19±8	18±18	19±18	21±18	20±21	22±21	
Cisplatin									
No	6±4	7±5	8±4	9±4	7±4	9±5	11±6	10±6	0.048
Yes	18±18	18±18	19±18	18±18	21±18	21±18	20±21	22±21	
D_{mean}[2]									
≤40 Gy	12±12	12±12	13±12	12±12	13±12	14±12	13±12	15±14	0.037
>40 Gy	20±22	22±22	21±21	23±21	22±22	26±22	27±24	27±24	
D_{max}[3]									
≤45 Gy	12±12	12±11	13±11	13±11	13±12	14±12	13±12	15±14	0.030
>45 Gy	22±23	22±23	22±23	23±22	24±23	27±23	28±25	27±26	

T_1: Start of RT, T_2: Completion RT, T_3: Six months after completion of RT, T_4: One year after completion of RT, T_5: Two years after completion of RT, T_6: Three years after completion of RT, T_7: Four years after completion RT, T_8: Five years after completion of RT, n: Number of ears
Treatment[1]: Treatment of head and neck cancers, D_{mean}[2]: Mean radiation dose of cochlea, D_{max}[3]: Maximum radiation dose of cochlea

to the above studies, found SNHL to be 14% at low frequencies.

As people age, the rate of SNHL increases as a result of the loss of the characteristics of the vessels of the ear, the deterioration of the auditory nerve and the decrease in the function of the hearing center in the brain (17, 18). Some studies have shown that the probability of SNHL occurrence is more common in elderly patients who received RT or CRT (12, 19). In the study conducted by Wang et al. (12), age was associated with significant loss at BC threshold at low frequencies in logistic regression analysis. In the study by Chan et al. (19), SNHL at low frequency was associated with patient's age, and SNHL at high frequency was associated with simultaneous cisplatin dose. Kwong et al. (16) reported that older patients were more susceptible to SNHL. In their series, permanent SNHL was 0% in patients under 30 years, 17.2% in patients 30–50 years, and 37.4% in patients over 50 years of age. However, unlike the above studies, Zuur et al. (20) reported that younger patients who underwent CRT with high-dose cisplatin were more susceptible to hearing loss.

In our study, while none of the patients aged under 40 years had SNHL, 19% of the patients aged over 40 years had permanent SNHL. Moreover, an advanced age had more statistically significant negative impact on the course of BC threshold over time. This suggests that care should be taken to better protect the cochlea when planning RT for elderly patients.

Many authors have identified a relationship between the occurrence of SNHL and high cochlear radiation doses (10, 19, 21-23). This, however, has not been demonstrated in some other studies (21, 24). In most studies, increased incidence of SNHL was reported in patients with a median cochlear dose of 45–55 Gy (10, 19, 21-23). Bhandare et al. (13) reported the five-year and 10-year actuarial risk of clinically overt SNHL as 3% at cochlear doses below 60.5 Gy and 37% at doses above 60.5 Gy. In a study conducted by Chan et al. (19) on NPC patients, they found that high-frequency SNHL was associated with the mean cochlear dose (>46 Gy). Chen et al. (22) audiologically followed up 22 patients who underwent CRT due to NPC for 29 months (range, 12–76 months). They reported that the occurrence of SNHL was higher in patients with D_{mean} cochlear dose >48 Gy at all frequencies. Petsuksiri et al. (23) examined the factors affecting SNHL in 68 NPC patients who received CRT. The researchers separately investigated the roles of mean cochlear dose, inner ear (cochlear and vestibule) and internal auditory canal (IAC) in SNHL opposite to other studies. In the study, the univariate analysis showed that the D_{mean} cochlear dose ≤50 Gy, the D_{mean} inner ear dose ≤45 Gy and the D_{mean} IAC dose ≤50 Gy appeared to lead to a lower incidence of SNHL at high frequency (4 kHz). However, they could not identify an important factor affecting the incidence of SNHL at low frequencies. The researchers further reported that in the bivariate analysis, the D_{mean} IAC dose >50 Gy tended to lead to a higher rate of SNHL at higher frequencies (relative risk 2.02).

Unlike the results of Petsuksiri et al. (23), in our study the D_{mean} cochlear dose >40 Gy at low frequencies was found to be a risk factor for SNHL. The cochlear D_{max} dose >45 Gy was also found to be a risk factor for SNHL. Analysis of the audiological tests done at eight different time points showed that the D_{mean} cochlear dose >40 Gy and the D_{max} cochlear dose >45 Gy negatively affected the course of BC thresholds at low frequencies over time. Compared to other studies, in our study the D_{mean} cochlear dose affecting SNHL was lower than 45–55 Gy. Therefore, the cochlear dose should be lower in RT planning.

Cisplatin-induced ototoxicity is observed at high frequencies and in the form of SNHL, which is due to the damage done by cisplatin to the outer hair cells and the stria vascularis of the organ of Corti (7-10, 25). Cisplatin CRT is frequently used in HNC patients due to better survival results with CRT. It is logical that the use of two ototoxic agents, RT and cisplatin, causes increased ototoxicity. However, this has not been demonstrated, especially in studies using weekly low-dose cisplatin (12, 15, 21). As shown in studies reported to date, high-dose cisplatin appears to increase the risk of SNHL (19, 26). Rezaeyan et al. (27) investigated rates of SNHL in 60 HNC patients in the short term (over a six-month period). The researchers applied RT or CRT with 3D-CRT to the head and neck regions of the patients and compared the SNHL incidence rates of these two applications. The result of the study showed that 47% of the patients that received RT and 88% of the patients that received CRT had SNHL. In their analysis of 17 studies, Schmitt and Page (26) reported that CRT with low-dose cisplatin (30–40 mg/m^2 weekly) could be associated with lower hearing loss incidences and lower severity of hearing loss. Chan et al. (28) investigated the effect of cisplatin in 142 patients who received RT or CRT for nasopharyngeal cancer. The researchers reported that the hearing loss in CRT patients tended to be seen in the first three months and at high frequencies, and that the severity of toxicity was higher compared to RT alone. They also reported that there was no significant hearing toxicity in patients who received only RT in the first two years. In their 2007 report of the study on HNC patients, Bhandare et al. (13) stated the results of univariate and multivariate analysis showed that age, cochlear dose and CRT were factors affecting SNHL. In their study, they determined that the five-year and ten-year actuarial risk of clinically overt SNHL was 18% in RT and 30% in CRT. In Chan et al.'s (19) study, pure-tone audiogram and tympanometry were performed on 87 NPC patients at the start of RT and then every six months. The researchers reported that patients receiving CRT had a higher rate of persistent SNHL at 4 kHz compared to low frequencies (51.2% vs. 9.4%). They showed that SNHL at

low frequency was related to patient age, and SNHL at high frequency was associated with simultaneous cisplatin dose (>1.008 mg/m^2) and mean cochlear dose (>46 Gy). Further, in the study conducted by Zuur et al. (20), a cumulative 1,050 mg dose of cisplatin was shown to cause SNHL with increasing frequency.

In our study, the chi-square test showed that the use of cisplatin and RT vs. CRT did not affect the occurrence of SNHL; however, the use of CRT adversely affected the course of BC threshold over time at low frequencies. In our study, although no relation was found between cisplatin dose (cumulative cisplatin dose >435 mg) and SNHL, this relationship was close to being statistically significant. Since we used weekly low-dose cisplatin in our study, a strong relationship between ototoxicity and cisplatin dose could not be demonstrated. Previous studies have shown quite different results regarding the relationship between SNHL and CRT. It seems, however, that CRT, especially with high doses of cisplatin (cumulative ~1000 mg), increases the likelihood of SNHL occurrence, especially at high frequencies.

It is known that IMRT provides better protection of normal tissue than 3D-CRT. By providing lower cochlear doses with IMRT, it may be possible to reduce the risk of SNHL. In fact, some studies reported lower rates of SNHL with IMRT. In the study conducted by Petsuksiri et al. (23), the incidence of SNHL was 48.75% at 4 kHz and 5% at low frequencies with conventional RT and 37% at 4 kHz and 7.4% at low frequencies with IMRT. Zhu et al. (29) reported that the incidence of SNHL was 8% at low frequency and 36% at high frequency in 70 patients who were irradiated with the IMRT technique due to NPC. Nutting et al. (30) compared 3D-CRT and IMRT techniques in terms of SNHL in 110 parotid cancer patients treated between 2008 and 2013. The researchers detected a statistically significant difference between the techniques in terms of cochlear doses; however, at one year after RT, they did not find any difference in hearing loss of ≥10 dB.

Like Nutting et al. (30), no relationship was found between RT techniques and SNHL occurrence in our study. This may be due to the lack of difference in the D_{mean} and D_{max} cochlear doses among RT techniques. In the IMRT technique, however, lower cochlear doses were used compared to 3D-CRT.

