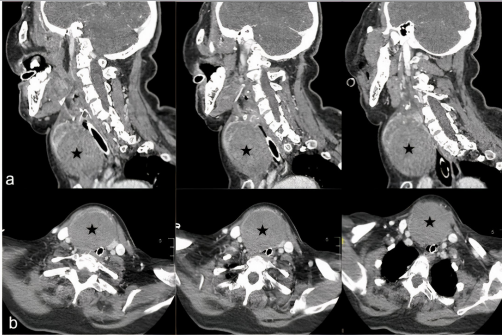


Turkish Archives of Otorhinology



Official Journal of the
Turkish Otorhinology
Head and Neck Surgery Society



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Turkish Archives of Otorhinolaryngology

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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. The journal is released at three-month intervals, in March, June, September and December, and one volume of the journal comprises four issues. 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 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readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

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 (doaj.org/bestpractice).

Turkish Archives of Otorhinolaryngology is indexed in PubMed Central, PubMed, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, DOAJ, EBSCO, CINAHL and ProQuest.

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

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Instructions to Authors

CONTEXT

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

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

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.

ETHICAL CONSIDERATIONS

Ethical Guidelines

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. Submission which do not have ethical approval will be reviewed according to COPE's Research, Audit and Service Evaluations guideline. Such manuscripts can be rejected after editorial review due to the lack of ethics committee approval.

For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo.

It is the authors' responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be enclosed, and the publication approval must be provided in the Methods section.

For studies carried out on animals, an approval research protocols by the Ethics Committee in accordance with international agreements (Guide for the care and use of laboratory animals, 8th edition, 2011" and/or "International Guiding Principles for Biomedical Research Involving Animals, 2012") is required. Also, the measures taken to prevent pain and suffering of the animals should be stated clearly in such studies.

Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Methods section of the manuscript.

Plagiarism and Ethical Misconduct

The Turkish Archives of Otorhinolaryngology is extremely sensitive about plagiarism. All submissions are screened by a similarity detection software (iThenticate by CrossCheck) at any point during the peer-review and/or production process.

When you are discussing others' (or your own) previous work, please make sure that you cite the material correctly in every instance.

Authors are strongly recommended to avoid any form plagiarism and ethical misconduct that are exemplified below.

Self-plagiarism (text-recycling): Overlapping sections or sentences with the author's previous publications without citing them. Even if



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you are the author of the phrases or sentences, the text should not have unacceptable similarity with the previously published data.

Salami slicing: Using the same data of a research into several different articles. Reporting the same hypotheses, population, and methods of a study is into different papers is not acceptable.

Data Fabrication: It is the addition of data that never occurred during the gathering of data or the experiments. Results and their interpretation must be based on the complete data sets and reported accordingly.

Data Manipulation/Falsification: It means manipulating research data with the intention of giving a false impression. This includes manipulating images (e.g. micrographs, gels, radiological images), removing outliers or 'inconvenient' results, changing data points, etc...

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act according to COPE flowcharts.

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Turkish Archives of Otorhinolaryngology does not consider preprint publications as prior publication. 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.

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

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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.

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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



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- Cover Letter,
- "ICMJE Conflict of Interest Statement Form" (<http://www.icmje.org/conflicts-of-interest/>) 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 in the title page),

- Abstract divided into appropriate sections,
- Keywords (For indexing purposes, a list of 4-8 key words 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 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),
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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019 - <http://www.icmje.org/icmje-recommendations.pdf>). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behaviour.

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.



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Authors are required to submit the following:

- Copyright Agreement and Acknowledgement of Authorship Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.turk-archotolaryngol.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 email address of the corresponding author,
- Acknowledgment 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 (<https://www.nlm.nih.gov/mesh/MBrowser.html>).

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” targeting 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 Otorhinology and Laryngology 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.

- 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, 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, Turkish Archives of Otorhinology and Laryngology accepts public registries that include 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 at <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>

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



Instructions to Authors

- 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

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Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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Mastoid Emissary Vein Canal Incidence and Its Relationship with Jugular Bulb and Sigmoid Sulcus Anatomical Variations

Original Investigation

✦ Rıdvan Pekçevik¹, Aylin Öztürk², Yeliz Pekçevik², Onur Toka³,
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Abstract

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Objective: We aimed to investigate the mastoid emissary vein (MEV) canal incidence and to identify its relationship with jugular bulb (JB) and sigmoid sulcus anatomical variations.

Methods: We retrospectively reviewed 1,300 patients with temporal bone computed tomography (CT) scans in January 2016 to March 2020. The presence and the diameter of the MEV canal, and the anatomical variations of the sigmoid sulcus and the JB were reviewed by two radiologists. High riding JB, JB diverticulum, dehiscence JB, and anterior and lateral protrusion of the sigmoid sulcus were evaluated. All variables were summarized using descriptive statistics. The differences between the groups for categorical data were investigated using the chi-square test. Numeric variables were compared with the Mann-Whitney and the Kruskal-Wallis tests. Logistic regression models were constructed.

Results: The study included 1,269 patients of whom 694 were female (54.7%) and 575 were male (45.3%). Their mean age was 39.01±18.47. Among them 915 (72.1%) had the right and 871 (68.6%) had the left MEV canal. Men were more likely to have the MEV canal on both sides. The presence of the right and left MEV canals was associated with the ipsilateral dominant JB/sigmoid sulcus. The left MEV canal was associated with the left high riding JB and right dehiscence JB.

Conclusion: This is the largest patient population reported in the literature and allows a more precise estimate of the MEV canal incidence. We also classified the diameter of the MEV canal to identify clinically relevant, prominent MEV incidence. This is also the first study to demonstrate a relationship between the presence of the MEV canal, and the JB and sigmoid canal variations. Since both the prominent MEV and the JB variations may be symptomatic, knowing this association between them may have clinical relevance.

Keywords: Temporal bone, anatomy, emissary veins, jugular veins, jugular foramina, multidetector computed tomography, radiology

Introduction

The sigmoid sinus begins at the junction of the transverse sinus and the superior petrosal sinus and runs inferiorly to communicate with the internal jugular vein (IJV). The jugular bulb (JB) located in the jugular fossa and connects to the IJV (1). Developmental abnormalities of the sigmoid canal and the JB have been proven to be clinically relevant, and may present with tinnitus, vertigo, and hearing loss (2).

While the IJV is the major extracranial venous drainage path, especially in prone position, the posterior fossa emissary veins are the primary route in upright position (3). The posterior fossa emissary veins connect the sigmoid sinus with the extracranial veins. The morphology of the posterior fossa dural sinuses, the emissary veins, and the JB are associated with the development of the brain, the shift to the postnatal type of circulation, and the postural hemodynamic change (1, 4). Regarding this close relationship, variations of the sigmoid sinus, the JB and the posterior fossa emissary veins may be associated.

A mastoid emissary vein (MEV) is a posterior fossa emissary vein that connects the sigmoid sinus and the posterior auricular or occipital vein crossing the mastoid foramen (4). Recognizing the MEV preoperatively is important. Because it may be a significant source of bleeding during skull base or middle ear surgery, detailed anatomical knowledge may prevent such complications (4). Air embolism may occur as a postoperative complication during a lateral suboccipital approach. Surgical materials used for hemostasis of the MEV may also cause complications (5).

The MEV may be the major drainage pathway to the extracranial venous system in the case of variations of dural sinuses or dural arteriovenous fistulas. It may also be used as an access route for the endovascular treatment of dural arteriovenous fistulas (6). The MEV may cause thrombosis of the sigmoid sinus after surgery of the middle ear. In addition, when the MEV is the major venous drainage of the posterior fossa, its ligation may result in venous ischemia and hemorrhage. Thrombosis of the MEV may occur as a complication of acute otomastoiditis. MEVs may also be a pathway for the spread of infections (7). Large MEVs may cause pulsatile tinnitus like JB and sigmoid sulcus variations (8).

MEVs can be evaluated with temporal bone computed tomography (CT) scan, CT angiography and magnetic resonance (MR) venography (8). Temporal CT scan and CT angiography are valuable tools for assessing the emissary veins and the venous vascular canals and are superior to MR venography in depicting venous structures with slower flow and smaller diameters (9, 10).

We evaluated the MEV canal incidence in a large patient population and to investigate their relationship with JB and

sigmoid sulcus anatomical variations using temporal bone CT scans.

Methods

Patients

This retrospective study was approved by the İzmir Health Sciences University, Tepecik Training and Research Hospital Ethics Committee (2020/14-66), and written informed consent was waived. In January 2016 to March 2020, we retrospectively reviewed 1,300 patients with temporal bone CT scans available at our department.

We excluded patients with previous mastoid, skull base, or posterior fossa surgery, dural sinus thrombosis or vascular malformations. Patients with poor technique or motion artifacts, and whose anatomy could not be properly assessed were excluded. We also excluded patients younger than five years old, since the JB may not be completely developed (10). Consequently, thirty-one patients were excluded, and 1,269 patients were included the study.

CT Examination

All temporal CT examinations were obtained using a 128-slice CT scanner (SOMATOM Definition AS, Siemens Healthcare, Erlangen, Germany) with a standard protocol without contrast administration. The scanning parameters included: detector collimation widths 128x0.6 mm, tube voltage of 120 kV. Patients were scanned in the caudal to cranial direction with a scan revolution time of 1 second and pitch of 0.8. Tube current was regulated by an automatic exposure control system (CARE Dose 4D; Siemens, Erlangen, Germany). Images were reconstructed in axial, coronal, and sagittal planes with a slice thickness of 1 mm. The images were transmitted to the picture archiving and communication systems (PACS).

Image Analysis

The anatomical variations in the MEV, sigmoid sulcus, and JB were evaluated on 0.6 mm slice thickness images that were transmitted from PACS to the workstation (Aquarius Workstation; TeraRecon, San Mateo, California, USA). The images were evaluated on this workstation, in the axial, coronal, and sagittal planes by two radiologists, A.A. and R.P. (with 4 and 15 years of experience, respectively).

The MEV canal runs from the sigmoid sulcus extracranially, crossing the mastoid foramen. The presence of the MEV canal was noted and classified according to its size: less than 2 mm, between 2 and 5 mm, and more than 5 mm (Figure 1).

Developmental abnormalities of the JB (high riding JB, JB diverticulum, dehiscent JB), and variations of the sigmoid sulcus (anterior and lateral protrusion) were evaluated.

When the roof of the JB was at the same level or above the floor of the internal acoustic canal, it was defined as high riding JB (Figure 2). A dehiscent JB was considered when the bony plate of the protruding JB toward the middle ear cavity was absent. Jugular bulb diverticulum was considered when there was an outpouching from the JB (11, 12) (Figure 3).

Sigmoid sulcus variation was characterized by an anterior and lateral position of the sigmoid sulcus in the mastoid bone (10, 13) (Figure 4). When the distance between the sigmoid sulcus lateral wall and the external tabula of the temporal bone was less than 2 mm, and the distance between the sigmoid sulcus anterior wall and the external acoustic canal was less than 2 mm, it was considered as a bulge of the sigmoid sulcus. The measurements were made on the axial images that showed the entire lateral semicircular canal.

Sigmoid sulcus/JB dominance was classified as right, left, or bilateral, according to the prominent vascular sulcus/bulb on one or both sides.

Statistics

IBM SPSS 23.0 statistical packages were used in statistical analysis. All variables were summarized with descriptive

statistics. For some comparisons between different groups, the Kolmogorov-Smirnov Goodness-of-Fit test was used to investigate numerical variables to identify whether their distributions were parametric or non-parametric. The differences between groups for categorical data were investigated using the chi-square test, while the numerical variables between different groups were compared to each other with Mann-Whitney U test in two labeled classes and the Kruskal-Wallis test in three or more labeled groups. Further statistical methods, logistic regression models were constructed for the right and the left MEV canals. The binary logistic regression models were explained and compared to each other with accuracy scores, odds ratios, and significances of some important independent variables. The models were also visualized using Receiver Operating Characteristic (ROC) graphics. $p < 0.05$ was considered



Figure 1. Temporal CT axial reformatted image shows the left mastoid emissary vein canal (arrow). The diameter of the canal is 2.5 mm

CT: Computed tomography

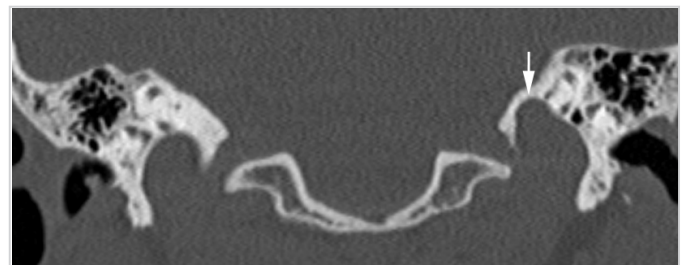


Figure 2. Temporal CT coronal reformatted image shows the left high riding jugular bulb (arrow)

CT: Computed tomography

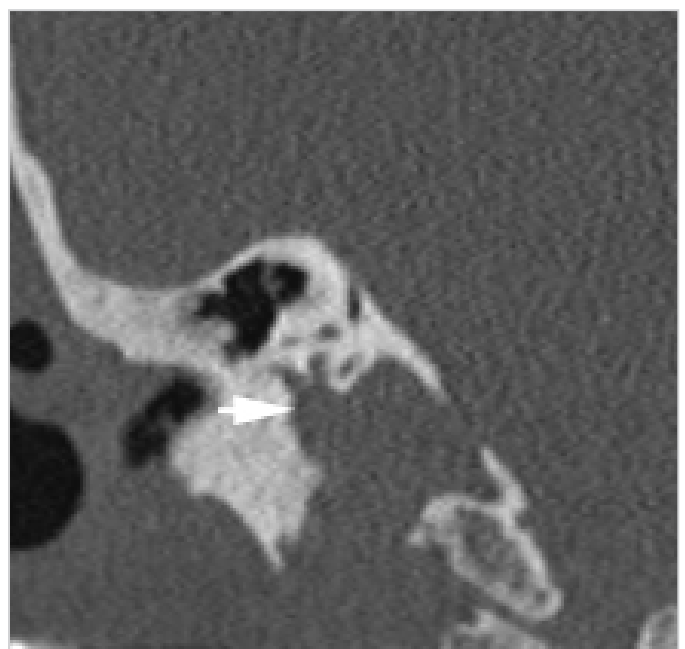


Figure 3. Temporal CT coronal reformatted image shows right high riding jugular bulb (JB) and JB diverticulum, an extraluminal outpouching from the JB (arrow)

CT: Computed tomography

statistically significant. An inter-observer reliability analysis with the kappa statistic was performed, and intraclass correlation coefficient (ICC) scores with 95% CIs were calculated.