The limitations of the study are the small number of patients and the heterogeneity of the group, and the lack of BC threshold measurements at 4 kHz, which means that the factors related to high frequency SNHL have not been investigated.

Conclusion

In our study, SNHL occurred at lower D_{mean} cochlear radiation doses at low frequencies than in other studies (>40 Gy vs. 45–55 Gy). Moreover, D_{mean} and D_{max} cochlear doses and age were found to be associated with permanent SNHL. Regardless of SNHL, in the patients who receive RT in the brain and the head and neck region, conduction thresholds worsen over time at all frequencies, and this poor trend is affected by cochlear doses, age, CRT, and cisplatin use.

Ethics Committee Approval: This study was conducted at the Department of Radiation Oncology at Sivas Cumhuriyet University Hospital in Turkey, in accordance with the principles of the Declaration of Helsinki following the approval of Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2017-11/22, date: 8.11.2017).

Informed Consent: All patients provided written consent for the use of their information.

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Main Points

- In this study, a relationship was found between radiation dose and hearing impairment.
- Bone and air conduction hearing deteriorates over time in the area of radiotherapy to the head and neck region.
- Patient age is an effective factor in the deterioration of hearing.

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The Elderly Voice: Mechanisms, Disorders and Treatment Methods

Review

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Abstract

The elderly population is increasing globally. In Turkey, the population aged 65+ is predicted to grow to more than 15% of the whole population by 2050. Just like the rest of the body, the voice also changes with age. Voice changes throughout life have been reported in up to 52.4% of aged individuals and may have a negative impact on their quality of life. Voice is affected by various factors, including age, disease, hormones, medications, and physiological, psychological, and social conditions. A multidisciplinary approach is therefore needed to achieve the best voice outcomes. In this review, we summarize the mechanisms involved in voice changes in the elderly together with the applicable diagnostic and treatment methods.

Keywords: Voice, elderly, presbyphonia, phonosurgery, voice disorders, voice therapy

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Introduction

In 2020, the elderly population accounted for 18.35% of the total population in high-income countries, but this rate is increasing annually and estimated to reach 24.66% by 2050 (1). The rate of the population aged over 65 years in Turkey was 5.7% in 2000, 7.2% in 2010, and 9.5% in 2020, and is anticipated to exceed 15% by 2050 (1-3).

The human larynx and vocal cords show some changes over time due to various factors, such as age, diseases, hormones, and medications (4). Majority of the elderly individuals have multiple medical conditions and need to use a range of medications. This population also presents with decreased sex hormone levels. It is therefore inevitable that they experience changes in their voice. Previous studies have shown that the prevalence of dysphonia in the elderly is 4.8–29.1% and rises to 52.4% throughout life (5). The most common voice complaints in the elderly include hoarseness, vocal fatigue, cough, breathy or rough voice, decreased volume and projection (6). Although

dysphonia has a negative impact on the quality of life of the elderly, almost one-fourth of this population consider it to be part of the normal course of aging (7-9). Similarly, in a recent study, Lindström et al. (10) found that although patients thought that the voice was important for them and were aware of the changes in their voices, they did not seek for healthcare professional as they considered it to be a normal part of aging. Voice changes due to aging had a negative effect on their communication skills and social life, particularly in those elderly who did not seek treatment. Nevertheless, the frequently encountered coexistence of voice disorders and hearing impairment may cause depression, anxiety, and social isolation (8). Accordingly, if left untreated, the quality of life can also be affected in many elderly individuals.

Given that this underestimated issue affects at least 10% of the population, we aimed to review the mechanisms, the diagnostic and treatment methods of voice changes in this population.

The Mechanisms of Voice Changes

Aging causes many changes in the body, and these may have physiological, psychological, and social impacts. The voice is affected by changes in the laryngeal structures as well as the respiratory, resonator, secretory, and velopharyngeal functions and the individual's emotional status (11). Presbylarynx is defined as age-related changes in the larynx, such as epithelial, thyroarytenoid muscle and elastic fiber atrophy resulting in incomplete glottal closure, vocal cord bowing and prominent vocal process (12). Turk and Hogg (13) showed how calcification and ossification of the laryngeal cartilage framework could differ among individuals as they age. Liu et al. (14) found that the antero-posterior dimensions of the cricoid cartilage change with age and gender. However, such changes are not limited to the laryngeal cartilage framework. Previous studies reported ankylosis, narrowing, and degeneration, including thinning and irregularities of the articular surfaces and disorganization of the collagen matrix of the cricoarytenoid joint, and concluded that the mobility capacity and smoothness of the vocal cords could be affected by age (11, 15, 16). Furthermore, decreases occur in the number of the myelinated fibers of the laryngeal nerves, the blood supply, and the size and number of motor units (11, 17, 18). The laryngeal muscles therefore atrophy with age. Rodeño et al. (19) found an increase in the type 1 and a decrease in the type 2 fibers of the thyroarytenoid muscles and further detected a decrease in the type 1 and an increase in the type 2 fibers of the posterior cricoarytenoid muscle. Nevertheless, the vocal cords of the elderly also demonstrate some histological differences when compared with those of younger individuals. The vocal cords include five histological layers: the epithelium, the superficial, intermediate, and deep lamina propria, and the thyroarytenoid muscle. An increase in epithelial thickness, yellowing with a loosening of the underlying lamina propria attachment, and reduced epithelial cell density have been reported (20). Hirano et al. (21) found that the vocal cord shortened in males and the mucosa thickened in females as they age. The authors also detected edema in the superficial layer of the lamina propria in both sexes, a deterioration and atrophying of the elastic fibers, thinning of the intermediate layer, and thickening in the deep layer in males. All these changes may therefore contribute to the development of presbylarynx, bowing and contour irregularities in the vocal cord mucosa. Atrophy, degeneration, and a decrease in the density, distribution, and number of the salivary glands of the larynx may cause both irregularities during vibration and laryngeal sicca syndrome (11, 22).

Ageing produces many changes in the respiratory function, such as decreases in muscle strength, lung function and elasticity, exercise capacity, and chest wall compliance and increases in the alveolar dead space and air space sizes (23). Adequate pulmonary function is needed for a sustained and effective voice. A sustained and effective voice is needed for adequate pulmonary function. It is therefore possible for the elderly to experience shortness of breath, coughing or increased mucus production, and a breathy and raspy voice irrespective of whether or not they have a pulmonary disease (24).

Voice is further affected by the hormonal status of individuals as vocal cords contain progesterone, androgen, and estrogen receptors (4). Previous studies have shown that voice changes occur during the menstrual cycle, menopause, and even precocious puberty (25). Vocal fatigue, lowered vocal intensity, and loss of high tones and voice quality are apparent in menopausal individuals as part of menopausal vocal syndrome (26). However, Gugatschka et al. (27) found that estrogen, but not androgen, levels had a significant correlation with voice parameters in males. They further determined that elderly people with low levels of estrogen had a low voice-related quality of life.

Voice can also be affected by many systemic and/or local factors, including thyroid disease, obesity, hypertension, cancer, coronary artery disease, diet, cerebrovascular disease, stroke, rheumatological diseases, neurological (i.e., Parkinson's disease, essential tremor, Alzheimer's disease) or psychological conditions (i.e., depression), intellectual capacity, dentition, and hearing loss (8, 28).

Meenan et al. (24) suggested that an evaluation of pulmonary function should be included in voice assessments. Correspondingly, Woo et al. (29) showed that pulmonary disease and hypertension were the most common accompanying diseases among the elderly with voice complaints. Furthermore, 53.6% of these patients had a systemic disease, and more than one-third had been prescribed one or more medications. Santos et al. (28)

identified presbylarynx in 41% of their patients with chronic medical illnesses; among whom type 2 diabetes mellitus, pulmonary disease, or psychiatric conditions were more common alongside presbylarynx. The authors concluded that presbylarynx could be an indicator of the health status of the elderly.

Martínez-Nicolás et al. (30) conducted a systematic review, and using voice analysis determined with an accuracy of over 80% that mild cognitive impairment and Alzheimer's disease could be present in individuals with decreased and wider variability in fundamental frequency (F_0), shimmer, and noise-to-harmonic ratio (NHR). The relationship between Parkinson's disease and voice changes is well established. A rough, weak/asthenic, breathy voice, hypophonia or monoloudness, higher pitch levels, and monopitch, which are reflected in voice analyses as decreased harmonics-to-noise ratio and increased F_0, jitter, and shimmer, are typical characteristics of the voice changes in patients with Parkinson's disease (31).

Edema, hyperemia, swelling in the larynx mucosa, and/or cricoarytenoid joint involvement, and/or vocal cord nodules are discernible in patients with rheumatoid arthritis or other rheumatological diseases. Different phases of rheumatoid arthritis cause some voice changes, such as higher jitter and NHR, during the remission phase (32). Meanwhile, diseases of the thyroid gland can cause shortness of breath when speaking and roughness of the voice due to changes in the lamina propria (33).

Diagnosis

Some voice changes, such as reduced volume and projection, easy fatigability, tremor, a higher pitch in men and a lower pitch in women, a rough or breathy voice, a decreased maximum phonation time, dysphagia, and hoarseness are observed in the elderly population (6, 7, 34). A detailed medical history should be taken before any voice examination to determine the presence of these diseases or conditions, trauma, surgery, intubation, infection, medications, tobacco and/or alcohol consumption, and signs of laryngopharyngeal reflux. Patients should be examined physically, followed by videostroboscopy, and an acoustic voice analysis should be performed. Determining hearing loss is also crucial to increase speech intelligibility and quality of life in the elderly (6, 7, 11).

Videostroboscopy

Videostroboscopy is an essential tool used in the examination of moving vocal cords. It allows high-speed vocal cord vibrations to be detected with the naked eye by slowing down the vibrations using flashing lights during the glottic cycle and provides the opportunity to assess vibration absence or asymmetry and laryngeal closure abnormalities (35). Nevertheless, videostroboscopy requires the cooperation of the patient, and prolonged phonation is needed to utilize the "slow-motion" effect and perform an optimal evaluation. It may therefore not be suitable for all individuals, particularly patients with neuropsychiatric disorders. Glottal incompetence, vocal cord atrophy, the prominence of the vocal process of the arytenoid cartilage, bowing, edema, reduced amplitude, and the periodicity of mucosal waves may be observed during evaluations of presbylarynx using videostroboscopy (Figure 1) (11). In addition, previous studies have shown that presbylarynx is generally accompanied by one or more voice disorders, including laryngopharyngeal reflux, vocal cord paralysis/paresis, muscle tension dysphonia, a benign (Figure 2), premalignant, or malignant vocal mass (Figure 3), tremor, and laryngitis (6, 34, 36).

Acoustic Voice Analysis

Acoustic voice analysis, which provides objective measurements of speech, is a software-based assessment tool. Descriptions of the outcome variables of voice analysis programs have been clearly defined in numerous studies. To summarize, F_0 demonstrates the number of times a sound wave occurs within a short time period. Short-term perturbation in F_0 is shown by jitter.

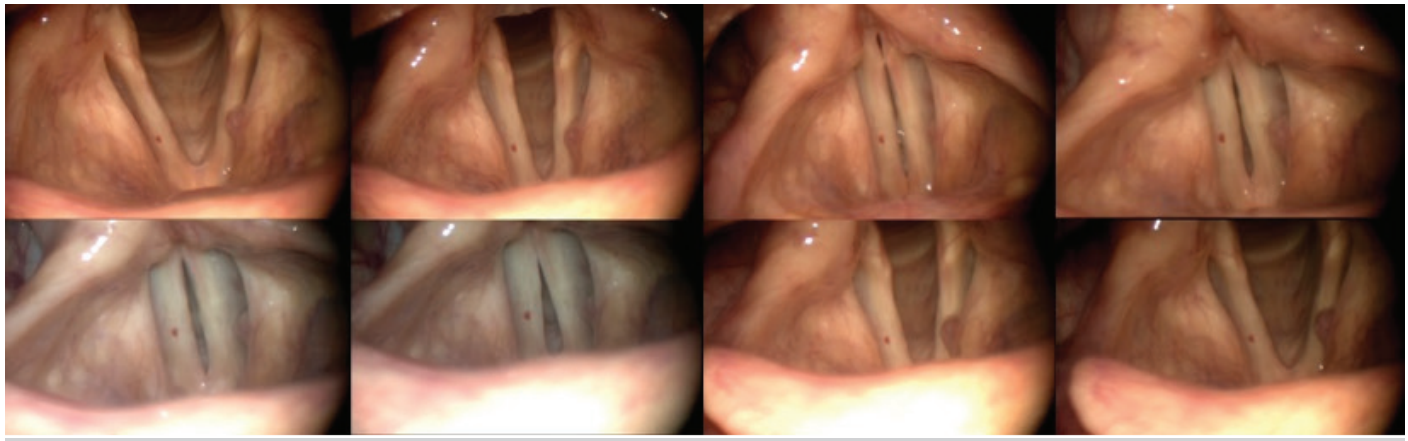

Figure 1. One glottic cycle during examination using videostroboscopy that shows vocal cord atrophy, prominence of vocal process and glottic insufficiency

Shimmer reflects the amplitude variation of a voice. NHR is the ratio between the periodic or harmonic components and the non-periodic or non-harmonic components of a voice. Notwithstanding, it is important to note that the values of the outcome variables may differ depending on the software used (37).

Voice parameters not only change with age, but also differ based on gender (8, 11). The results of voice analyses in previous studies have demonstrated a higher F_0 in males and lower F_0 in females, as well as higher variability in intensity and F_0, increased jitter (perturbation), shimmer (perceptual qualities of harshness and roughness), and NHR, and decreased maximum intensity levels and maximum phonation time in both sexes in the elderly compared to younger subjects (6, 8, 11, 38). On the other hand, the Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS) scale, the Roughness, Breathiness, Hoarseness scale, and the Consensus Auditory-Perceptual Evaluation of Voice are widely used tests to assess perceptual voice (39). More specifically, Etter et al. (40) described the Aging Voice Index (AVI) as including the following six items: the ability to be understood by others, a feeling of being inhibited by one's voice, the energy and effort required to make a sound, dissatisfaction with the sound of one's voice, the emotional impact of a lack of voice quality, and the inhibiting effect of one's voice on activities one enjoys. The authors found that the mean AVI scores were 6.05 and 37.82 in normal larynx and presbylarynx, respectively.

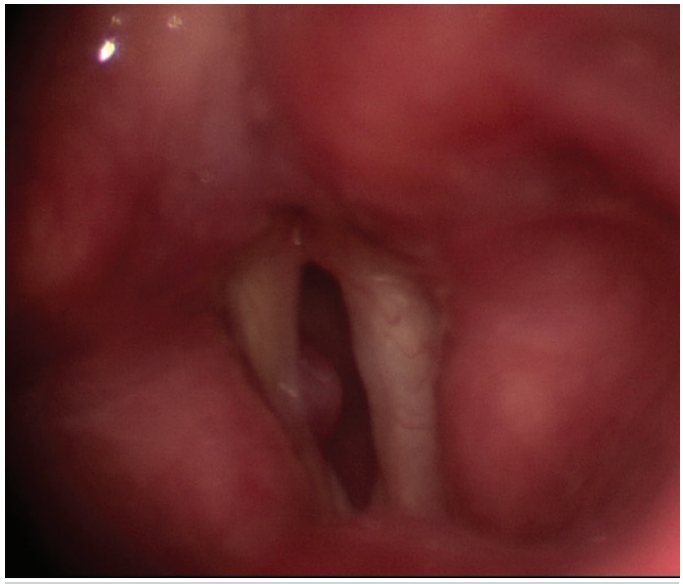

Figure 2. Right-sided hemorrhagic polyp and glottic insufficiency in a 65-year-old male patient

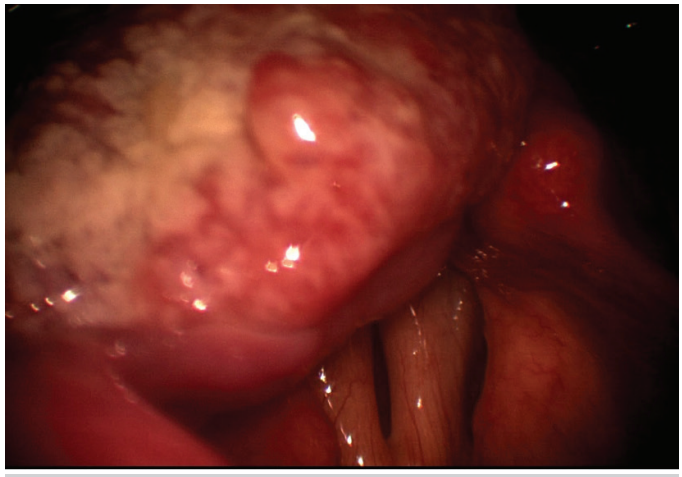

Figure 3. Right-sided supraglottic laryngeal carcinoma in a 67-year-old female patient

Voice Disorders

Although presbylarynx itself causes voice changes, it is generally accompanied by one or more organic and/or functional voice disorders. Gregory et al. (6) reported that laryngopharyngeal reflux (91%) to be the most common condition present with presbylarynx, followed by muscle tension dysphonia (73%), paresis (72%), vocal cord mass (31%), varicosity/ectasia (19%), glottic insufficiency (19%), Reinke's edema (14%), tremor (13%), vocal cord stiffness (12%), scarring/fibrosis (11%), leukoplakia (3%), and cancer (2%). Spasmodic dysphonia, hemorrhage, pseudosulcus vocalis, fluctuating neuro-asymmetry, neurogenic dysphonia, anterior glottic web, sulcus vocalis, sulcus vergeture, and candida were the other conditions (29%). While the incidence of presbylarynx was only 11.6% in the series of the elderly with voice complaints by Mahmoud et al. (36), benign vocal fold lesions (34%) was the most common voice disease in the elderly in the study by Çiyiltepe and Şenkal (34). It may be concluded that although the incidence and frequency of age-related voice disorders vary, the reasons are similar.