Results

After the initial screening, 1,269 patients, 694 females (54.7%) and 575 males (45.3%) with a mean age of 39.01±18.47 were included in the study. Descriptive findings are given in Table 1.

We did not have any patients with the MEV canal larger than 5 mm. In our study population, 915 patients (72.1%) had a right MEV canal, and 871 patients (68.6%) had a

left MEV canal. Among all, 334 (26.3%) of the right MEV canals and 291 (22.9%) of the left MEV canals were larger than 2 millimeters.

Table 2 shows the mean age of the patients with right and left MEV canals. Comparison of patients by age showed no difference between the right (p=0.063) and the left MEV canals (p=0.367).

The frequency of the right and the left MEV canals in males and females are demonstrated in Table 3. MEV canals with a 2-5 mm diameter were less frequent in female patients (p=0.002 and p<0.001, respectively).

The frequencies and percentages of the right and the left MEV canals by the existence of other variables are demonstrated in Tables 4 and 5. There was no relationship between the presence of a right MEV canal and JB or sigmoid sulcus

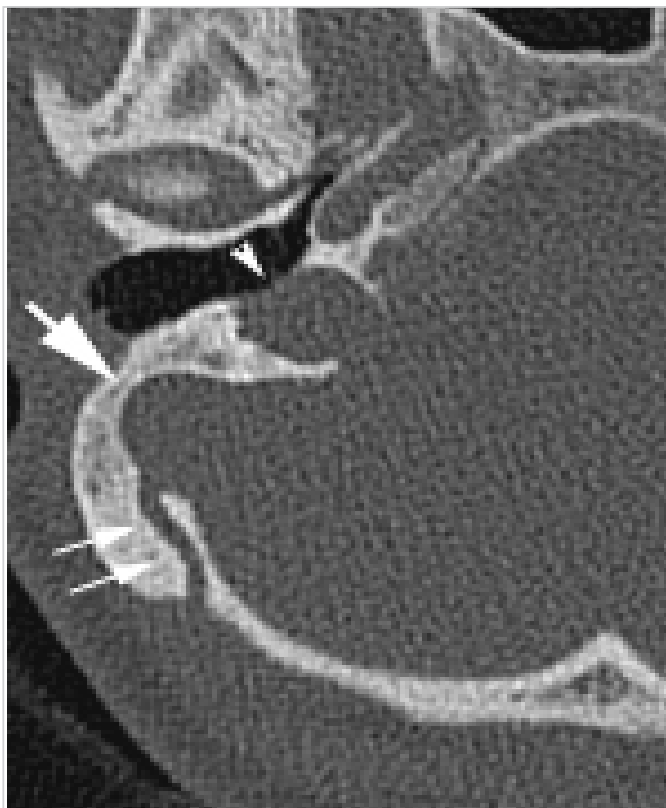


Figure 4. Temporal CT axial reformatted image shows lateral protrusion of the sigmoid sulcus into the mastoid bone (arrow). There is also a small (<2 mm) mastoid emissary vein canal (double arrow) and dehiscent jugular bulb (arrowhead)

CT: Computed tomography

Table 1. The frequency of anatomical variations

Variables	Labels	Patients (n)	%
R MEV	<2 mm	581	45.8
	2-5 mm	334	26.3
L MEV	<2 mm	580	45.7
	2-5 mm	291	22.9
High riding JB	R	480	37.8
	L	423	33.4
JB Diverticulum	R	134	10.6
	L	108	8.5
Dehiscent JB	R	88	6.9
	L	69	5.4
SS variation	R	146	11.5
	L	121	9.5
Venous dominance*	R	570	44.9
	L	284	22.4
	B	415	32.7
MEV dominance**	R	428	33.7
	L	309	24.3
	B	532	41.9

R: Right, L: Left, B: Bilateral, MEV: Mastoid emissary vein, JB: Jugular bulb, SS: Sigmoid sulcus, *venous drainage dominance determined by the diameter of the SS and JB, **emissary vein dominance determined by the diameter of the MEV canal, n: Number

Table 2. Mean ages of patients with right and left MEV canals

		Mean SD	p-value
Right MEV	<2 mm	37.2918.90	0.063
	2-5 mm	39.7117.46	
Left MEV	<2 mm	38.9618.82	0.367
	2-5 mm	40.2917.44	

MEV: Mastoid emissary vein, SD: Standard deviation, n: Number

Table 3. Frequency distribution of MEV canals according to gender

		Men		Women		p-value
		f	%	f	%	
Right MEV	<2 mm	254	44.2%	327	47.1%	0.002
	2-5 mm	181	31.5%	153	22.0%	
	Total	575	100.0%	694	100.0%	
Left MEV	<2 mm	251	43.7%	329	47.4%	<0.001
	2-5 mm	158	27.5%	133	19.2%	
	Total	575	100.0%	694	100.0%	

MEV: Mastoid emissary vein, f: frequency of MEV canals

Table 4. Frequencies and percentages of the right MEV according to the presence of JB and sigmoid sulcus variations

		Variables				p-value
		No		Yes		
		f	%	f	%	
R high riding JB						
R MEV	<2 mm	360	45.6%	221	46.0%	0.342
	2-5 mm	199	25.2%	135	28.1%	
L high riding JB						
R MEV	<2 mm	396	46.9%	185	43.7%	0.106
	2-5 mm	229	27.1%	104	24.6%	
R JB diverticulum						
R MEV	<2 mm	518	45.6%	63	47.0%	0.894
	2-5 mm	301	26.5%	33	24.6%	
L JB diverticulum						
R MEV	<2 mm	540	46.5%	41	38.0%	0.231
	2-5 mm	302	26.0%	32	29.6%	
R dehiscent JB						
R MEV	<2 mm	548	46.4%	33	37.5%	0.213
	2-5 mm	305	25.8%	29	33.0%	
L dehiscent JB						
R MEV	<2 mm	555	46.3%	26	37.7%	0.381
	2-5 mm	313	26.1%	21	30.4%	
R SS variation						
R MEV	<2 mm	510	45.4%	71	48.6%	0.159
	2-5 mm	305	27.2%	29	19.9%	
L SS variation						
R MEV	<2 mm	523	45.6%	58	47.9%	0.072
	2-5 mm	312	27.2%	22	18.2%	

R: Right, L: Left, MEV: Mastoid emissary vein, JB: Jugular bulb, SS: Sigmoid sulcus, f: frequency of MEV canals

variations. A left MEV canal was associated with left high riding JB (p=0.014) and right dehiscent JB (p=0.006).

The frequencies and percentages of right and left MEV canals by venous dominance, as determined by the sigmoid sulcus/JB diameter, are given in Table 6. The presence of

right and left MEV canals was associated with ipsilateral venous dominance. There was a relationship between a right dominant sigmoid sulcus/JB and the presence of a right MEV canal. A left dominant sigmoid sulcus/JB was associated with the presence of a left MEV canal.

Table 5. Frequencies and percentages of the left MEV according to the presence of JB and sigmoid sulcus variations

		Variables				p-value
		No		Yes		
		f	%	f	%	
R high riding JB						
LMEV	<2 mm	361	45.8%	219	45.6%	0.515
	2-5 mm	188	23.8%	103	21.5%	
L high riding JB						
LMEV	<2 mm	403	47.7%	176	41.6%	0.014
	2-5 mm	174	20.6%	117	27.7%	
R JB diverticulum						
LMEV	<2 mm	522	46.0%	58	43.3%	0.062
	2-5 mm	268	23.6%	23	17.2%	
L JB diverticulum						
LMEV	<2 mm	539	46.4%	41	38.0%	0.103
	2-5 mm	258	22.2%	33	30.6%	
R dehiscent JB						
LMEV	<2 mm	549	46.5%	31	35.2%	0.006
	2-5 mm	275	23.3%	16	18.2%	
L dehiscent JB						
LMEV	<2 mm	554	46.2%	26	37.7%	0.165
	2-5 mm	269	22.4%	22	31.9%	
R SS variation						
LMEV	<2 mm	510	45.4%	70	47.9%	0.194
	2-5 mm	266	23.7%	25	17.1%	
L SS variation						
LMEV	<2 mm	523	45.6%	57	47.1%	0.951
	2-5 mm	264	23.0%	27	22.3%	

R: Right, L: Left, MEV: Mastoid emissary vein, JB: Jugular bulb, SS: Sigmoid sulcus, f: frequency of MEV canals

Table 6. Frequencies and percentages of right and left MEVs by venous dominance

		Venous dominance*						p-value
		Right		Left		Bilateral		
		f	%	f	%	f	%	
Right MEV	<2 mm	262	46.0%	126	44.4%	193	46.5%	0.003
	2-5 mm	163	28.6%	55	19.4%	116	28.0%	
Left MEV	<2 mm	276	48.4%	112	39.4%	192	46.3%	0.003
	2-5 mm	104	18.2%	83	29.2%	104	25.1%	

MEV: Mastoid emissary vein, *determined by the jugular bulb/fossa and sigmoid sulcus diameter, f: frequency of MEV canals

According to the logistic regression model, males were 1.3 times more likely to have a left MEV canal than females. Males were 1.88 times more likely to have a 2-5 mm left MEV canal than females. Further, patients with a left high riding JB were 1.59 times more likely to have a 2-5 mm left MEV canal.

Inter-observer agreement for the evaluation of the variations was excellent, with an ICC score ranging from 0.91 to 0.95 (95% CI).

Discussion

We evaluated MEV canal incidences and JB and sigmoid sulcus variations in 1,269 patients. While the presence

of a MEV canal was not found associated with age, males were more likely to have MEV on both sides in this large patient group. Regarding the closely related developmental factors between the dural sinuses and the emissary veins of the posterior fossa and the JB, we expected that the variations of the sigmoid sinus, the JB and the MEV could be associated (1). The presence of a right or a left MEV canal was associated with the prominent JB/sigmoid sulcus, ipsilaterally ($p=0.003$). Although a right MEV canal was not related to JB or sigmoid sulcus variations, a left MEV was associated with a left high riding JB ($p=0.014$) and a right dehiscent JB ($p=0.006$). Patients with a left high riding JB were more likely to have a prominent left MEV in our study. Both the prominent MEV and the JB variations may be symptomatic and cause tinnitus as described by Kizildag et al. (10); thus, knowing this association may have clinical relevance.

Given its high spatial resolution, temporal bone CT scan is a valuable tool for assessing the temporal bone anatomy. It allows visualizing the fine anatomic structures of the middle and inner ears. The presence and variations of posterior fossa vascular canals can also be easily evaluated with temporal bone CT scans. With the introduction of multidetector techniques, images of less than 1 mm in diameter with multiplanar reformation improved diagnostic accuracy in the evaluation of the submillimetric structures (9). Brain CT angiography is also a valuable tool for assessing emissary veins. It allows to evaluate both emissary veins and dural venous sinuses (14). It is superior to MR venography in depicting venous structures with slower flow and smaller diameters (15). The major advantage of MR venography is lack of ionizing radiation.

In our study, the frequency of a right MEV, both <2mm and 2-5 mm, was slightly higher (72.1%) than that of a left MEV (68.6%). Frequency of MEV in cadaveric and imaging studies are reported within a wide range, mostly because of the number of patients and the methods used. Whether the MEV canal is more common on the right or on the left side is also controversial. A cadaveric study described a MEV in 63% of 12 specimens (3). Louis et al. (5) reported a MEV prevalence of 98% on the right and of 72% on the left side in their cadaveric study of 200 specimens. Reis et al. (16) reported MEV in 89% of their specimens. Koesling et al. (11) described the MEV canal incidence as 82% using high-resolution CT imaging. Pekçevik et al. (14), using CT angiography, identified MEV in 77.7% of their 166 patients, and more commonly on the left side. In their study using MR venography, Gulmez Cakmak et al. (15) found the MEV prevalence as 82.7% on the right side and as 81.4% on the left side in 247 patients. Tsutsumi et al. (17), using MRI, described the MEV incidence as 89.5%, 51.8% on the right and 24.7% on the left side. The relatively high incidence of right MEV, in our study and most of the other studies in the

literature, may be related to the similar mechanisms that are suggested to be the cause of the right JB and sigmoid sulcus dominance (1).

The major advantage of our study is that it is the largest patient population reported in the literature and allows a more precise estimate of the MEV canal incidence.

We also classified the MEV canals according to their diameter, especially to find the incidence of large-sized MEVs. There is no classification for the MEV canal in the literature. Previous studies only reported about the incidence of the MEV and did not classify these veins according to their diameter. We classified the MEV canal in our study, first to search for whether the relationship with JB and sigmoid sulcus variations is related to the diameter of the MEV, and second to find the incidence of a large MEV canal. Recognizing prominent mastoid emissary veins may have clinical significance.

A large MEV may cause bleeding during the skull base or middle ear surgery (4). Air embolism or embolism of the surgical material that are used to achieve hemostasis of the MEV may occur (5). Emissary veins may be prominent in patients with high-flow vascular malformations and hypoplasia or aplasia of the jugular veins. A large MEV may be a potential target for cannulation during endovascular procedures involving the transverse or sigmoid sinus (6).

In our study, the MEV canal was accepted as prominent when larger than 2 mm. We found the MEV canal prominent in 334 patients (26.3%) on the right and 291 patients (22.9%) on the left. Koesling et al. (11) described the MEV canal as prominent when larger than 1 mm, and found this in 6% of the patients in their study. This is significantly lower compared to our study and may be due to either the CT image resolution or a lesser number of patients.

Enlarged posterior fossa emissary veins were found to be associated with craniofacial syndromes (18). Sarioglu et al. (19) found prominent MEV, larger than 2 mm, more commonly in cochlear implant candidates (19.11%) compared to the control group (6.3%) in pediatric patients. Our study included both adult and pediatric patients older than 5 years old.

The presence of the MEV canal was not related to age in our study. Although the reason is not clear, males were more likely to have MEV on both sides than females in our large patient group. Louis et al. (5) found no relationship between gender or age. Gulmez Cakmak et al. (15) described the left MEV diameter higher in males, while Lang and Samii (20) observed that the MEV canal was less frequent in females. Dural venous sinus anomalies may also show gender differences like those in MEV. Hypoplasia of the left transverse sinus was reported to be more common in males (21). This may also give a clue about the relationship between

the presence of the MEV and the JB and sigmoid sulcus variations.

The sigmoid sinus and jugular sinus, primitive JB, occur at a similar period in the fetus. The MEV vein originates from the ipsilateral sigmoid sinus and communicates with the extracranial veins (1, 4). Enlargement of the jugular sinus for becoming a JB is a dynamic process and not present at birth. It occurs after two years. Standing upright (rather than the horizontal position maintained in the in-utero and neonatal periods) causes an upward negative pressure generating from the heart to strike the jugular sinus at the jugular foramen. This results in bulbous enlargement of the primitive JB and sigmoid sinus. It is suggested that the relatively long left brachiocephalic vein may cause the dissipation of the energy transmitted to the left primitive JB. This may contribute to the higher incidence of large right JB and sigmoid sinus (1, 4). We identified an association between the dominant sigmoid sulcus/JB and the presence of the ipsilateral MEV. This may be due to the postural hemodynamic change that affects the morphology of the JB, dural sinuses and emissary veins of the posterior fossa at the same time.