Treatment Methods

Although there are many treatment options, including medical, surgical, and voice therapy, the management of voice disorders mainly consist of one or more combinations of these. Moreover, given their complexity, a multidisciplinary approach is crucial to achieve an optimal improvement in voice quality.

Medical

Medical therapy should include the treatment of any underlying medical diseases and be evaluated by the relevant department. Regardless of such diseases, given that physical age has a notable effect on voice, physical exercise and proper nutrition should be recommended to maintain muscle function, increase lung capacity, and reduce cardiovascular risk (8, 11). Treatment of a loss of dentition and hearing loss is also crucial to enhance life quality.

Laryngopharyngeal reflux, infectious laryngitis, and oral care are some of the reasons medical therapy might be needed (6, 8). Moreover, hormonal replacement therapy may be an option in patients with voice changes resulting from menopause (4). Karbiener et al. (41) used chronic electrostimulation of the recurrent laryngeal nerve as a novel technique to reverse age-related muscle atrophy in an animal model and found a statistically significant difference between the stimulated and non-stimulated sides of the mean muscle fiber diameters ($p<0.001$). Gugatschka et al. (42) reported a statistically significant improvement in voice-related quality of life and subjective voice perception in patients treated with electrostimulation of the recurrent laryngeal nerve, but an improvement was not apparent in objective voice assessments. Although this procedure is promising, the long-term effects are still unknown.

Voice Therapy

Voice therapy is a widely used and effective method for the treatment of benign vocal cord pathologies. According to a survey conducted with laryngologists, most of them preferred voice therapy as a first-line treatment of presbyphonia (12). Various studies have demonstrated the effectiveness of voice therapy in the elderly (43). For example, Bick et al. (44) reported a significant improvement in the results of voice analyses and voice-related quality of life in the elderly with vocal cord atrophy who underwent voice therapy. Kaneko et al. (45) showed voice therapy to be an effective treatment for improving vocal function and thyroarytenoid muscle activity confirmed with laryngeal electromyography in patients with aged vocal cord atrophy. Interestingly, Lin et al. (46) showed that both tele-practice and face-to-face voice therapy led to statistically significant improvements in voice outcomes, including Voice Handicap Index-10 outcomes, and no significant difference was evident between the methods. Tele-practice may be an alternative for patients who cannot participate in face-to-face voice therapy.

Surgery

Laryngeal surgery is mainly considered in patients with malignancy or those who have not benefitted from voice therapy, and have a benign vocal mass or glottic insufficiency due to presbylarynx or paralysis (47). It is crucial to understand when such procedural intervention is needed as a first-line treatment. Sund et al. (12) found in their survey among laryngologists that severe glottal insufficiency (87%), high occupational/social voice demands (76%), voice not stimulable for change (73%), difficulty attending voice therapy (70%), severe dysphonia (65%), and dysphagia (61%) were the causes of choosing a procedural intervention as a first-line treatment. Injection laryngoplasty using calcium hydroxyapatite or hyaluronic acid can be performed as an office procedure; however, repeated injections may be required due to absorption. Vocal fold injection augmentation by autologous adipose tissue may be preferably performed under general anesthesia in the operating room. Kwon et al. (48) reported that 12 months after injection laryngoplasty with calcium hydroxyapatite, patients showed improvement in both subjective and objective voice measurements. González-Herranz et al. (49) found that elderly patients treated with autologous adipose tissue for presbyphonia had improvement in Voice Handicap Index-10 outcomes, maximum phonation time, and GRBAS scale during a mean 22.89-month follow-up. Another method, as a durable treatment option, for glottic incompetence is type I (medialization) thyroplasty which needs to be performed in an operating theater under local anesthesia in patients with larger glottic gap or those who did not sufficiently benefit from voice therapy or injection laryngoplasty (8, 47).

Allensworth et al. (50) demonstrated the effectiveness and safety of bilateral type I thyroplasty in patients with presbylarynx. Further, Sund et al. (12) reported that most of the laryngologists (81%) preferred injection laryngoplasty [calcium hydroxyapatite (15%) and lipoinjection (11%)] before a permanent treatment method [bilateral type 1 thyroplasty (71%)]. Botulinum toxin injection has been established as an effective treatment method for spasmodic dysphonia (6), while vocal cord polyp, sulcus vocalis, Reinke's edema, and vocal cord scar could be treated with laryngeal phonosurgery to protect the vibratory properties of the vocal cords.

Conclusion

Voice changes in the elderly involve complex mechanisms and require a multidisciplinary approach from the early stages of diagnoses through to the final phases of treatment. Recognition of voice problems, which are thought to be normal part of aging, by physicians and the elderly population, and referring them to a laryngologist and a speech-language pathologist are crucial steps in increasing voice outcomes. While voice therapy is the first method of choice, expectations of the patients, laryngoscopic findings, coexistence of dysphonia and dysphagia may indicate a need for surgical intervention.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.B., L.Y., Design: S.B., H.B., Data Collection and/or Processing: S.B., H.B., Z.Ç.B., Literature Search: S.B., L.Y., H.B., Z.Ç.B., Writing: S.B., L.Y.

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Main Points

- Just like the organs in the human body, also voice changes with age. The prevalence of dysphonia in the elderly is up to 52.4% throughout life.
- Although dysphonia has a negative impact on the life quality of the elderly, almost one-fourth of this population consider it to be part of the normal course of aging.
- Some voice changes, such as reduced volume and projection, easy fatigability, tremor, a higher pitch in men, a lower pitch in women, a rough or breathy voice, a decreased maximum phonation time, dysphagia, and hoarseness are observed in the elderly population.
- Glottal incompetence, vocal cord atrophy, prominence of the vocal process of the arytenoid cartilage, bowing, edema, reduced amplitude, and periodicity of mucosal waves may be observed during evaluations of presbylarynx using videostroboscopy.
- While there are many treatment options, including medical, surgery, and voice therapy, the management of voice disorders mainly consists of one or more combinations of these and requires a multidisciplinary approach from the early stages of diagnosis through to the final phases of treatment.

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A Rare Incidental Diagnosis After Adenoidectomy: Sarcoidosis

Case Report

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Abstract

Sarcoidosis is a systemic disease of unknown etiology. It is characterized by non-caseating granulomatous inflammation. It most commonly affects the pulmonary and intrathoracic lymph nodes. Isolated nasopharyngeal involvement is very rare. Pediatric sarcoidosis and isolated nasopharyngeal involvement are rare entities. Symptoms of nasopharyngeal involvement can mimic adenoid hypertrophy. In this case report, we present a nine-year-old female who was diagnosed coincidentally with sarcoidosis with the adenoidectomy specimen.

Keywords: Sarcoidosis, nasopharynx, adenoidectomy, case report

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Introduction

Sarcoidosis is a systemic disease of unknown etiology, characterized by non-caseating granulomatous inflammation (1, 2). Its incidence has been reported to range from 0.1 to 109 per 100,000 and to be more common in females (1, 2). Sarcoidosis is most commonly encountered between the ages of 20 and 40 years (2). Approximately 2% of the patients with sarcoidosis are younger than 10 years old. The disease may be asymptomatic or can represent varying symptoms depending on the organs involved. It most commonly involves the pulmonary and intrathoracic lymph nodes. Extrapulmonary involvement has been reported in approximately 35% (3). The most common extrapulmonary involvements are skin lesions such as erythema nodosum. Eye, skin, liver, bone, joint, heart, and brain involvements are other examples of extrapulmonary lesions (2). Approximately 9% of the cases are observed in the head and neck. Only 1% of the cases are encountered in the sinonasal region (4). Isolated nasopharyngeal localization is extremely rare and only a few cases have been reported in the literature (5). In this case report, we

present a pediatric patient who was diagnosed coincidentally with sarcoidosis after adenoidectomy.

Case Presentation

A nine-year-old female patient was admitted to our tertiary ear nose and throat clinic with complaints of mouth breathing, snoring, and nasal blockage. The patient did not have a cough or dyspnea. These symptoms were present for several years. The patient did not have any history of recurrent tonsillitis or allergic rhinitis; she had no history of chronic diseases, surgery, or chronic drug use. She had no family history of chronic disease. The patient's tonsils were grade 2 according to the Brodsky scale. She had no tonsillar asymmetry. Anterior rhinoscopy and bilateral ear examinations were normal. The fiberoptic endoscopic nasopharyngeal examination was consistent with adenoid vegetation. The lesion almost completely blocked the nasopharyngeal airway. Neck examination was normal, there were no palpable lymph nodes. There were no skin eruptions. Transoral adenoidectomy was performed with curettes and angled cup forceps under general anesthesia. The patient was discharged one day after the operation with oral antibiotics and analgesics. Histopathological examination reported non-caseating granulomatous inflammation areas and reactive lymphoid hyperplasia (Figure 1). Decision was made to investigate the patient in terms of granulomatous diseases because of the non-caseating granulomatous lesion reported in the histopathological examination. The patient was referred to the pediatric rheumatology department. The rheumatology department investigated the patient for serum angiotensin-converting enzyme (ACE), immunoglobulin G (IgG) and blood calcium levels and found ACE: 72.2 U/L, IgG: 15.26 g/L, and blood calcium level 9.52 mg/dL (reference values: 8.0-52.0 U/L, 5.72-14.74 g/L, 8.5-10.4 mg/dL, respectively). Anti-cytomegalovirus IgG, Epstein–Barr virus (EBV)-EBNA IgG, and EBV-VCA IgG were positive. Complete blood tests, complete urinalysis, other serological tests, and routine biochemical tests were normal. Tuberculin skin test was negative. No pathology was observed in the chest X-ray and the patient was accepted as Stage 0 according to the Siltzbach Classification. The patient was diagnosed with sarcoidosis based on tissue diagnosis and blood parameters after other possible pathologies were eliminated. In the pediatric rheumatology department, treatment was not initiated, and follow-up was recommended because the patient had no systemic involvement and no active complaints. The patient's airway obstruction had improved in the 6th month of the follow-up. She had no signs of recurrence in the nasopharynx and had no systemic symptoms related to sarcoidosis.

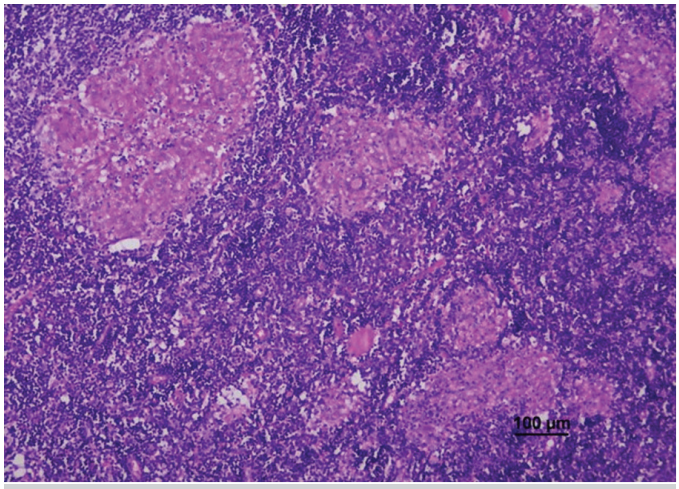

Figure 1. Image of histopathological examination of the adenoidectomy specimen, granulomas are seen (100x, Hematoxylin & Eosin)

Informed consent was obtained from the parents of the patient for this case report.

Discussion

While the symptoms of sarcoidosis are quite variable depending on the organs involved, shortness of breath, chest pain, and cough are the most common. Systemic symptoms may include weakness, fever, weight loss, and arthralgia. Approximately 16% of the cases are asymptomatic at diagnosis (2). Since sinonasal involvement presents non-specific rhinitis symptoms, the diagnosis of sarcoidosis can be missed due to possible pathologies such as septum deviation, allergic rhinitis, turbinate hypertrophy in the same patients (6). In their 2022 article Benettini et al. (7) presented two cases of nasopharyngeal sarcoidosis and reviewed the relevant literature. They identified 27 cases of nasopharyngeal sarcoidosis reported between 1952 and 2020. Nasal obstruction was the most frequently reported symptom among these cases. There was no significant gender difference, and mean age at diagnosis was 35 years. There were lung and/or intrathoracic lymph node involvement in 16 of the cases. Four of these cases were in the pediatric age group, ages were 5, 12, 13 and 15 years, and the gender distribution was equal. Two of the pediatric cases had lung and/or intrathoracic lymph node involvement. Systemic treatment was required in two of the four cases (7). Also in our case, sarcoidosis caused nasal obstruction by creating adenoid hypertrophy, which is a very rare clinical condition for this disease.

The diagnosis of sarcoidosis is defined by the presence of appropriate clinical and radiological findings, histological demonstration of non-caseating granulomatous inflammation, and elimination of other granulomatous diseases (2, 8). Chest radiography is sufficient for radiological diagnosis, and follow-up. High serum ACE activity is present in 40–90% of the active sarcoidosis cases. ACE activity can also reflect the total burden of granulomas (8). The tuberculin skin test is negative in 30–70% of the cases. In

their study, Güngör et al. (2) found negative tuberculin skin tests in 51.6% of the patients. Serum calcium concentrations have been reported to be elevated in 2% to 10% of patients with sarcoidosis.

In a study conducted with 27 pediatric sarcoidosis patients, the most common blood parameters were ACE elevation (74%), IgG elevation (64%), anemia (54%), high erythrocyte sedimentation rate (51%), and hypercalcemia (12%) (9). The chest X-ray of our patient was normal. She did not have lower respiratory tract symptoms, so thorax computed tomography was not done. She had high ACE and IgG values which supported the diagnosis of sarcoidosis. She did not have anemia, increased erythrocyte sedimentation rate, or hypercalcemia. Her tuberculin skin test was also negative.

One of the diagnostic criteria for sarcoidosis is the demonstration of non-caseating granulomatous inflammation in tissue samples (2, 8). Biopsy should be taken from the most easily accessible tissue (2). In our case, sarcoidosis was detected coincidentally during the histopathological examination of the adenoidectomy specimen. While pathology reports of the adenoidectomy samples mostly indicate lymphoid hyperplasia, different pathologies can also be rarely detected, as in our patient. Current studies on adenoidectomy specimens recommend histopathological examination when atypical pathology is suspected. Some authors suggested that histopathological examination would not be necessary if there is no preoperative risk factor (10). But we believe that every surgical specimen should pathologically be examined to be able to diagnose any rare and differentiated conditions as was the case in our patient. Otherwise, the diagnosis of some rare systemic diseases involving lymphoid tissue can be missed, and this would cause delays in the diagnosis and the treatment of the patient.

Corticosteroids are the first choice of treatment in patients with symptomatic sarcoidosis (8). Sarcoidosis has high spontaneous remission rates. Given the possible side effects of the treatment, asymptomatic or mild symptomatic cases should be followed closely before initiating the treatment. Medical treatment should be considered for symptomatic or progressive patients (2, 8). There are also local treatment options with corticosteroids, such as intralesional administrations. Nasal steroids are a treatment option for localized nasal disease (5). The symptoms of our patient regressed after adenoidectomy. Therefore, systemic and topical treatment was not used and the patient was followed closely.

Sarcoidosis generally has a good prognosis (2). In the study of Tunçay et al. (8), 57% of 338 patients were followed without treatment, and spontaneous remission was observed in 30%. During the six-month follow-up of our case nasal obstruction resolved and no recurrence was observed in the nasopharynx.

Conclusion

Pediatric sarcoidosis and isolated nasopharyngeal involvement are rare entities. Symptoms of nasopharyngeal involvement can mimic adenoid hypertrophy. Histopathological examination of adenoidectomy specimens is important, and we believe that every surgical specimen should be examined to avoid diagnostic delays.

Informed Consent: Informed consent was obtained from the parents of the patient for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.E.S., V.A., M.D., Concept: M.E.S., V.A., M.D., Design: M.E.S., V.A., M.D., Data Collection and/or Processing: M.E.S., V.A., M.D., Analysis and/or Interpretation: M.E.S., V.A., M.D., Literature Search: M.E.S., V.A., M.D., Writing: M.E.S., V.A., M.D.

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Main Points

- Sarcoidosis is a systemic disease of unknown etiology and characterized by non-caseating granulomatous inflammation.
- Approximately 2% of the patients with sarcoidosis are younger than 10 years old.
- The rate of involvement of the head and neck region is approximately 9%. Isolated nasopharyngeal involvement is extremely rare and only a few cases have been reported to date.
- Symptoms of nasopharyngeal involvement can mimic adenoid hypertrophy.