Although we did not find any relationship between the presence of a right MEV and JB or sigmoid sulcus variations, a left MEV was associated with the existence of left high riding JB ($p=0.014$) and right dehiscent JB ($p=0.006$). In our study, patients with left high riding JB were more likely to have a 2-5 mm left MEV. This relationship between a prominent left MEV and a high riding JB was not described previously. This is the first study to demonstrate the relationship between the presence of a MEV canal and JB and sigmoid canal variations. Both the prominent MEV and the high riding JB may be symptomatic and cause tinnitus (8). Knowing this relation may be clinically important. Gulmez Cakmak et al. (15) described an association between the presence of the MEV and variations of the transverse sinus, especially hypoplasia and aplasia of the transverse sinus, on the left side using MR venography. These findings are supported by the strong relationship between the embryological development of the posterior fossa emissary veins and dural venous sinuses (1). Although this study used MR venography to evaluate the MEV and dural venous sinuses, the findings support our hypothesis.

Our study also has some limitations. It is a retrospective study and we evaluated non-contrast CT images. The depiction of very small emissary veins, which is beyond the capability of the CT examinations, could have been missed. We evaluated the MEV in our study. Other posterior fossa emissary canals were not evaluated, since the MEV is considered as the most clinically important posterior fossa emissary vein and expected to show an association with the JB and sigmoid sulcus variations.

In conclusion, we evaluated the MEV canal incidence as well as JB and sigmoid sulcus variations. This is the largest patient population in the literature and allows for a more precise estimate of the MEV canal incidence. We also classified the diameter of the MEV canal to identify clinically relevant prominent MEV incidences. This is the first study to demonstrate the relationship between the presence of a MEV canal and JB and sigmoid canal variations. The presence of right and left MEV canals were associated with a prominent JB/sigmoid sulcus on the same side. A left MEV was associated with a left high riding JB and a right dehiscent JB. Patients with left high riding JB were more likely to have a prominent left MEV. Since both the prominent MEV and the JB variations may be symptomatic, knowing the incidence and association between the MEV canal and JB or sigmoid sulcus variations may have clinical relevance.

Ethics Committee Approval: This retrospective study was approved by the institutional review board of İzmir Health Sciences University, Tepecik Training and Research Hospital) (approval no: 2020/ 14-66, date: 23/12/2020).

Informed Consent: Written informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: R.P., Y.P., A.Ö., G.G.A., İ.Ç., Design: R.P., Y.P., A.Ö., G.G.A., İ.Ç., Data Collection and/or Processing: R.P., Y.P., A.Ö., Analysis and/or Interpretation: R.P., Y.P., O.T., G.G.A., İ.Ç., Literature Review: R.P., Y.P., A.Ö., Writing: R.P., Y.P., Critical Review: R.P., Y.P., A.Ö., O.T., G.G.A., İ.Ç.

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Main Points

- Developmental abnormalities of the sigmoid canal and jugular bulb (JB) have been proven to be clinically relevant, and can present with tinnitus, vertigo, and hearing loss.
- The mastoid emissary vein (MEV) is a posterior fossa emissary vein. It connects the sigmoid sinus and posterior auricular or occipital vein. Recognizing the MEV is clinically important.
- Presence of both right and left MEVs was associated with the ipsilateral prominent JB/sigmoid sulcus.
- The left MEV was associated with left high riding JB and right dehiscent JB. Patients with left high riding JB were more likely to have a prominent left MEV.
- Both prominent MEV and JB variations may be symptomatic and knowing this association may have clinical relevance.

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Caffeine Enhances the Balance System and Postural Balance in Short Time in Healthy Individuals

Original Investigation

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Abstract

Objective: This study aimed to explore the effects of caffeine on balance function by determining the extent to which caffeine consumption affects postural sway and balance control in healthy individuals.

Methods: Thirty healthy participants aged 20–35 years without any vestibular disorder were enrolled in this study. The participants were randomly divided into two groups, and those in Group 1 were given two cups of regular coffee (300–350 mg) while those in Group 2 were given two cups of decaffeinated coffee. The sensory organization test, the head shake sensory organization test, the limits of stability test, and the adaptation test were performed on all participants before and after coffee intake using computerized dynamic posturography.

Results: The sensory organization test composite scores ($p=0.001$) and the head shake condition 5 (C5) equilibrium scores ($p=0.001$) of the participants in Group 1 showed a statistically significant increase after coffee intake while the composite scores ($p=0.001$) and the head shake condition (C5) equilibrium scores ($p=0.001$) of those in Group 2 showed a statistically significant decrease. There was a statistically significant difference between the two groups in the equilibrium scores in the pitch plane ($p=0.001$), the yaw plane ($p=0.001$), and the roll plane ($p=0.001$) of C5 after coffee intake.

Conclusion: Consumption of an appropriate dose of caffeine may enhance body position, postural stability, and voluntary motor control ability. The combined use of the sensory organization test, the head shake sensory organization test, the adaptation test, and the limits of stability test in evaluating the balance mechanism in individuals with normal vestibular findings provides detailed information about postural sway.

Keywords: Postural balance, posturography, vestibular function tests, caffeine, psychoactive agents

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Introduction

Caffeine, a xanthine alkaloid found in coffee, soft drinks, green tea, energy drinks, chocolate, and medications, is the most widely consumed psychoactive substance and central nervous system stimulant worldwide (1). While consumption of an appropriate dose of caffeine (200–300 mg) is beneficial for reducing physical fatigue, it causes increased wakefulness, and is good for improving motor performance, attention, and visual acuity (2). In a study by Liguori and Robinson (4), consumption of 200–400 mg of caffeine was reported to produce similar effects as alcohol consumption. Alcohol consumption, however, reduces balance stability, but such reduction is not generally associated with the effects of caffeine (3). Caffeine is readily absorbed by the body (approximately within 45 minutes), and reaches plasma concentration within 15–45 minutes in humans (4). Moreover, the half-life of caffeine ranges from 2.5 to 5 hours (5). Caffeine reaches various organ systems (e.g., the central nervous system, the peripheral system) after absorption and may reduce the nerve conduction velocity by blocking adenosine receptors (particularly A1 and A2) in these systems (2). The adenosine receptors in the organs are found in the hippocampus, the cerebral cortex, the somatosensory cortex, the cerebellum, and the hypothalamic nuclei (6). In the central nervous system, many sensorimotor systems (proprioceptive, visual, vestibular), such as the cerebellum and the brain stem, are necessary for balance (7). Among its various other tasks, the central nervous system is responsible for ensuring postural control in activities during the complex interaction between the neurological and the musculoskeletal systems (8, 9). At the same time, caffeine affects the cognitive function as it has three important mechanisms of action that have a psychostimulant effect on the central nervous system (10). Caffeine indirectly affects the release of neurotransmitters as it can act as a competitive antagonist against the depressant effects of adenosine (11). When this system is affected, mood, memory, alertness, cognitive function, and balance system are also affected.

While some studies have shown that the postural sway of healthy individuals had increased after caffeine intake despite the improvement of their physical endurance, others asserted that caffeine intake did not have any effect on postural sway (7, 12–14). Although there are studies conducted on the effects of caffeine (alcohol, energy drinks, etc.) on postural sway, most of the research questions (e.g., “Does caffeine increase/decrease postural sway?” “Does caffeine have a placebo effect?” “How much does daily caffeine consumption affect the balance system?”) have not yet been answered. While there are various methods of assessing a person’s balance performance, posturography tests are the most common and the most effective tests to that end. Computerized dynamic posturography (CDP) is the gold standard, differentiating

among sensory, motor, and central adaptive impairments of postural control (15).

Sensory Organization Test (SOT), Head Shake Sensory Organization Test (HS-SOT), Limits of Stability (LOS) Test, and Adaptation Test (ADT) are the subtests of CDP for assessing different parts of the vestibular system (16). SOT is one of the most widely used protocols for CDP, evaluating a person’s ability to use the visual, vestibular, and somatosensory information required to sustain balance, and whether a person can maintain their body’s center of gravity when the flow of visual and proprioceptive information is interrupted (17). Also, HS-SOT is more sensitive than SOT, especially in dizzy patients, because of the elimination of the somatosensory and visual systems and the addition of head shake movements to the standard SOT with the eyes closed (18).

This study aimed to investigate the effects of caffeine on the balance performance of healthy individuals. The extent to which caffeine affects postural sway and balance control and the effects of daily caffeine consumption on the balance function were determined in this study.

Methods

The study was approved by the Ethics Committee of Hacettepe University (approval no: GO 17/208) and conducted in compliance with the guidelines of the Declaration of Helsinki. All participants provided their informed consent for the study. All hearing and balance measurements were conducted at the Audiology Unit of Hacettepe University Hospital.

Participants

This study included 30 healthy subjects aged 18–35 years. They were provided with detailed information about the study, after which their informed consent to participate in the study was obtained. Individuals who regularly consumed little (≤ 100 mg/day) or no caffeine were included in the study. Those who had any vestibular or neurological problems or a medical condition that would have impaired their balance and those who needed to avoid caffeine consumption due to health problems were not included. The participants were asked to fill out a medical history form and were given a list of caffeinated drinks that they were recommended not to consume at least 48 hours before each study session.

Experimental Design

The components of CDP (Neurocom® International Inc., Clackamas, Oregon, USA) that were used to evaluate the study participants’ balance performance were SOT, HS-SOT, ADT, and LOS test. The participants were randomly assigned to one of the two groups: Group 1 was given two cups of specially prepared caffeinated coffee (300–350 mg)

and Group 2 was given two cups of decaffeinated coffee prepared using the same method. Short breaks were given between tests. The tests were performed in two sessions per group. The coffee was given 45–60 minutes before the tests, and the participants were allowed to put additives in their coffee (milk and sugar or artificial sweeteners) if they did not want to drink black coffee. Also, the participants were not given any information about the type of their coffee and the amount of caffeine they consumed. In the first session, in Group 1, some individuals drank caffeinated, others did not; in Group 2, some of the individuals drank decaf, others did not drink at all. The second session was carried out after approximately 10 days, where the participants who had not drunk coffee in the first session drank coffee before the test and vice versa.

Sensory Organization Test

The SOT included six test positions, from easy to difficult (Figure 1). After the test procedure was explained to the participants, they were asked to wear a harness secured to the bars on the device and stand on a platform. Each of these six conditions was repeated three times to calculate the mean value of the measurements for the condition, and every trial lasted 20 seconds. The SOT equilibrium scores were the mean scores for the three trials. The mean equilibrium score for each condition and the composite equilibrium score for all the conditions were calculated within the 0–100 range according to the participant's postural sway at the limits of stability. A composite score of 0–59 indicated falls; 60–69, a risk of falling; and 70–100, normal results (19).

Head Shake Sensory Organization Test

HS-SOT is a modified test that was created by adding head shake movements to the standard SOT with the eyes closed. The use of somatosensory information is evaluated in condition 2 (C2), and vestibular inputs are tested in

condition 5 (C5). The participants were asked to wear a gyro headband for detecting their movements and velocity, and to move their heads in the yaw, pitch, and roll planes in the C2 and C5 positions of SOT simultaneously with a rhythmic audio signal. The mean equilibrium score and equilibrium score ratio were used for the evaluation of the subjects in each plane (20).

Adaptation Test

The ADT measures the adaptation ability of the motor system by evaluating the automatic postural responses of a person to reaction forces. In this test, the subjects were asked to stand on the CDP platform and were exposed to five equivalent surface irregularities in two different conditions (i.e., toes up and toes down). The sway energy score for each of the conditions and the mean score for each of the toes-up and toes-down perturbations were calculated from the test results (19).

Limits of Stability Test

The LOS Test was performed on all subjects in eight directions (front, left-front, right-front, right, left, back, right-back, and left back). It is used to provide information about the subjects' abilities to move their center of gravity on a support surface using ankle strategies and weight transfer while staying in an upright position. The mean value of the eight completed trials for each target (front or back) was calculated to determine the five parameters of LOS: reaction time (RT), movement velocity (MV), endpoint excursion (EE), maximum excursion (ME), and directional control (DC) (16).

Statistical Analysis

IBM SPSS 23.0 was used for data analysis. Parametric tests were used because both Group 1 and Group 2 showed normal distributions. The paired-samples t-test was used to

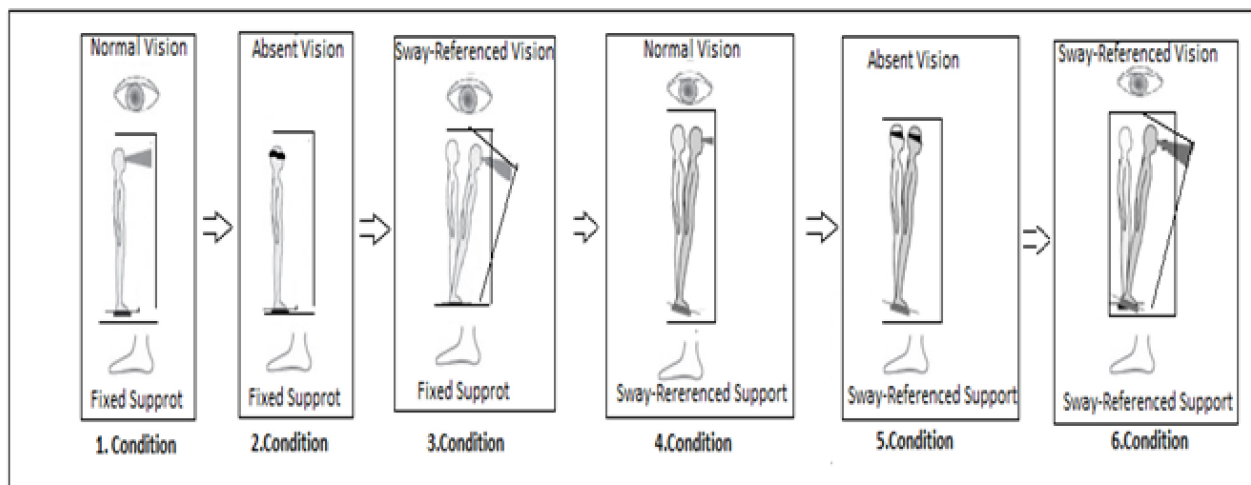


Figure 1. Six conditions of the Sensory Organization Test

compare intragroup differences (before and after drinking coffee), and the independent-samples t-test was used to compare intergroup differences. Statistical significance was set at <0.05.