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A Unique Cause of Upper Airway Obstruction in a Child: Laryngeal Lipoma

Case Report

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Abstract

There are lots of diseases causing pediatric upper airway obstruction and stridor. They can be both congenital or acquired. While congenital causes are laryngomalacia, vocal cord palsy, congenital subglottic stenosis, acquired ones range from infections to foreign bodies or neoplasms. Laryngeal neoplasms develop almost epithelial in origin. Non-epithelial tumors consist 1% of laryngeal neoplasms. Although lipoma is the most common soft tissue tumor, laryngeal involvement is very rare and seen in the ages between 40–60 years. A 13-month-old child who had laryngeal lipoma and upper airway obstruction was aimed to present in this paper.

Keywords: Infant, larynx, neoplasm, lipoma, stridor, otorhinolaryngology, case report

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Introduction

Disorders that cause respiratory distress in children may occur anywhere from the pyriform aperture to the distal bronchi. They can be both congenital or acquired. Laryngomalacia, vocal cord palsy, stenosis and webs are the most common causes of stridor in children (1).

Almost all laryngeal neoplasms develop from epithelial cells. Non-epithelial tumors make a small portion of laryngeal neoplasms and can arise from mesenchymal tissues such as bone, cartilage, muscle, lipomatous and connective tissue; neuronal, blood and lymphatic vessels as well. These tumors are rare. Lipoma is the most common soft tissue tumor and consists half of all benign mesenchymal neoplasms nearly. Its incidence is 1% and its peak incidence is seen in patients aged 40–60 years. They are asymptomatic mostly. However; its location matters and can cause respiratory distress if it places in laryngeal inlet surely (2).

Here, a laryngeal lipoma is presented in a 13-month-old child who was treated via transoral way. It was an extremely rare case.

Case Presentation

A 13-month-old girl child was brought to an otolaryngology clinic because of noisy breathing, shortness of breath and neck collapse. She had these symptoms for six months and they got worse and became permanent lately. Her prenatal and natal histories were normal. Her parents denied any previous surgery, intubation history and medication. There was inspiratory stridor in her physical examination. Her respiratory rate was 24/min with 95% oxygen saturation. She had no cyanosis. She had supraclavicular retractions. There was a mass in her laryngeal inlet in the awake flexible fiberoptic laryngoscopic examination. Other otolaryngologic examinations were normal.

A semi-urgent surgery was planned because of her respiratory distress. There was a hipodense, multilobule mass in 20x15 mm size, on the right side of her larynx in computed tomography (CT) scan. Its density was estimated - 84 Hounsfield units (Figure 1). There was a smooth, submucosal mass in her direct laryngoscopy (Figure 2). After laryngeal suspension, the mass was identified and a mucosal incision was performed through just lateral edge of aryepiglottic plica by diode laser (3 watt power). The fatty mass was found and dissected bluntly and removed (Figure 3). Mucosal wound edges were tilted towards each other and not sutured to provide drainage and prevent hematoma as well. She was intubated for three days to avoid an emergency respiratory condition such as bleeding, edema or hematoma. She was able to feed at postoperative first week without aspiration. She had a nasogastric tube during this period. The mass was reported as lipoma in histopathological examination. She was asymptomatic at a 2-year follow-up period. Informed consent was obtained for publication from the parents of the child.

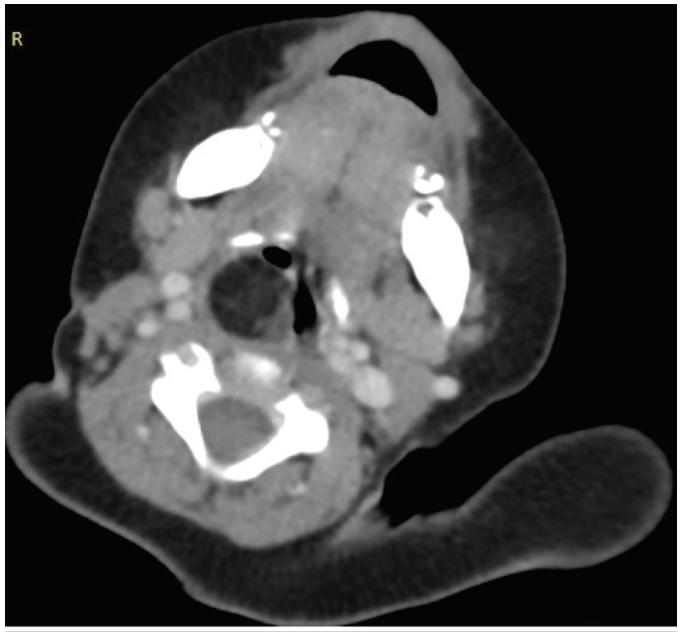

Figure 1. There is a hypodense (HU: -84), properly limited mass on the right side of the laryngeal inlet in the axial section of computerized tomography
HU: Hounsfield units

Discussion

A turbulent airflow through a partially obstructed or stenotic upper airway causes a hearable high-pitched sound called stridor. Because stridor is an important symptom indicating an underlying disease, the reason must be immediately

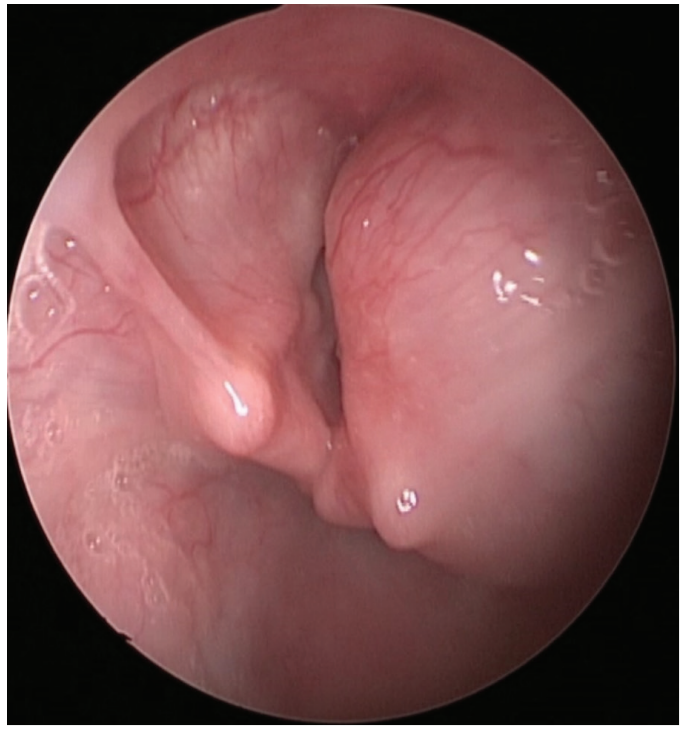

Figure 2. Endoscopic image of the mass on the right side of the larynx. The right aryepiglottic fold is obscured

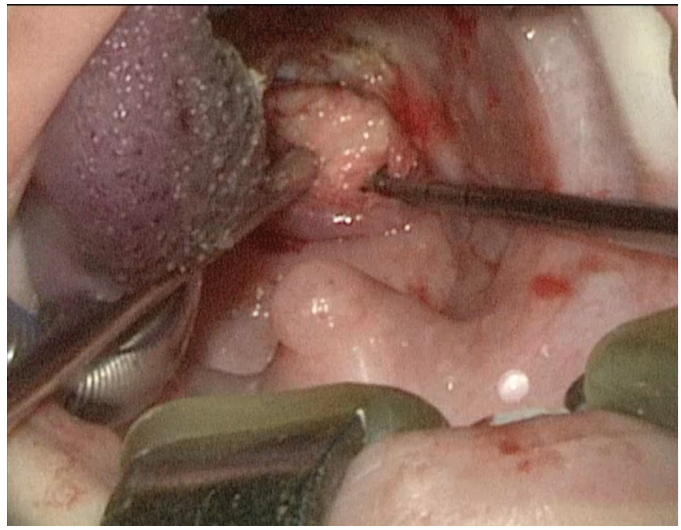

Figure 3. Blunt dissection of the mass transorally. There is a fatty mass compatible with lipoma

illuminated. There are many possible causes of acquired stridor such as infections, foreign bodies, neoplasms and iatrogenic insults. Prevalent congenital causes include laryngomalacia, vocal cord paresis, laryngeal webs, congenital subglottic stenosis, tracheomalacia, and subglottic hemangioma. Although acquired diseases incline to manifest acutely and at any age; congenital stridor presents at birth or shortly subsequent. Hence, inquiring about symptom initiation and duration can help to create a focused differential diagnosis (3). The respiration of the presented patient was normal at birth, then began to get worse after seven months, which made us think acquired reasons. There was a smooth mass on the right side of larynx in the presented patient. Because of the patient's semi-urgent conditon, neck CT was performed instead of magnetic resonance imaging (MRI) which requires a longer time procedure. It was better to perform an MRI for such a soft tissue mass.

It is a challenge to make a differential diagnosis for such laryngeal neoplasms from other conditions such as malignancy, laryngocele, or retention cyst. Laryngeal lipoma seems a submucosal or yellow mass endoscopically. Imaging methods are good indications for differential diagnosis. A CT scan ensures a definitive diagnosis of lipoma in almost all cases by figuring out the actual density of the mass. Fatty tissue has a negative CT attenuation number. Thus, lipomas have peculiar CT aspects of a homogeneous mass with few septations, a low CT attenuation number, and no contrast increment (2). The presented case had typical features of lipoma in CT scan and this was confirmed histopathologically.

Non-epithelial tumors of larynx are rare and form less than 1% of all primary laryngeal neoplasms. Lipoma is the most common mesenchymal tumor. It places in the subcutaneous tissue where fat is abound. Posterior area is more frequent in the neck, while it is rare in the upper aerodigestive tract, nearly 0.6% (2). Surgery is the treatment choice for lipoma. It is possible to perform an internal approach for lipomas less than 2 cm with or without laser. For larger tumors of more than 2 cm an external approach is indicated (2). We performed a transoral laryngeal microsurgery to excise the mass.

Friedman et al. (4) reported 38 cases having non-epithelial laryngeal tumors in a 9-year period, 16 of whom were benign conditions. The mean age was 56. There were two lipoma cases in their series. But ages of cases could not be determined from the article. In a literature review spanning 43 years, Reid et al. (5) reported 24 cases who had spindle cell lipoma in airway, 10 of whom had laryngeal. The youngest patient was 38 years old in their series. There were children reported with laryngeal lipoma in the literature as well. Jakobsen et al. (6) reported a six-year-old child admitted with obstructive apnoea, respiratory distress and dysphagia. Abtahi et al. (7) reported an eleven-year-old child who had paraglottic lipoma. Both cases were treated by open surgery.

Laryngeal soft tissue tumors are very rare conditions even in adults. They can cause respiratory and nutritional symptoms. They can be managed by excision via external or internal way. Internal approaches should be preferred in compatible cases.

Informed Consent: Informed consent was obtained for publication from the parents of the child.

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Authorship Contributions

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

Conflict of Interest: There is no conflict of interest to disclose.

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Main Points

- Inspiratory stridor should be enlighted in children as early as possible.
- Laryngeal neoplasms are generally in epithelial origin.
- Although rare, laryngeal neoplasms should be kept in mind in children with inspiratory stridor.

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Frontal Sinus Cholesteatoma Presenting with Intracranial and Orbital Complications: Diagnosis and Treatment

Case Report

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Abstract

Frontal sinus keratoma or cholesteatoma is a rare disease of paranasal sinuses and presents as a slow-growing mass that becomes symptomatic as it grows to the surrounding structures. Intracranial complications are not a common presentation and are potentially life-threatening. Frequently the final diagnosis is only made intraoperatively because several other frontal sinus tumors behave likewise. Definitive treatment requires complete removal of the keratoma, and a combined endoscopic and external frontal sinus approach is a good treatment option. In this report, we presented a 68-year-old female with frontal sinus cholesteatoma with diagnostic and therapeutic features of this pathology with the review of the literature.

Keywords: Fontal sinus, cholesteatoma, complication, orbit, surgery, case report

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Introduction

Paranasal sinus keratoma or "cholesteatoma" is a tumour-like mass composed of keratinizing squamous epithelium involved by a sac within an air-filled space. This type of lesion is frequent in the middle ear but rare on paranasal sinuses (1). The term "cholesteatoma" is a misnomer and to avoid confusing and inaccurate classification of paranasal sinuses cholesteatoma Hopp and Montgomery (2) proposed the use of the term "keratoma". Keratomas have been reported at the ethmoidal cells and the maxillary sinus, but the most frequent location at the paranasal sinuses is the frontal sinus (3). Treatment involves complete surgical excision, which sometimes can be challenging considering the size and structures involved by the tumour. We report a case of frontal sinus keratoma presenting with intracranial and orbital complications submitted to combined endoscopic Draf type III procedure and frontal sinus external approach with osteoplastic flap technique.

Case Presentation

A 68-year-old female patient was evaluated with complaints of headache and fever lasting two days. She also presented right eyelid oedema, ptosis, proptosis, chemosis and conjunctival redness. There was no restriction of eye movements, decreased visual acuity, focal neurologic signs, or nasal symptoms. She reported a previous history of acute frontal sinusitis complicated with subdural fronto-parietal empyema 10 years before. At that time, she was treated in a different institution, by a combined frontoparietal craniotomy and endoscopic drainage of frontal sinus.

Computed tomography (CT) scan revealed right frontal sinus filled with heterogenous soft tissue mass. The lesion eroded the posterior wall of the frontal sinus and a small extra-axial collection was present in-between (Figure 1). The orbital roof was also eroded allowing the mass to contact with orbital contents. Cerebrospinal fluid (CSF) analysis revealed hyperleukocytosis with a predominance of polymorphonuclear neutrophils. The diagnosis of frontal mucocele complicated with orbital cellulitis, meningoencephalitis and subdural empyema was established. Empirical antibiotic therapy was initiated with ceftriaxone, metronidazole, and vancomycin. Magnetic resonance imaging (MRI) of the paranasal sinuses showed a heterogeneous expansive mass filling the frontal sinus predominantly hyperintense on T2 weighted fat saturated images and hypointense on T1-weighted images (Figure 2, 3).

We performed an endoscopic sinus surgery, to drain the right frontal sinus mucocele. However, intraoperatively we found a thick white cheese-like mass filling the right frontal sinus (Figure 4). Given the lack of frozen section analysis availability, a definite surgical excision was postponed. The patient completed 12 days of antibiotic therapy, with progressive clinical improvement. Reduction of sinus inflammation and resolution of the empyema was reported on CT-scan three days after surgery. The patient was discharged from hospital with no neurologic or ophthalmologic sequels.

Final diagnosis of frontal sinus keratoma was made after histopathologic examination. We performed a revision surgery through a combined endoscopic Draf type III procedure and frontal sinus external approach with osteoplastic flap technique via a coronal incision (Figure 5). The keratoma was well delimited and not attached to the anterior fossa dura so we were able to perform a complete macroscopic excision with no iatrogenic CSF leak. At 6-month follow-up, no endoscopic signs of recurrence were present (Figure 6), and MRI evaluation did not show signs of cholesteatoma. Written informed consent regarding publishing her data and photographs were provided by the patient.

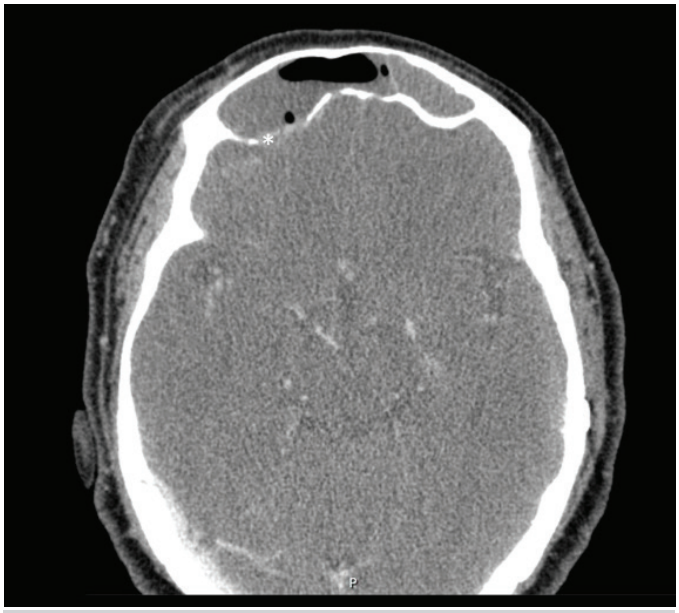

Figure 1. CT-scan at the emergency department (before any therapeutic intervention) a soft tissue opacification of frontal sinus and erosion of the posterior wall of the frontal sinus with associated extradural empyema (*)

CT: Computed tomography

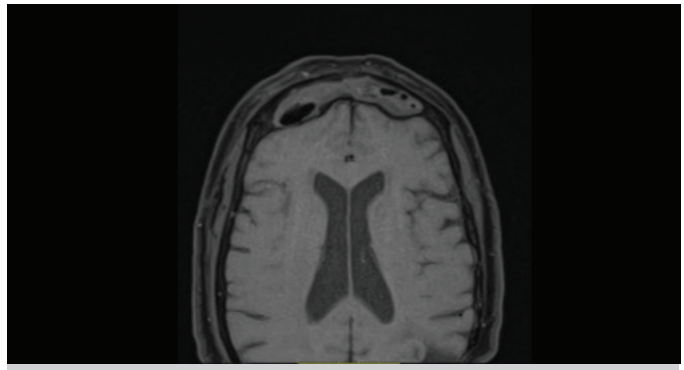

Figure 2. MRI T1 weighted imaging sequence showing a frontal sinus mass with a predominant hypointense sign