Results

The mean age of the 15 participants (seven males, eight females) in Group 1 who consumed caffeinated coffee was 23.66 years [range: 20–35 years; standard deviation (SD): ±1.11], and the mean age of the 15 participants (eight males, seven females) in Group 2 who consumed decaffeinated coffee was 25.91 years (range: 20–35 years; SD: ±1.59). All the balance scores before and after coffee intake for Group 1 and Group 2 were measured separately. The SOT, HS-SOT, ADT, and LOS test mean scores of the participants, and the comparison data, are shown in Table 1.

Differences between the SOT composite and equilibrium scores of the participants

Regarding the participants' composite and balance scores from SOT (C2 and C5), the C5 and composite balance scores of the participants in Group 1 showed a statistically significant increase after caffeine intake. In Group II, the C5 and composite balance scores of the participants who consumed decaffeinated coffee showed a statistically significant decrease (p=0.001). There was no statistically significant difference between the C2 equilibrium scores of Group 1 (p=0.199) and Group 2 (p=0.277) before and after coffee intake (Figure 2). The composite and mean C5 scores of the participants in both Group 1 and Group 2 are shown in Table 1.

Relationship between coffee intake (caffeinated and decaffeinated) and the HS-SOT and SOT scores

There was a statistically significant difference between the mean equilibrium scores of Group 1 in HS-SOT C5 in the vertical plane (p=0.001), horizontal plane (p=0.001), and roll plane (p=0.009) after coffee intake. In Group 2, after coffee intake, there was a statistically significant difference between the mean balance scores in HS-SOT C5 in the vertical plane (p=0.009), horizontal plane (p=0.001), and roll plane (p=0.008), and between the mean balance scores in HS-SOT C2 in the vertical plane (p=0.046) and roll plane (p=0.025). There was a statistically significant difference between the equilibrium scores of both groups in the vertical plane (p=0.001), horizontal plane (p=0.001), and roll plane (p=0.001) of HS-SOT C5 after coffee intake.

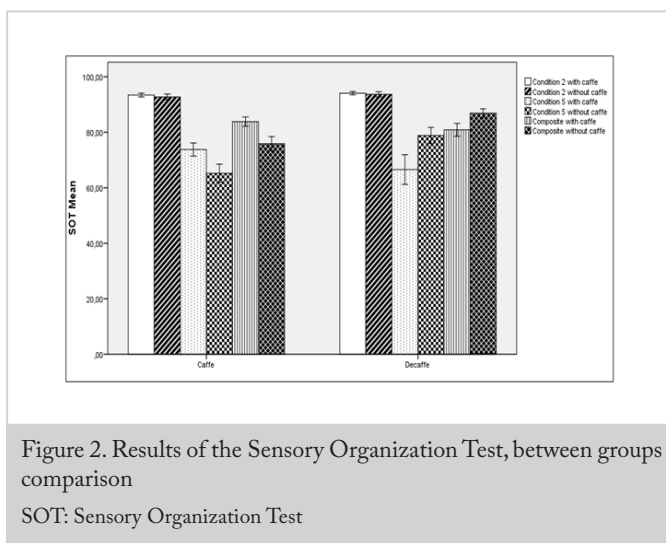


Figure 2. Results of the Sensory Organization Test, between groups comparison
SOT: Sensory Organization Test

Table 1. Comparison of Sensory Organization Test, Head Shake Test and Adaptation Test Scores between the two groups

	Group1 (with caffeinated coffee) (n=15)	Group 1 (without coffee) (n=15)	p-value	Group 2 (with decaffeinated coffee) (n=15)	Group 2 (without coffee) (n=15)	p-value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
SOT 2	93.31±1.60	92.11±2.58	0.411	94.08±1.08	93.66±1.68	0.479
SOT 5	71.88±6.22	63.2±5.06	0.001*	66.57±9.65	78.84±5.25	0.001*
CS	81.46±3.94	73.40±6.52	0.001*	80.86±4.15	86.86±2.87	0.001*
HS-SOT 2(v)	94.08±1.08	93.66±1.68	0.657	86.26±3.92	87.95±3.61	0.046*
HS-SOT 5(v)	78.84±5.67	66.57±9.65	0.005*	47.28±12.65	57.21±11.95	0.009*
HS-SOT 2(h)	90.85±2.28	91.84±2.57	0.127	92.84±1.38	91.82±2.22	0.090
HS-SOT 5(h)	57.83±12.24	37.41±11.61	0.001*	54.93±7.2	66.18±4.85	0.001*
HS-SOT 2(r)	88.64±2.66	88.53±2.69	0.065	91.35±2.2	90.06±2.35	0.025*
HS-SOT 5(r)	49.75±11.1	41.31±13.52	0.009*	56.95±12.67	63.05±8.51	0.008*
ADT Up	57.80±9.54	65.86±12.81	0.027*	72.4±15.6	70.73±19.41	0.551
ADT Down	43.73±10.19	44.19±10.86	0.637	43.26±8.27	40.26±5.04	0.073

*p<0.05; SD: Standard deviation, CS: Composite Score, (v): Vertical, (h): Horizontal, (r): Roll, SOT: Sensory Organization Test, HS: Head Shake Test, ADT: Adaptation Test

Relationship between coffee intake and the ADT score

There were no statistically significant differences between Group 1’s ADT up scores (p=0.886) and ADT down scores (p=0.637) or between Group 2’s ADT up scores (p=0.551) and ADT down scores (p=0.073) before and after coffee intake. While there was a statistically significant difference between the groups in the mean ADT up scores after coffee intake (p=0.042), there was no significant difference between the groups in the mean ADT down scores (p=0.196).

Relationship between coffee intake and the LOS test score

Regarding the mean values of the eight conditions in the LOS test parameters, a statistically significant decrease was observed in the endpoint excursion value after caffeine intake in Group 1 (p=0.001).

Considering the LOS test parameters in Group 1 and Group 2 after coffee intake, a statistically significant difference was observed only in the endpoint travel parameter in the back direction (p=0.001) and the maximum travel parameter in the left direction (p=0.007). No statistically significant differences were found among the reaction time (p=0.225), movement velocity parameters (p=0.127), and endpoint excursion parameters in the right direction (p=0.074), left direction (p=0.0245), and left–front direction (p=0.610) in Group 1 after coffee intake (Table 2). Intragroup and intergroup comparisons of the different LOS test parameters are shown in Figure 3.

Discussion

In addition to their effects on the cognitive and cellular functions of the brain, caffeinated beverages are known to

affect the audio-vestibular system. This study proved that healthy individuals who consume caffeinated coffee have significantly better postural control than those who do not consume caffeinated drinks or consume only decaffeinated coffee, particularly in conditions that do not involve difficult vestibular cues. Caffeine consumption increases wakefulness, improves the mood, and causes a release of catecholamines in the central nervous system, but it also impacts the heart, skeletal muscle, and adipocyte tissues (21).

Moreover, the aforementioned findings were thought to imply that a more effective use of the vestibular system could be achieved by caffeinated drink consumption despite the lack of visual support, and that caffeine intake could lead to more effective postural control. It has been stated that consumption of a moderate dose of caffeine can be effectively used as an ergogenic aid before exercise to increase the performance variables in various sports (22).

In addition, the SOT performance was found to be higher because the level of alertness was increased after caffeinated drink consumption, thereby leading to increased balance performance that would enable postural control as per voluntary motor control (23). McNerney et al. (24) stated that as caffeine enhances balance performance, it increases the level of alertness and the ability to focus on a task. In a previous study, however, the difference in the equilibrium scores between the caffeinated and non-caffeinated drink consumption sessions for individuals who consume large amounts of caffeine daily was higher than that for regular caffeine consumers.

Because the central and peripheral vestibular anomalies involving body balance may affect our ability to use vestibular

Table 2. Direction-specific analysis of limits of stability in individuals with/without caffeinated and decaffeinated coffee

Variables		Reaction time (RT) (s)		Movement velocity (MVL) (deg/s)		Endpoint excursion (EPE) (%)		Maximal excursion (MXE) (%)		Directional control (DCL) (%)	
		Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Group 1	With caffeinated coffee	0.7±0.2	0.225	4.4±1.0	0.585	82.8±7.9	0.001*	93±5.3	0.347	80.3±6.1	0.409
	Without caffeinated coffee	0.7±0.2		4.6±1.5		75.3±7.8		94±5.2		81.3±4.6	
Group 2	With decaffeinated coffee	0.7±0.2	0.518	5.9±3.3	0.341	73.4±13.5	0.065	89±10.4	0.104	80.2±6.1	0.443
	Without decaffeinated coffee	0.7±0.2		4.9±1.7		78.6±9.9		90±7.2		81.4±4.6	

*p<0.05, SD: Standard Ddeviation

stimuli, increased sensory input to the central nervous system after caffeine intake is consistent with the results of our study which demonstrated the role of caffeine in postural balance (25). This finding is contrary to those of previous studies which reported that caffeine consumption did not affect postural balance, as the mean equilibrium scores (both when the eyes were open and were closed) minimally increased after caffeine intake (8).

However, it was surprising that the participants had lower mean equilibrium scores after consuming decaffeinated coffee than when they did not consume any drink. This could be a placebo effect because most of the participants had lower daily coffee consumption and caffeine is believed to negatively affect balance.

A study by Kim et al. (26), in which only static balance was measured, reported that the usual amount of caffeine intake influenced the postural stability of stroke patients using the somatosensory function by reducing the visual deprivation effect. In this study, the static and dynamic balance performances were also evaluated with the SOT, HS-SOT, ADT, and LOS test. The LOS test is a reliable tool for

assessing a person's voluntary motor control skills in terms of the body's center of gravity and body position (27). Juras et al. (28) conducted a study with healthy individuals and found that the most reliable LOS test parameter for assessing the body's ability to control its center of gravity is excursion. In the presented study, there was a statistically significant difference in the endpoint and maximum excursion (%) values, as observed in the comparison of the LOS test results before and after caffeinated and decaffeinated drink consumption. Moreover, there was a statistically significant increase in the endpoint and maximum excursion (%) values from baseline in the participants who consumed caffeinated drink than in those who consumed decaffeinated drink. As the differences in endpoint and maximum excursion values can be observed during the most complex movements of the body, it is thought that caffeine has a positive impact on the balance system during dynamic movements against the center of gravity (16).

We found that the HS-SOT results were significantly better in all the planes in the participants who consumed caffeinated drink than in those who consumed decaffeinated drink, which also demonstrated the positive effect of caffeine intake on the dynamic balance system despite the addition of head shake movements. Interestingly, this study, to date, is the only one that investigated the impact of caffeine intake on HS-SOT performance.

The head shake test leads to an increased neural activity especially in those with unilateral peripheral vestibular weakness, even though they have normal results in the standard tests, and thereby facilitates the diagnosis in such individuals (18). As the active head movement in SOT C2 and C5 may lead to disruption in postural control and the body's compensation mechanism, even small differences in postural balance are easily detectable (29). One of the most important advantages of the head shake test is the simultaneous stimulation of the peripheral vestibular system with postural control (30).

The ADT, the least reliable among posturography tests assessing motor skills, can be influenced by other factors not associated with balance, such as anxiety, fear, and biomechanical factors (15). Although this test was a part of the SOT, its results were not compared with those of the other tests because its parameters are not comparable with those of other test batteries (19). Also, as there was no significant difference between the mean ADT scores of the groups in this study, we conclude that ADT is not an effective tool for evaluating the effects of caffeine intake on balance. Taken together, these findings suggest that the SOT, the HS-SOT, and the LOS test are beneficial tools for determining the effects of caffeine intake on functional balance. It was also thought that consuming two cups of coffee daily would have positive impacts on balance and attention in individuals with normal vestibular findings.

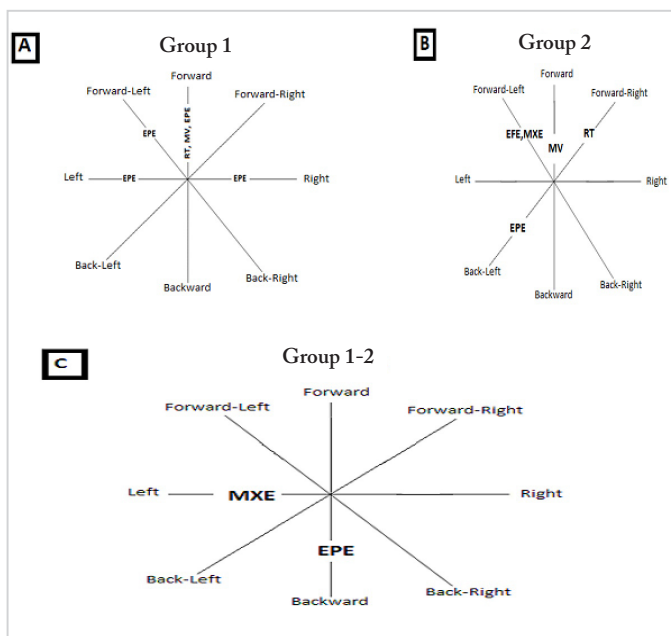


Figure 3. Limits of Stability Test Results: (a) differences parameters and locations in Limits of Stability Test, between before and after consuming coffee for Group 1; (b) parameters and locations in Limits of Stability Test, between before and after consuming coffee for Group 2; (c) differences parameters and locations in Limits of Stability Test between groups. The Wilcoxon Test was used for in-group comparison and the Mann-Whitney U Test was used for comparison between groups.

EPE: Endpoint excursion, MXE: Maximum excursion, MV: Velocity of movement, RT: Reaction time

Forward, backward, right, left, forward-right, forward-left, back-right and back-left shows shift in eight different directions

This study has several limitations, including the small number of participants and the fact that different doses of caffeine were not used. Also, as we did not check the body mass index (BMI) of the participants, we do not know whether the intake of the same dose of caffeine always has the same effect on the subject.

Conclusion

The consumption of an appropriate amount of caffeine can enhance postural control under different conditions because caffeine increases attention and provides stimulation. This study is important in that it showed the positive effects of caffeine consumption on static and dynamic balance performance. It was found that the effect of caffeine consumption, particularly on balance performance, could be evaluated with the SOT and the HS-SOT. Future studies investigating the effects of the consumption of different amounts of caffeine and the BMI of the participants on the balance system will add valuable contributions to the literature.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hacettepe University Non-Interventional Clinical Trials (GO 17/208).

Informed Consent: Written informed consent was obtained from trainers and trainees who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Ç., B.A., Design: B.Ç., B.A., Supervision: B.Ç., B.A., S.A., Data Collection and/or Processing: B.Ç., B.A., Analysis and/or Interpretation: B.Ç., B.A., S.A., Literature Search: B.Ç., B.A., Writing: B.Ç., B.A., Critical Review: B.Ç., B.A., S.A.

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

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Main Points

- Caffeine has a stimulating effect on posture and automatic motor control.
- A certain amount of caffeine consumption has a positive impact on the balance system during dynamic movements against the center of gravity.
- Head shake-sensory organization test and limit of stability test are useful tests used for the detailed evaluation of the balance mechanism.

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Mycobiome in the Middle Ear Cavity with and Without Otitis Media with Effusion

Original Investigation

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Abstract

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Objective: No data have yet been published revealing the composition and the diversity of fungal communities (mycobiome) in the human middle ear cavity. The presented study investigated the mycobiome in the middle ear cavities of individuals with healthy middle ears and patients with otitis media with effusion.

Methods: A total of 77 middle ear and four adenoid samples were collected from 47 individuals (35 children and 12 adults) in Group 1 and from 20 children in Group 2. The mycobiome profile was analyzed with nuclear ribosomal internal transcribed spacer 2 (ITS2) based metabarcoding using an Illumina MiSeq metagenomics kit.

Results: ITS2-based metabarcoding detected 14 different genera and 17 different species with a mean relative abundance of $\geq 1\%$ in the samples analyzed. Mycobiome profile was similar between the adenoid tissue and the middle ear cavity, between Groups 1 and Group 2, and between children and adults. *Fusarium*, *Stemphylium*, *Candida*, and *Cladosporium* were the most abundant genera detected in all samples. The mean relative abundances of the genera *Candida* and *Fusarium* were remarkably higher in Group 2 compared to Group 1.

Conclusion: The species *Candida glabrata*, *Candida cretensis*, *Aspergillus ruber*, *Penicillium desertorum*, and *Rhizopus arrhizus* were significantly more abundant in patients with otitis media with effusion (OME), raising the possibility that they affect the pathogenesis of OME.

Keywords: Mycobiome, fungus, middle ear, adenoid, otitis media with effusion, high-throughput sequencing, metabarcoding

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Introduction

Mycobiome, the fungal community in and on an organism, makes up less than 1% of the human microbiome (1). Although the diversity and relative abundance of mycobiome are lower than those of the bacteriome of microbiota, certain body sites such as the oral cavity, respiratory tract, gastrointestinal tract, skin, and vagina host several fungal genera in addition to bacteriome (2,3). Regarding the mycobiome of the oral cavity and the respiratory tract, which interacts with the middle ear cavity, culture-dependent and molecular techniques revealed diverse genera such as *Candida*, *Cladosporium*, *Saccharomyces*, *Penicillium* and *Aspergillus*, in these anatomic sites (4-6).

Fungi on and in humans play an important role in health and disease development alike by modifying basic physiology and maintaining microbial community profiles (7). Due to the small number of studies, however, we have limited knowledge on the interaction between mycobiome and host. Accurate identification of the fungi causing invasive and noninvasive infection is of critical importance. Advances in molecular technologies offer far-reaching insight into the human mycobiome in health and disease (5). High-throughput sequencing (HTS) approaches used to characterize the microbiome commonly rely on the amplification and sequencing of relatively short DNA regions. For fungi, the internal transcribed spacer 1 (ITS1) located between ribosomal subunits 18S and 5.8S rRNA regions and ITS2 located between 5.8S and 28S regions in the ribosomal RNA (rRNA) operon have been widely used as targets for analyzing the mycobiome composition in diverse ecosystems (3, 6, 8). Recent studies indicate a preference for targeting the ITS2 region as it includes more universal primer sites and leads to less taxonomic bias (3, 8).

Otitis media with effusion (OME) are a common problem in children, although its pathogenesis remains incompletely understood (9). According to general opinion, immunological, anatomic, genetic, microbial, and environmental factors contribute to the development of this condition (10, 11). Using polymerase chain reaction (PCR) and HTS-based approaches revealed a diverse bacteriome in the middle ear cavities of individuals with and without otitis media with effusion (12-14). There are no published data indicating fungal compositions in the middle ear cavity, which is connected to the respiratory tract. There are also no data on whether mycobiome profile changes in the presence of OME.

Previously we reported, for this same set of samples, that both healthy middle ears and ear with OME have diverse bacteriomes and viromes (12, 14, 15). Here, we hypothesize that the middle ear hosts a mycobiome and the composition of the mycobiome differ according to the health condition of the middle ear. To pursue this hypothesis, 77 middle ear and four adenoid tissue samples collected from 47 healthy

individuals (12 adults and 35 children) undergoing cochlear implant surgery and 20 children with OME were analyzed using High-throughput sequencing of the ITS2.

Methods

A total of 81 samples, which were previously collected for bacteriome analyses in our previous studies and stored at -32 °C, were used in this study. Briefly, of the 77 middle ear fluid samples, 57 were taken from the 47 individuals (20 samples were obtained from both right and left ears) with no middle ear disease and who had undergone cochlear implant surgery. Thirty-five of the 47 patients were in the child (younger than 4 years) and 12 in the adult (≥ 18 years) age group (Group 1) (12). Twenty middle ear samples were obtained from 20 children (aged 1.5 to 9 years) who had bilateral or unilateral persistent chronic OME for six months or longer (Group 2). Additionally, four adenoid tissue samples of the participants in Group 2 were analyzed (14).

The research protocols for Groups 1 and 2 were approved by the İstanbul Medeniyet University Clinical Research Ethics Committee with the protocol numbers 2018/0313 and 2011/103, respectively. The protocols were applied in accordance with the Declaration of Helsinki. Informed consent was obtained from all adult patients and from the parents of the children included in the study.

DNA isolation was done using the GeneMATRIX Plant & Fungi DNA Purification kit (EURx Ltd. 80-297, Gdansk, Poland) following the manufacturer's instructions (<https://eurx.com.pl/docs/manuals/en/e3595.pdf>). To eliminate environmental contamination, we followed strict sterility conditions. The Qubit 3.0 Fluorometer (Thermo Fisher Sci, Warrington, England) was used for the quantitation of DNA, and 12.5 ng DNA of each sample was used to amplify about 390 bases of the ITS2 region.

Amplification of the ITS2 region was performed using the MiSeq adaptor (underlined) containing primers ITS3 (TCGTCGGCAGCGTCAGATGTGTA TAAGAGACAGGCATCGATGAAGAACGCAGC) and ITS4 (GTCTCGTGGGCTCGGAGATGTGTATAAG AGACAGTCCCTCCGCTTATTGATATGC) following the Illumina fungal metagenomic-sequencing demonstrated protocol (<https://support.illumina.com/downloads/fungal-metagenomic-sequencing-demonstrated-protocol-1000000064940.html>).

PCR products were purified using the Agencourt AMPureXP kit (Beckman Coulter Inc., Brea, CA, USA). DNA concentrations were measured in a Qubit 3.0 Fluorometer device using the Qubit™ dsDNA HS Assay Kit (http://tools.thermofisher.com/content/sfs/manuals/qubit_3_fluorometer_man.pdf). Following Illumina's ITS metagenomics demonstrated protocol (<https://support.illumina.com/downloads/fungal-metagenomic-sequencing-demonstrated-protocol-1000000064940.html>).

illumina.com/downloads/fungal-metagenomic-sequencing-demonstrated-protocol-1000000064940.html), the PCR products were barcoded using the Nextera index primers 1 and 2 (Illumina, San Diego, CA, USA) and the 2X KAPA HotStart PCR mixture (Kapa Biosystems, Wilmington, MA, USA). AMPure XP beads were used to clean up the index PCR products. Barcoded samples were quantified using the Qubit™ dsDNA HS Assay Kit (Thermo Fisher Sci, Warrington, UK) and equally multiplexed into a single library. Sequencing of paired end libraries was performed on an Illumina MiSeq Sequencing platform (Illumina, San Diego, CA, USA) employing the MiSeq Reagent Kit v3 (2×300 cycles) as recommended by the manufacturer (https://sapac.support.illumina.com/content/dam/illumina-support/documents/documentation/chemistry_documentation/metagenomic/fungal-metagenomic-demonstrated-protocol-1000000064940-01.pdf). All samples were sequenced on the same MiSeq run.

Raw sequencing data were demultiplexed and adaptor was trimmed using the MiSeq system. The paired end raw reads obtained were controlled using specific filtering conditions according to the Quantitative Analysis in Microbial Ecology (QIIME2 version 2019.10.0) (16). The raw reads were imported as a QIIME2 artifact. Then, the data were cleaned using DADA2. QIIME DADA2 denoise-paired option was used with specific options based on sequencing statistics to filter out errors, chimeras, low-quality reads, and quality trimming (17). The amplicon sequence variants (ASVs) produced by DADA2 were mapped to Unite (v8.2) database. Fungal taxa were created based on a clustering at the 97% threshold level (18).

Statistical Analysis

Alpha diversity metrics were calculated using the microbiome R package (19). For statistical analysis, R packages phyloseq (v1.34), vegan (v2.5) and microbiome (v1.13) were used (20). P values of alpha diversity metrics were calculated with the Kruskal-Wallis test. Spearman's correlation coefficient was used to evaluate the degree of correlation between the microbiomes of the patients with and without OME (<https://statistics.laerd.com/statistical-guides/spearman-rank-order-correlation-statistical-guide-2.php>). The beta diversity of the microbial community profile between samples of adenoid tissue and the middle ear cavity with and without OME was tested by Permutational Multivariate Analysis of Variance (PERMANOVA) using the Bray-Curtis dissimilarity, the unweighted and weighted UniFrac distances, the Jaccard parameters (<https://www.rdocumentation.org/packages/vegan/versions/2.4-2/topics/adonis>). Analysis of similarities (ANOSIM) based on UniFrac distances were used to evaluate the dissimilarity in microbiome composition within and between study groups (<https://sites.google.com/site/mb3gustame/hypothesis-tests/anosisim>).

We used the linear discriminant analysis (LDA) effect size (LEfSe) to define the potential biomarkers with differences in abundance between the samples (21). Relative abundances were calculated by normalizing the ASVs table of raw counts and statistical analysis was performed on the taxa with $\geq 1\%$ total relative abundance across samples. A non-parametric Mann-Whitney test was applied to determine whether there were statistically significant differences in the relative abundances of taxa detected between patients with and without OME (22).

Results

ITS2 metabarcoding analysis of the 81 samples yielded 1 074 970 mapped sequence reads. Two samples (ID numbers S94 and S574) collected from Group 1 were excluded because of very low number of reads. A total of 14 different fungal genera and 17 species with a mean relative abundance of $\geq 1\%$ were found from the 79 samples analyzed (Table 1). Alfa diversity analysis showed no statistically significant difference in the number of taxa, community richness and the diversity between the mycobiome of the adenoid samples and the middle ear cavity samples of the patients in Group 2, between mycobiome of Groups 1 and 2, and between the mycobiome of children and adults in Group 1 (Supplementary Figure 1). Spearman's correlation coefficient revealed slightly negative correlation between Group 1 and Group 2 (-0.06256937) and between adenoid samples and Group 2 (-0.1025119).

The analysis of samples collected from the patients with OME (Group 2) revealed that the relative abundance of the genera detected within each adenoid and middle ear sample showed substantial variation. For instance, the abundance of the predominant genus *Fusarium*—which was found in all samples—varied between 14.9% and 42.4% in the adenoid, between 8.2% and 62.5% in the middle ear samples. Similarly, the second most common genus *Stemphylium* was detected in all samples and its relative abundance varied from 16.8% to 40.8% in the adenoid and from 4.5% to 48.4% in the middle ear samples. The relative abundance of the third most common genus *Candida* found that all samples were between 1.1% and 9.4% in the adenoid tissue and between 1.8% and 64.8% in the middle ear samples (Figure 1).

According to the mean relative abundance of the 14 genera found in Group 2, *Fusarium* had the highest mean relative abundance accounting 30.4% of the total abundance followed by *Candida* (15.9%) *Stemphylium* (15.7%), and others with a mean relative abundance between 0.6% and 6.6%. The prevalence of the 14 genera varied from 95% to 100%. In the adenoid samples, *Fusarium*, *Stemphylium* and *Candida* were the three dominant genera accounting 59.4% of the total abundance. According to the Mann-Whitney test results, there was only statistically significant differences

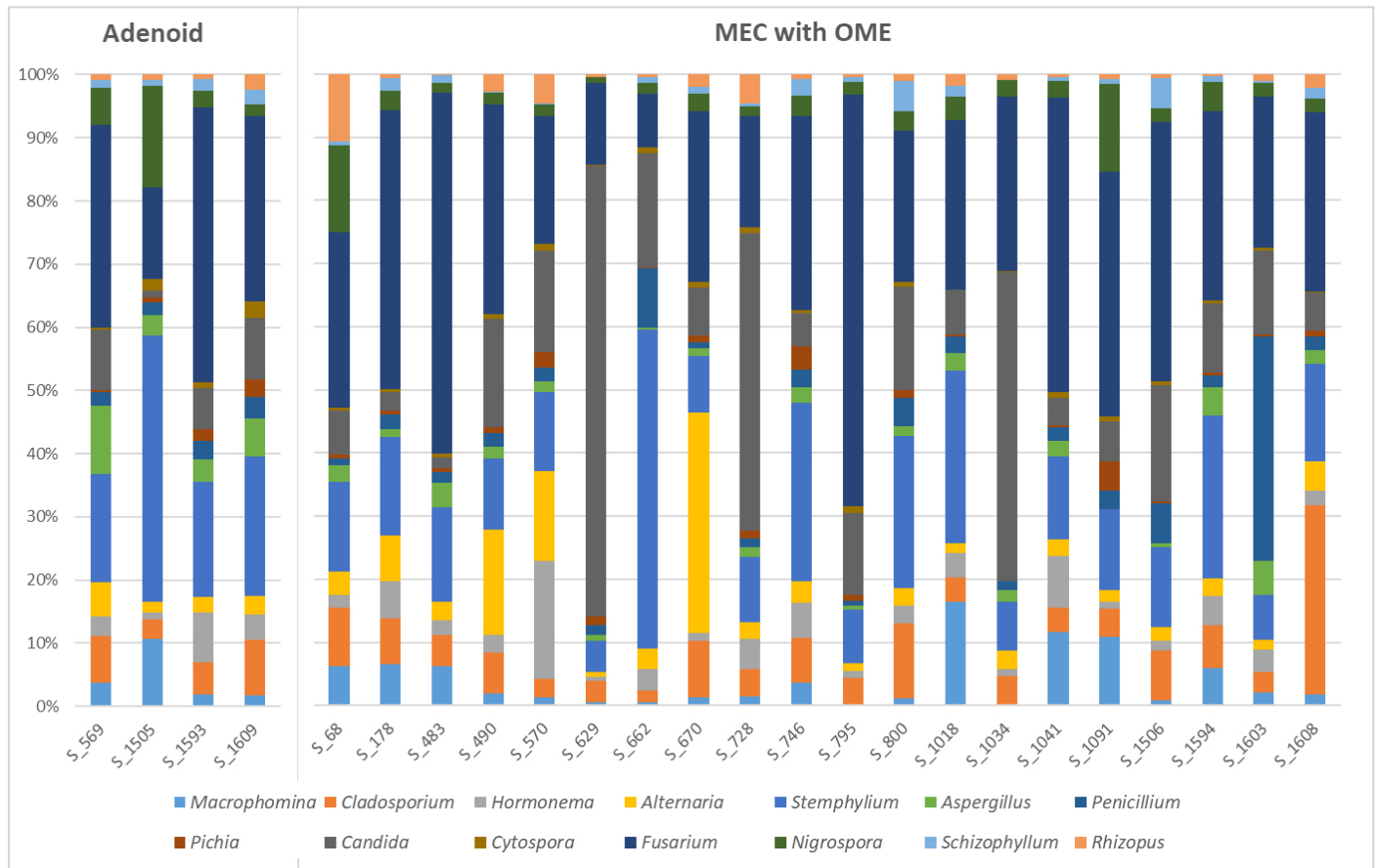


Figure 1. The relative abundance of fungal genera detected from the samples of adenoid and the middle ear cavities (MEC) with OME. *Fusarium*, *Stemphylium* and *Candida* were the most abundant genera found in all adenoid and middle ear samples. Each had different relative abundance, 8.2% to 62.5% for *Fusarium*, 4.5% to 48.4% for *Stemphylium* and 1.1% to 64.8% for *Candida*.