MRI: Magnetic resonance imaging

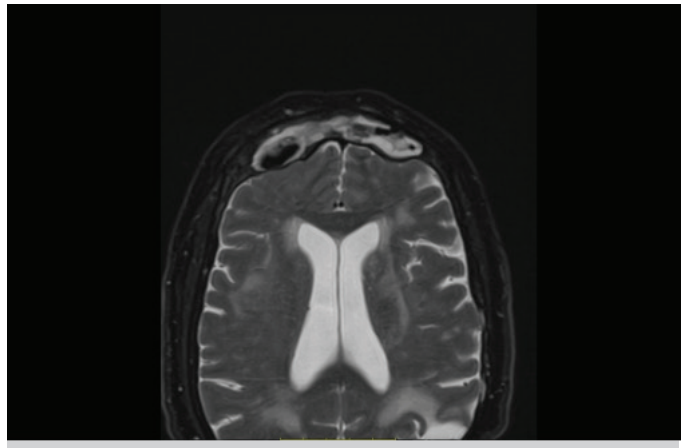

Figure 3. MRI T2 + fat saturation weighted imaging sequence showing a frontal sinus mass with a predominant hyperintense sign

MRI: Magnetic resonance imaging

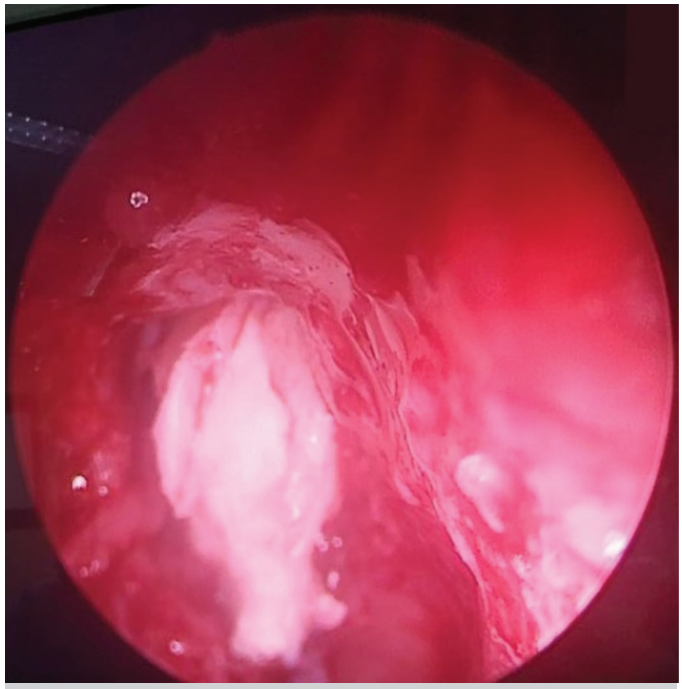

Figure 4. Endoscopic view of the frontal sinus during urgent sinus drainage, reveals a white cheesy mass suggestive of keratoma

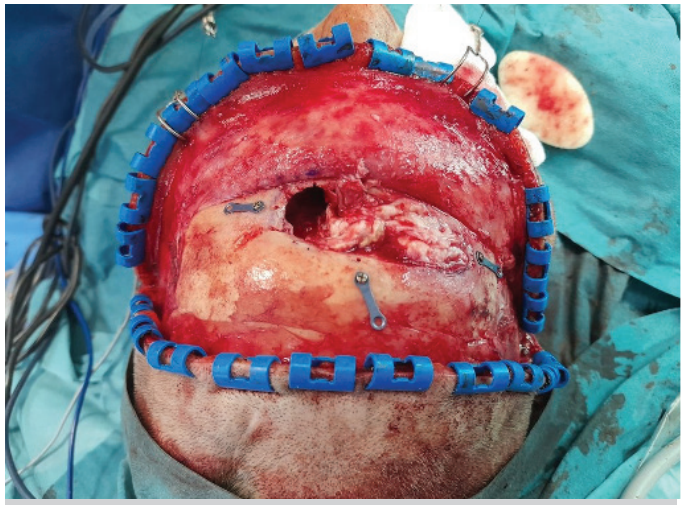

Figure 5. Surgical revision procedure: a combined approach with endoscopic Draf type III procedure and frontal sinus external approach with osteoplastic flap technique

Discussion

Frontal sinus keratomas are rare, a literature review in 2006 revealed 13 cases (1). The etiopathogeneses is not clear (2). Acquired cholesteatomas can be explained by implantation theory (squamous epithelium transport from other locations to the sinuses by surgery or trauma), migration theory (epithelium migrates from the nasal vestibule to the frontal sinus) or squamous metaplasia theory. In our case, the history of previous nasal surgery combined with craniotomy may favour the implantation theory, however we consider more plausible the previous presence of the cholesteatoma that kept undiagnosed until now.

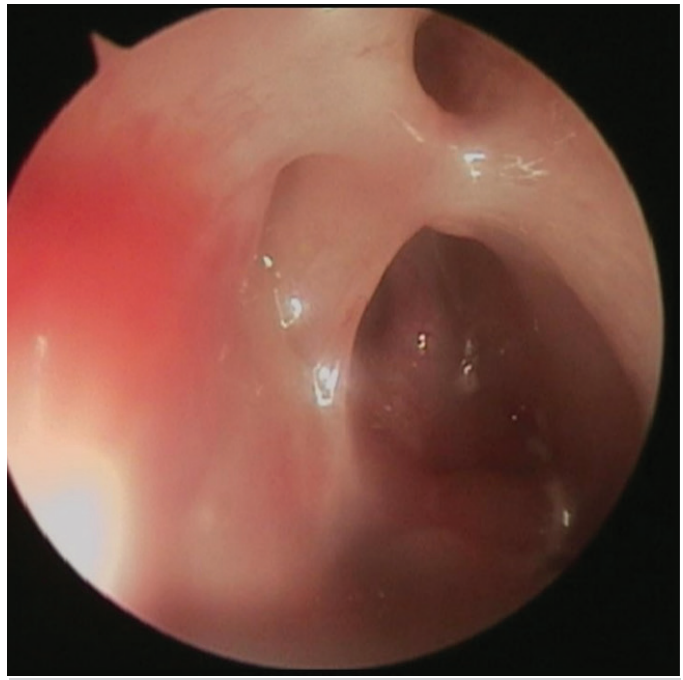

Figure 6. Endoscopic view of a Draf type III procedure, after 6 months, reveals no signs of keratoma

Frontal sinus keratomas are slow growing lesions, and most symptoms are secondary to erosion of the surrounding bone (2, 4). Anterior growing causes frontal headache and forehead deformity, on the other hand, inferior erosion allows growing into the orbit causing diplopia and ocular pain (1). Erosion of the posterior wall may cause intracranial complications like meningitis, empyema, and cerebral abscess (2). Our case is one of the few that presented with intracranial complications (3, 4). Chronic sinusitis symptoms are not typically present because the keratomas tend to lie laterally on the frontal sinus not blocking the frontal sinus duct (2).

Several other lesions of the frontal sinus behave like the keratoma. On MRI, keratomas usually appear hypointense on T1 and hyperintense on T2 imaging sequences, like the mucoceles (depending on the degree of fluid content) (3). However, keratomas lack enhancement with contrast and are hyperintense in diffusion-weighted imaging compared with CSF and brain parenchyma (5). However, frequently the keratoma is only diagnosed intraoperatively or after histopathologic examination (1).

The treatment is surgical excision. Osteoplastic frontal sinus obliteration procedure is frequently described in the literature (2). However, given the progressive improvements of endoscopic paranasal sinus surgery, re-establishing the draining route, allows a patent frontal sinus and may represent a good alternative, but evidence on this subject is sparse (4). Nevertheless, endoscopic approach is frequently insufficient for removal of the entire lesion, especially in a well pneumatized frontal sinus, so a combined osteoplastic frontal sinus approach should be considered. Once the frontal

sinus is cleared from the keratoma, obliteration may be performed, usually with abdominal fat (4). When it's possible to create a good tract of flow, frontal sinus obliteration is not required and leaving an open cavity will allow better control of recurrence (6). Clinical examination with nasal endoscopy and MRI are appropriate for follow-up (3).

Conclusion

Frontal sinus keratoma is a slow growing tumour that can reach significant proportions before any symptoms are reported and present with intracranial complications that are fortunately uncommon.

The combined endoscopic and external approach to the paranasal sinuses is a good therapeutic option, restoration of the frontal sinus recess offers an alternative to sinus obliteration.

Informed Consent: Written informed consent regarding publishing her data and photographs were provided by the patient.

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Authorship Contributions

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

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Main Points

- Frontal sinus keratoma may present with intracranial complications.
- Diagnosis of frontal sinus keratoma is challenging because other diseases like mucoceles can mimic this entity.
- Treatment with a combined endoscopic and external frontal sinus approach is a good treatment option.

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