OME: Otitis media with effusion

in mean relative abundance of the genus *Aspergillus* (Table 1). ANOSIM analysis confirmed that there were no significant dissimilarities in the microbiome compositions within and between the adenoid tissues and the middle ear cavity samples of the patients with OME ($p=0.65$).

ITS2 metabarcoding analysis of the 45 middle ear samples collected from the patients without OME (Group 1) showed that *Fusarium*, *Stemphylium*, *Cladosporium* and *Candida* were the most commonly detected genera in all samples from adults and children, however their relative abundance within the samples showed variations. For instance, the relative abundance of *Fusarium* was between 14.0% and 34.5% in adults, and between 8.3% and 46.0% in children (Figure 2).

Regarding the mean relative abundance of the genera detected in Group 1, *Fusarium* was the most abundant genus with a mean relative abundance of 24.9% in children and 26.1% in adults, followed by *Stemphylium* (18.6% and 19.0%, respectively), *Candida* (11.7% and 8.8%, respectively) and *Cladosporium* (9.3% and 9.5%, respectively). Other genera detected in both children and adults had mean relative abundance between 0.62% and 7.6%. There was no

significant difference between children and adults in terms of the mean relative abundance of each. The prevalences of these genera were more than 98%. Like the distribution of genera, the mean relative abundance of the fungal species identified in adults and children did not show a statistically significant difference, except for the significant abundance of *Penicillium atrosanguineum* in the children.

ANOSIM analysis revealed the presence of significant dissimilarity in the microbiome composition within and between Groups 1 and 2 ($p=0.049$). *Aspergillus* and *Rhizopus* were significantly more abundant in Group 2 than in Group 1 ($p=0.000$). However, *Cladosporium*, *Pichia*, *Cytospora*, *Nigrospora* and *Schizophyllum* were more abundant in Group 1 (p -values ≤ 0.001). Although there were no significant differences, the mean relative abundances of the genera *Candida* (15.9% vs 11.1%) and *Fusarium* (30.4% vs 25.1%) were higher in Group 2 vs Group 1 (Figure 3). The species *Candida glabrosa*, *Candida cretensis*, *Aspergillus ruber*, *Penicillium desertorum*, and *Rhizopus arrhizus* were significantly more abundant in patients with OME than in patients with a healthy middle ear (Table 1). Significant difference between Group 1 and Group 2 in the species

Table 1. Mean relative abundance of the genera and the species detected in the study groups

Taxa	Mean relative abundance (%)			p-value*
	Adenoid (n=4)	MEC with OME (n=20)	MEC without OME (n=55)	
Genus				
<i>Macrophomina</i>	4.4	3.9	5.2	0.073
<i>Cladosporium</i>	5.9	6.6	9.2	0.000
<i>Hormonema</i>	3.9	3.7	4.2	0.685
<i>Alternaria</i>	3.0	5.5	4.1	0.245
<i>Stemphylium</i>	24.1	15.7	18.7	0.153
<i>Aspergillus</i>	5.7	1.9	1.0	0.000
<i>Penicillium</i>	2.5	4.1	3.7	0.343
<i>Pichia</i>	1.4	1.1	1.8	0.001
<i>Candida</i>	6.5	15.9	11.1	0.522
<i>Cytospora</i>	1.3	0.6	1.3	0.001
<i>Fusarium</i>	28.8	30.4	25.1	0.115
<i>Nigrospora</i>	6.4	3.4	6.7	0.001
<i>Schizophyllum</i>	1.5	1.2	3.3	0.000
<i>Rhizopus</i>	1.2	1.8	1.3	0.000
Species				
<i>M. phaseolina</i>	5.6	5.3	6.7	0.112
<i>C. cladosporioides</i>	7.3	8.4	11.2	0.001
<i>H. macrosporum</i>	5.0	4.7	5.1	0.839
<i>A. infectoria</i>	3.8	7.0	5.0	0.475
<i>S. globuliferum</i>	30.6	20.0	22.9	0.394
<i>A. ruber</i>	7.1	2.5	1.2	0
<i>P. atrosanguineum</i>	1.0	1.5	1.8	0.34
<i>P. desertorum</i>	1.6	2.9	1.1	0.001
<i>P. fermentans</i>	1.7	1.4	2.2	0.001
<i>C. cretensis</i>	1.5	7.9	2.6	0.025
<i>C. ethanolica</i>	0.6	0.3	4.5	0
<i>C. glaucosa</i>	1.5	5.7	1.9	0.001
<i>C. prunicola</i>	1.7	0.8	1.6	0.002
<i>F. oxysporum</i>	12.6	6.8	7.6	0.536
<i>F. solani</i>	8.2	11.1	11.2	0.639
<i>S. commune</i>	1.9	1.7	4.0	0
<i>R. arrhizus</i>	1.4	2.3	1.5	0

*p- values are for relative abundances of taxa detected between MEC with and without OME.

Significant values are shown in bold.

MEC: Middle ear cavity,. OME: Otitis media with effusion, n: Number

compositions was confirmed with Bray-Curtis dissimilarity ($p=0.001$), the unweighted ($p=0.011$) and weighted ($p=0.003$) UniFrac distances, and the Jaccard analysis ($p=0.003$). LEfSe analysis revealed that these species except *A. ruber*, could be used as biomarker for the diagnosis of otitis media with effusion (Table 2).

Discussion

Analysis of the mycobiome by using HTS technologies has highlighted the presence of diverse cultivable and non-cultivable fungi in all areas of the human body explored, including areas thought to be microbiologically barren (1,23). PCR approaches

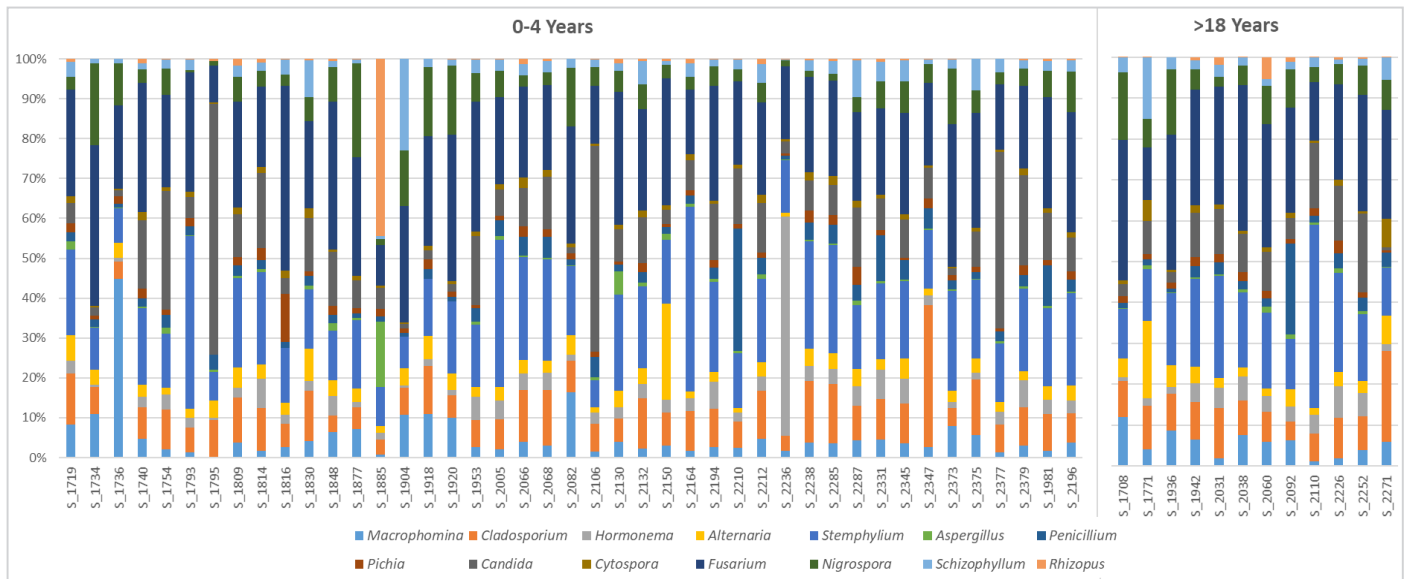


Figure 2. The relative abundance of fungal genera detected from the middle ear cavities without OME. *Fusarium*, *Stemphylium*, *Cladosporium*, and *Candida* were the most commonly detected genera in all samples from both adults and children. Their relative abundance showed big differences within each sample. The relative abundance varied between 8.3% and 46.0% for *Fusarium*, 6.4% and 44.8% for *Stemphylium*, and 0.7% and 56.4% for *Candida*. Similar variation was observed for the remaining rare genera.

OME: Otitis media with effusion

Table 2. Potential biomarkers defined using LEfSe analysis for diagnosis of the otitis media with effusion

Marker Species	LDA score	p-value	p-value adjusted
<i>Candida cretensis</i>	4.753616259	0.001852798	0.001852798
<i>Candida glabrosa</i>	4.645068076	0.000139425	0.000139425
<i>Penicillium desertorum</i>	4.284159638	0.005567622	0.005567622
<i>Trichosporon asabii</i>	4.209985054	0.001420361	0.001420361
<i>Rhizopus arrhizus</i>	4.202264894	0.000131602	0.000131602

LEfSe: Linear discriminant analysis effect size, LDA: Linear discriminant analysis

showed fungal DNA in the middle ear cavities of the patients; however, these studies did not give any information about fungal genera and or species (24, 25). Our study is the first study that used high-throughput sequencing to evaluate the mycobiome profiles in the middle ear with and without OME.

The presented study showed diverse fungal DNA in the middle ear cavity. With regards to the mycobiome in the middle ear samples of patients with OME (Group 2), the presented study is the first report showing at least 14 different fungal genera with a relative abundance of $\geq 1\%$ in the middle ear cavity. In contrast to a previous study reporting high diverse bacteriome, we found a lower number of fungal genera in the same samples (14). These data agreed with the idea indicating that the diversity of the fungal taxa per sample was lower than those of bacteria in the microbiota (2).

The genera detected in the middle ear cavities of the patients in Group 2 were previously reported in samples of human oral mycobiome (1, 4). As in our results, *Candida* and *Cladosporium* were reported as the most prevalent genera found in 75% and 65% of oral samples of the 20 healthy participants in a previous study. In that study, *Fusarium*, *Aureobasidium*, *Saccharomycetales*, *Aspergillus* and *Cryptococcus* were also found with a remarkable prevalence varying between 20% and 50% (4). We found that the prevalence of genera varied from 90% to 100%. Besides profile similarity, the relative abundance, richness, and prevalence of the genera detected within each individual in Group 2 showed remarkable variation. The reason for these differences may stem from the personal characteristics, lifestyles, and life histories of the participants (2, 5).

To conclude whether the mycobiome in the middle ear originates from adenoid or whether there is a core mycobiome in the middle ear cavity, we analyzed both adenoid and

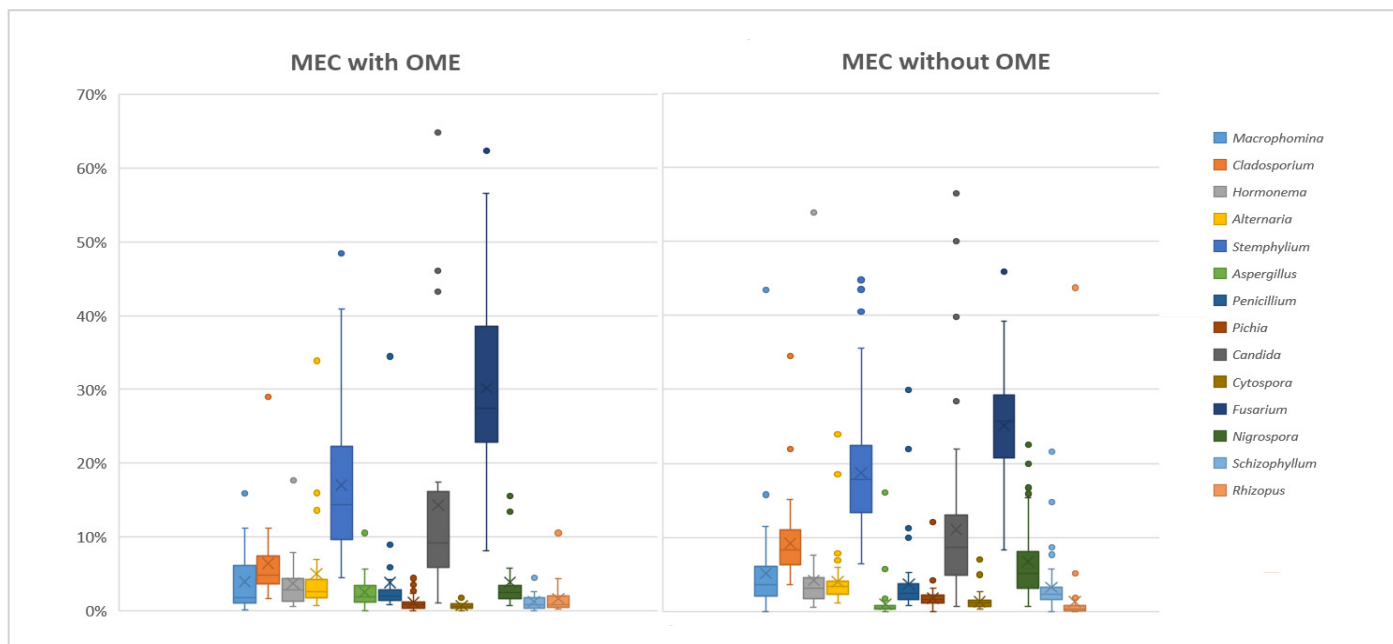


Figure 3. Box and whisker plot of relative abundance of fungal genera detected in the middle ear cavity with and without OME. Fourteen common genera were found from all samples. The genera *Aspergillus* and *Rhizopus* were significantly more abundant in the middle ear cavities with OME (p-values 0.000 and 0.000, respectively), whereas the genera *Cladosporium*, *Pichia*, *Cytospora*, *Nigrospora* and *Schizophyllum* were more abundant in Group 1 (p-values ≤ 0.001).

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middle ear samples of the four patients. There was an overlap between adenoid and middle ear mycobiome. Although the number of samples was too limited for us to arrive at a robust conclusion, this finding supports the idea that the microbiome of the middle ear come from the oropharynx and/or nasopharynx (13). Cui et al. (26) revealed overlapping of the mycobiome communities between bronchoalveolar lavages and oral washes, suggesting that some fungi detected in lung originated from the mouth. Although no a study that compared the oral and middle-ear cavities, the results of Cui et al. (26) lend weight to a mycobiome transfer between adenoid tissue and the middle ear cavity.

To analyze whether the middle ear without OME had mycobiome and whether mycobiome varied by age, we analyzed 55 middle ear samples, 12 were from adults and 35 were from children. Our study did not show any dissimilarity in the mycobiome profile between children younger than 4 years and adults (≥ 18 years). There were also no significant differences in relative abundance, and prevalence of the detected genera and species, except for significantly more abundance of *P. atrosanguineum* in the children. From these results we can speculate that the mycobiome in the middle ear is established during the first years of life and stabilized in adults. In parallel to these results, in our previous study conducted on the same samples, we found similar bacteriome composition between adults and children (12).

ANOSIM and PERMANOVA analyses revealed significant dissimilarities in the observed fungal taxa between the middle ear with and without OME. *Fusarium* (*F. solani* and *F. oxysporum*) and *Candida* (*C. cretensis*, *C. glabrata* and *C. ethanolica*) were the two genera showing remarkably more abundance in the middle ears with OME. These opportunistic fungi can invade different organs and cause serious diseases. The genus *Candida* is the most common fungus resulting in different invasive infections (27). Recently, human infections caused by *F. oxysporum* and *F. solani* (*Neocosmospora solani*) have increased and become the second most common mold infections after aspergillosis (28). Although their mean relative abundance was too low (less than 2%) *Aspergillus* (*A. ruber*) and *Rhizopus* (*R. arrhizus*) were significantly more abundant in Group 2 than in Group 1 (p-values, 0.000). A recent meta-analysis indicated the predominance of *Rhizopus* spp. in patients with rhino-orbital-cerebral mucormycosis (29). In concordance with the literature, one can speculate that these opportunistic taxa contribute to the development of effusion in the middle ear cavity.

The detection of *Cladosporium*, *Pichia*, *Nigrospora*, *Cytospora* and *Schizophyllum* with significantly lower abundances in the middle ear with OME than in the middle ear without OME and presence of these genera also in adenoid samples indicate their portal entry into the middle ear via Eustachian tube. From these data, one can speculate that these genera are present in the middle ear as transient mycobiome members

and they may not be involved in the development of effusion. However, *Stemphylium* (*S. globuliferum*) was the second most abundant genus in the middle ear with and without OME (15.7% vs 18.7%), respectively. Since this genus is mainly known as a ubiquitous environmental saprobic fungus, it can be evaluated as a mere colonizer in middle ear cavity (30). As *Stemphylium* was found in oral mycobiome, the genus in middle ear cavity stems from the oral cavity (4).

This study has some limitations that should be noted. While the high-throughput sequencing revealed diverse mycobiome in the healthy middle ear cavities with and without OME, based on these results, we cannot say that the presence of fungal DNA is evidence for viable fungal cells. Further studies using culture-based approaches are needed to clarify whether this fungal DNA detected in the middle ear represents living fungi and to confirm the clinical relevance for the presence of a diverse fungal population in the middle ear cavity. Another limitation of our study is the low number of the adenoid samples.

Conclusion

This study conducted on many samples to target the middle-ear mycobiome provided some new data. First, we report evidence for the presence of diverse fungi in middle ear cavities with and without OME. Second, the presence of similar mycobiomes across the middle ear cavity and adenoid sample of the same participant supports the idea that the mycobiome in the middle ear stems from adenoid tissue. Third, the microbiome profile in the middle ear cavities of children and adults had similar relative abundance, richness, and prevalence. Four, higher abundance of the species *C. glabrosa*, *C. cretensis*, *A. ruber*, *P. desertorum* and *R. arrhizus* in patients with OME suggests that these taxa contribute to inflammation and development of effusion. Based on LEfSe analysis, these species except *A. rubrum*, can be potential biomarkers for microbiologic diagnosis of otitis media with effusion. We believe that these results will point to a novel perspective to evaluate the pathogenesis of the effusion.

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Ethics Committee Approval: The research protocols were approved by the İstanbul Medeniyet University Clinical Research Ethics Committee with the protocol numbers 2018/0313 and 2011/103, respectively.

Informed Consent: Informed consent was obtained from all adult patients and from the parents of the children included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Investigation: R.D., Conception: B.D., Methodology: O.A., Ol.A., S.C., M.T.K., Data Curation: R.D., S.C., M.T.K., Analysis of Data: R.D., O.A., Writing: R.D., Ol.A., Editing Manuscript: B.D., M.T.K., Review: B.D., M.T.K.

Conflict of interest: All authors declare no conflict of interest.

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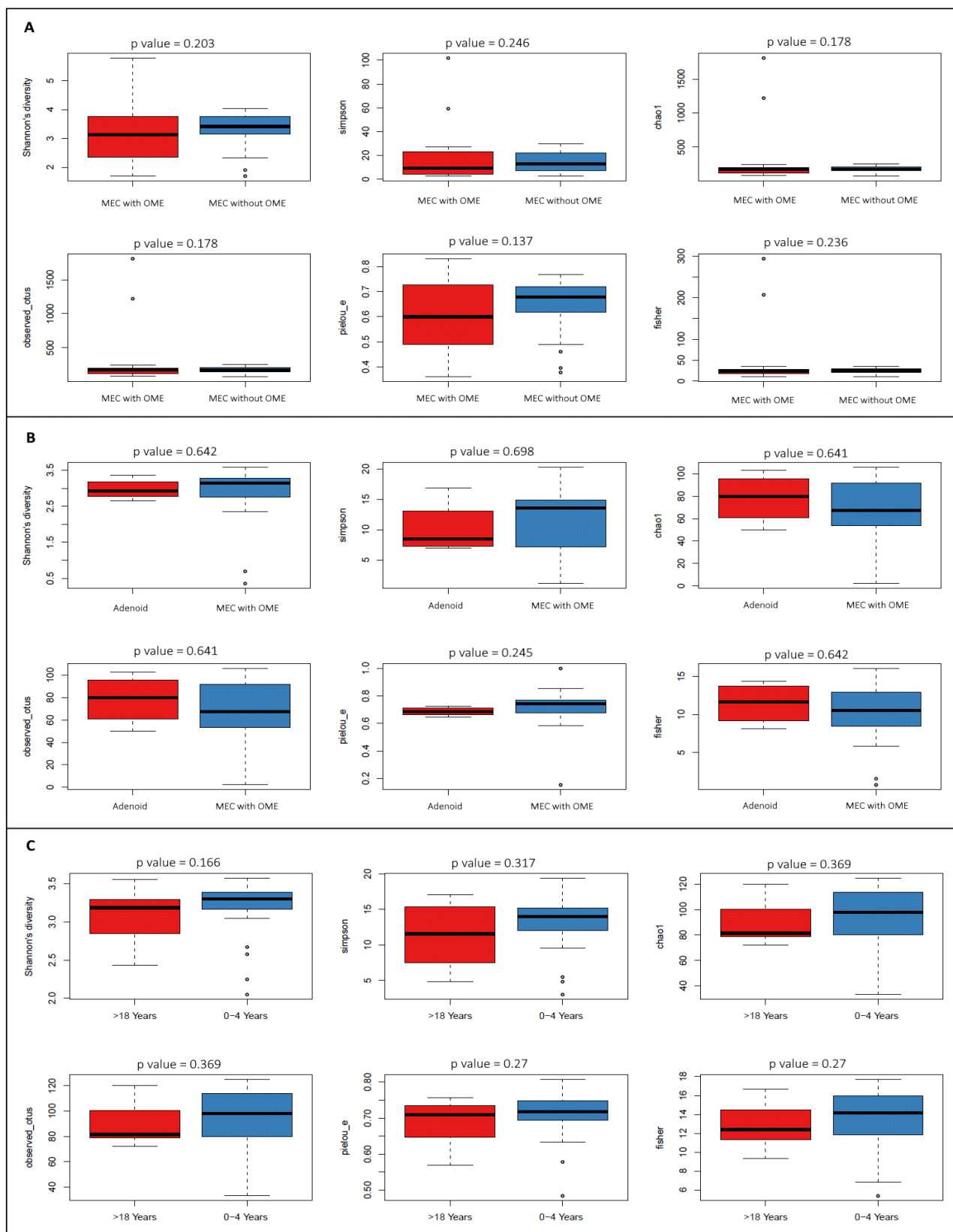
Main Points

- This is the first study that used high-throughput sequencing to evaluate the mycobiome profiles in middle ears with and without OME.
- We report evidence for the presence of diverse fungi in middle ear cavities with and without OME.
- We found similar mycobiomes across the middle ear cavity and adenoid samples of the same participant.
- The microbiome profile in the middle ear cavities of children and adults had similar relative abundance, richness and prevalence.
- Higher abundance of the species *C. glabrosa*, *C. cretensis*, *A. ruber*, *P. desertorum* and *R. arrhizus* in the patients with OME suggests that these taxa might contribute to inflammation and development of effusion.
- These results will point to a novel perspective to evaluate the pathogenesis of the effusion.

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Supplementary Figure 1. a) Alfa diversity analysis of mycobiome detected in middle ear cavity samples of the patients with and without effusion, b) the adenoid and the middle ear cavity samples of the patients with effusion, and c) the middle ear cavity samples of the children and adults.

MEC: Middle ear cavity, OME: Otitis media with effusion



Early Transthyrohyoid Injection Laryngoplasty Under Local Anaesthesia in a Single Tertiary Center of Southeast Asia: Multidimensional Voice Outcomes

Original Investigation

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Abstract

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Objective: To study the effectiveness of early percutaneous transthyrohyoid injection laryngoplasty under local anesthesia in improving voice quality in unilateral vocal fold paralysis (UVFP) patients.

Methods: Longitudinal data of 29 UVFP patients who underwent injection laryngoplasty within six months from the onset of the symptoms were studied. The injectate (0.5–1 mL) was hyaluronic acid-based material (Juvéderm ULTRA XC; Allergan Industrie, France) that was delivered under local anesthesia with transthyrohyoid approach using a double-bend 21G needle. Multidimensional voice outcomes employing: 1) Malay-Voice-Handicap Index-10 (mVHI-10); 2) maximum phonation time (MPT); and 3) acoustic analysis [jitter%, shimmer% and noise-harmonic ratio (NHR)] were used to assess the treatment progress. The voice parameters were measured at baseline (2 weeks pre-injection), and at the first and third months post-injection.

Results: The mean age of the 29 patients was 44.69 years, with a female-to-male ratio of 3.14:1. The voice outcomes measured at different time points were evaluated with repeated measures ANOVA. Significant improvement was observed from baseline to three months post injection laryngoplasty for mVHI-10, jitter, and NHR ($p < 0.001$), shimmer ($p = 0.005$) and MPT ($p = 0.018$). Following the procedure, none of the patients developed any major complications.

Conclusion: Office setting early transthyrohyoid injection laryngoplasty using a double-bend needle is a safe and effective procedure in patients with UVFP with evidence of significant improvement in voice and life quality.

Keywords: Larynx, vocal cords, vocal cord paralysis, laryngoplasty, acoustic analysis, office surgery

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Introduction

Voice plays an important role in human life. It is vital for efficient communication and expression of emotion. One of the causes of an abnormal voice is glottic insufficiency, which is commonly caused by unilateral vocal fold paralysis (UVFP). Glottic insufficiency leads to not only adverse voice quality, but also to the risk of aspiration of fluid and food material due to improper glottal closure (1). Given the considerable risks in glottic insufficiency and its adverse effects on the quality of life, early treatment is recommended.

One of the effective and less invasive modalities of early treatment for UVFP, without doubt, is injection laryngoplasty. Traditionally performed under general anesthesia, recent advancements allowed injection laryngoplasty to be performed in office settings, and thereby rendered the procedure increasingly popular in the early treatment of UVFP (2, 3). With the augmentation of the vocal fold by medializing the leading edge of the vocal fold, it improves the closure of the glottis (3).

Injection laryngoplasty in office settings is largely adopted via percutaneous technique which was first introduced by Ward et al. (4). One of the modifications of this technique is transthyrohyoid double-bend needle technique which was described by Achkar et al. (5). The double-bend-needle technique, a technique in which the needle was modified by creating two 45-degree angle bends with one at the needle hub and another 1-cm proximal to the tip of the needle, allows the laryngologist to not only estimate the needle tip depth during injection, but also facilitates access to the endolarynx, which includes the entire medial and superior surface of the true and false vocal folds and the interarytenoid regions, regardless of the thyroid cartilage angulation or the chin position during the procedure (5). A study by Song et al. (6) reported that 87% of the patients who had their vocal fold augmented using this technique demonstrated subjective improvement in voice, as measured by the Voice Outcome Survey, and all patients tolerated the procedure well without complications. There are very few comprehensive studies published with multidimensional voice outcomes data on early injection laryngoplasty using the transthyrohyoid double-bend needle technique under local anesthesia.

The objective of our study was to assess the effectiveness of early injection laryngoplasty in patients with UVFP of less than 6 months, utilizing this unique double-bend needle technique under local anaesthesia. Multidimensional voice outcomes were employed to assess its efficacy in improving the voice quality objectively and subjectively.

Methods

Longitudinal data of 29 patients with UVFP who underwent injection laryngoplasty within six months from the onset of

the symptoms were studied retrospectively. The cases that were included were those with UVFP of less than six months duration, who had voice issues and/or aspiration symptoms, and had undergone injection laryngoplasty under local anesthesia with temporary biomaterials. We excluded cases that had injection laryngoplasty under general anesthesia or had received long-term biomaterials, or the injection laryngoplasty was done as a touch-up procedure. Cases with incomplete data were excluded from this retrospective study.

Surgical technique

Injection laryngoplasty was performed under local anesthesia using a transthyrohyoid approach with a double-bend 21G needle (5). A hyaluronic based material, Juvéderm ULTRA XC (Allergan Industrie, France), was used as the injectate to augment the paralyzed vocal fold. The injection laryngoplasty was performed in an office setting in the clinic while the patient was sitting upright on an examination chair. First, local anesthesia was given by spraying the nostrils with Co-phenylcaine (Ent Technologies, India). Second, the subcutaneous of superior thyroid notch area were infiltrated with 1 cc of 2% lignocaine. Third, the upper airway was anesthetized by performing intratracheal anesthesia with 3 to 4 cc of 2% lignocaine. Following this, a 21G needle was bent at two points as described by Achkar et al. (5). The injection was then performed under flexible nasopharyngolaryngoscope assistance, whereby the double bend-needle was introduced at the soft tissue of the superior thyroid notch and the tip of the needle appeared in the larynx below the petiole (Figure 1a). The needle was then pushed further in the midline until the distal bend was seen. Subsequently it was aimed at lateral to the vocal fold ligament in the paraglottic space, next to the vocal process (Figure 1b). Finally, the hyaluronic acid gel was slowly injected about 0.5–1 mL until the vocal fold was augmented with about 10%–20% over correction (Figure 1c).

Multidimensional voice assessment

Measurement of voice outcomes following the injection laryngoplasty was multidimensional, consisting of subjective and objective assessments. For subjective assessments, patients were evaluated with the Voice Handicap Index-10 (Bahasa Malaysia version; mVHI-10) (7). VHI-10 is a validated patient-administered subjective questionnaire that consists of physical, functional and emotional components to quantify the patient's perception of their own voice function (8). mVHI-10 is the culturally adapted Malaysian version of VHI-10 with a total score of 40 whereby score of more than 11 is considered abnormal (7).

The objective assessments include: 1) maximum phonation time (MPT); and 2) acoustic analysis that comprises jitter % (frequency variation), shimmer % (amplitude variation) and noise-to-harmonic ratio (NHR). The analysis of the acoustic parameters were performed using On Person Rapid

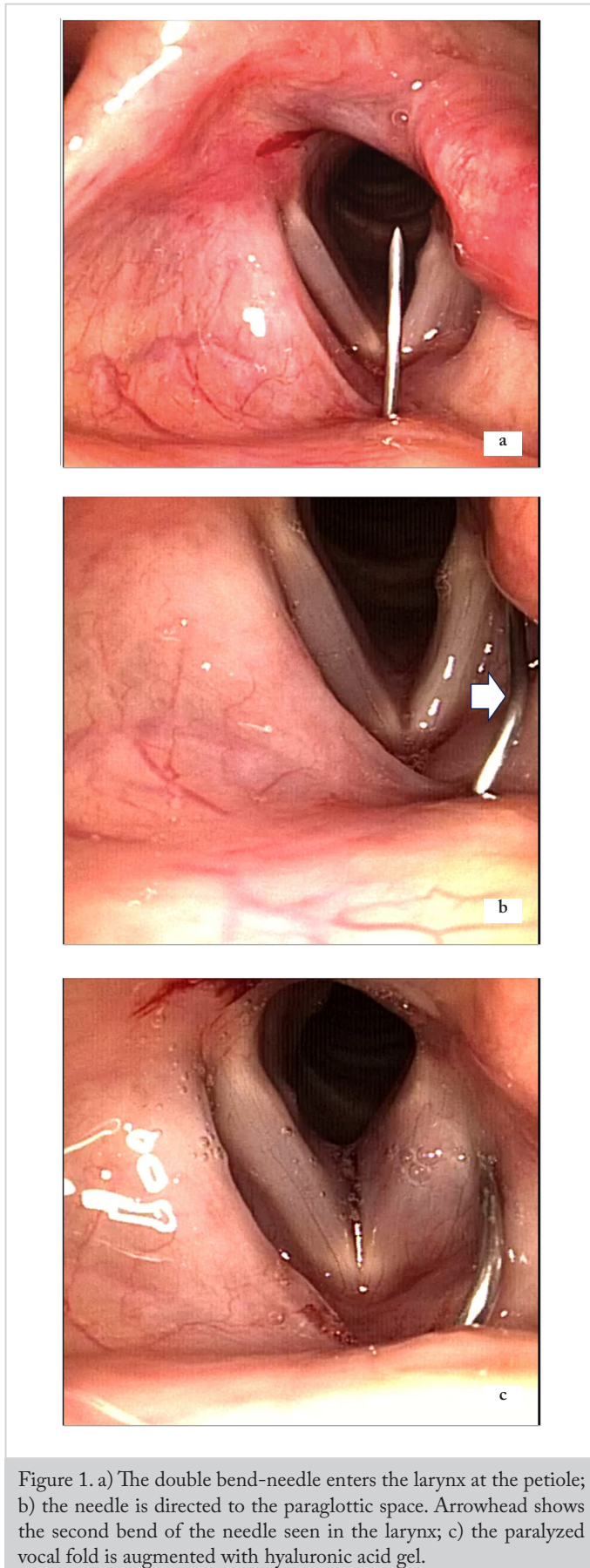


Figure 1. a) The double bend-needle enters the larynx at the petiole; b) the needle is directed to the paraglottic space. Arrowhead shows the second bend of the needle seen in the larynx; c) the paralyzed vocal fold is augmented with hyaluronic acid gel.

Voice Examiner, Oxford Research Wave Ltd (OperaVOX) in a quiet room (9). OperaVOX is objective, non-invasive, inexpensive and characterizes voice quality using intelligent tools (10). Jitter is affected by the poor control of the vocal cord vibrations with depiction of the parameter of frequency variation from cycle-to-cycle, and shimmer is affected by the glottal resistance with relation to the amplitude variation of the sound wave, while NHR assesses the components that determine speech efficacy (11). MPT, on the other hand, measures the glottic efficiency (12).

Statistical Analysis

Voice outcomes were measured at baseline, and at the first and third months post-injection. Baseline assessments were performed within the two weeks prior to the injection laryngoplasty. Multidimensional voice measurement outcomes of mVHI-10, MPT, and acoustic analysis of jitter, shimmer and NHR were analyzed with IBM SPSS Statistics version 26. Descriptive analyses of mean and standard deviation (SD) of each element were measured. Significance of the non-categorical data of multidimensional voice outcomes were analyzed with repeated measures ANOVA.

Results

In total, there were 58 UVFP patients who received temporary injection laryngoplasty (50 under local and 8 under general anesthesia). Of the 50 patients that had the procedure under local anesthesia, 21 were excluded either because of incomplete data such as incomplete documentation on the duration of UVFP or because patients did not come for the assessment of multidimensional voice outcomes. In consequence, data of 29 patients (22 females and 7 males) with a mean age of 44.69 years were reviewed. The demographic data are summarized in Table 1.

Causes of glottic insufficiency were identified as iatrogenic post thyroid surgery (72%), idiopathic (14%), secondary tumor (7%), and others (7%). The 7% other causes were secondary to old pulmonary tuberculosis and base of skull osteomyelitis. All patients underwent injection laryngoplasty under local anesthesia.

The mean and standard deviation of mVHI-10, MPT, jitter, shimmer, and NHR showed evidence of improvement from baseline pre injection laryngoplasty to months 1 and 3 post injection laryngoplasty (Table 2). Statistical analysis with repeated measures ANOVA depicted significant improvement from pre-injection to 3 months post injection laryngoplasty for mVHI-10, jitter, NHR ($p < 0.001$), and shimmer ($p = 0.005$). Patients could sustain a longer MPT in post injection laryngoplasty compared to pre injection laryngoplasty with $p = 0.018$. These results are presented in Table 2.

Table 1. Demographic data of patients with unilateral vocal fold paralysis

Case	Age (years)	Gender	Etiology	Duration of paralysis (day)
1	57	F	Iatrogenic post thyroid surgery	14
2	38	M	Iatrogenic post thyroid surgery	85
3	45	M	Iatrogenic post thyroid surgery	1
4	47	F	Iatrogenic post thyroid surgery	14
5	67	F	Iatrogenic post thyroid surgery	14
6	63	F	Iatrogenic post thyroid surgery	14
7	59	F	Iatrogenic post thyroid surgery	14
8	31	F	Iatrogenic post thyroid surgery	1
9	65	M	Idiopathic	86
10	31	F	Iatrogenic post thyroid surgery	59
11	36	F	Base of skull osteomyelitis	112
12	45	F	Iatrogenic post thyroid surgery	90
13	34	F	Iatrogenic post thyroid surgery	49
14	32	F	Secondary tumor	6
15	40	F	Idiopathic	179
16	37	F	Iatrogenic post thyroid surgery	90
17	31	M	Idiopathic	31
18	47	F	Iatrogenic post thyroid surgery	110
19	56	M	Iatrogenic post thyroid surgery	51
20	48	F	Iatrogenic post thyroid surgery	167
21	33	F	Iatrogenic post thyroid surgery	115
22	30	F	Iatrogenic post thyroid surgery	13
23	61	F	Iatrogenic post thyroid surgery	11
24	61	M	Iatrogenic post thyroid surgery	116
25	48	M	Base of skull tumor	3
26	24	F	Iatrogenic post thyroid surgery	4
27	31	F	Idiopathic	54
28	31	F	Iatrogenic post thyroid surgery	67
29	68	F	Secondary to old pulmonary tuberculosis	168

F: Female, M: Male

Table 2. Baseline pre injection, 1 month and 3 months post injection laryngoplasty (IL) vocal function assessment

Parameter	n	Data of vocal function assessment (mean ± SD)			Variation within samples F	Statistical significance p-value
		Baseline	1-month post IL	3-month post IL		
Jitter	29	6.71 (3.41)	4.04 (3.53)	2.86 (2.28)	18.780	0.001
Shimmer	29	13.37 (8.41)	8.47 (5.32)	7.02 (4.21)	6.459	0.005
NHR	29	1.24 (1.07)	0.59 (0.83)	0.33 (0.42)	9.343	0.001
MPT	29	5.99 (4.60)	7.54 (4.02)	9.36 (4.23)	4.713	0.018
mVHI-10	29	22.03 (12.01)	11.72 (10.70)	8.68 (8.77)	16.561	0.001

SD: Standard deviation, n: Number

None of the patients required nasogastric tube feeding following the injection.

Discussion

UVFP can be of various causes. In our case series, surgical iatrogenic injury represented the highest percentage in the cases of UVFP, which is in accordance with the study by Rosenthal et al. (13) who reported surgical iatrogenic injury as the most common cause with a percentage of 46.3%. Unlike Rosenthal et al.'s (13) longitudinal study, in which non-thyroid surgeries had caused most of the surgical iatrogenic injuries, in our study the most common cause was post thyroid surgery with a rate of 72%. Idiopathic and other etiologies were just at 14% and 7%, respectively.

While the strong evidence of optimal management algorithm for glottic insufficiency secondary to UVFP remains a research question, injection laryngoplasty under local anaesthesia has been recommended to be a safe and effective procedure (2, 3, 13). The aim of the procedure is to augment the flaccid vocal fold by means of injecting filler substance into the paraglottic space.

For this purpose, in recent years, a variety of injectable materials with various biocompatibility and less triggering factor of foreign body reactions have been developed (14, 15). With the development of advanced digital imaging technology, injectable material can be delivered via a fine gauge needle into the paraglottic space under direct visualization (3, 15, 16). These advances have spurred the consideration of injection laryngoplasty as one of the effective treatments for glottic insufficiency (17, 18). In office setting, injection laryngoplasty is generally performed via percutaneous approaches which can be subdivided into transthyroid, transthyrohyoid and transcricothyroid (19).

Avoidance of general anesthesia is the most favorable aspect of injection laryngoplasty done in an office setting. With the patient awake and seated upright, injection laryngoplasty under local anesthesia allows real-time phonation monitoring together with the titration of the injected material amount, which is not possible under general anesthesia (3). Measurement of the voice and the airway status with the rate of permeability of the injected material location can be assessed simultaneously during injection laryngoplasty under local anesthesia (19).

Office setting injection laryngoplasty is particularly advantageous for patients with multiple comorbidities and high anesthetic risk, as it reduces perioperative morbidity with shortened hospital stay (15, 17). Notably, anticoagulation is not a contraindication as the risk of bleeding and hematoma

formation is low for injection laryngoplasty under local anesthesia (18). Office setting injection laryngoplasty is more cost-effective compared to general anesthesia, and thereby more affordable and accessible for the general population. Moreover, it helps to reduce the burden of the already rising healthcare cost to the country (3, 15). An added advantage of injection laryngoplasty under local anesthesia is the possibility of avoiding the long waiting time for an operation theater (OT) slot, which can in turn be reserved for more urgent, i.e., malignant cases that require longer OT times.

Prediction of the prognosis of UVFP is uncompromising as the best timing for performing injection laryngoplasty has been controversial previously, and there has been rationale on a waiting period of 6 to 12 months prior to intervention in certain selected cases of UVFP for possible spontaneous recovery occurrence. Recent research advocated early injection laryngoplasty in UVFP as it has been reported to statistically reduce the need for future open laryngeal framework surgery (19-21). A study by Choi et al. (22) showed that early injection laryngoplasty within one month following iatrogenic UVFP significantly improved the voice outcomes with reduction of aspiration risk.

With the convenience of the facilities in the office setting and its low complication rate, this concept provides an excellent early therapeutic option for patients with UVFP. Comprehensive clinical measurement of the voice outcome post injection laryngoplasty is essential.

A retrospective study by Bové et al. (3) comparing the clinical efficacy of injection laryngoplasty under general and local anesthesia revealed that both outcomes demonstrated similar promising improvement of voice quality based on VHI-10, thus advocated awake injection laryngoplasty in prudent patients. Powell et al. (14) assessed the subjective clinical outcome of injection laryngoplasty under local anesthesia with hyaluronic acid and calcium hydroxylapatite in 68 subjects using Voice Performance Questionnaires and GRBAS, whereas a study by Mohammed et al. (17) studied the clinical outcome of injection laryngoplasty with calcium hydroxylapatite in outpatient setting in 21 subjects solely with VHI-10. Singh and Gupta (17) evaluated videostroboscopic findings, acoustic analysis and VHI post injection laryngoplasty with calcium hydroxylapatite in only 12 patients. All three studies demonstrated relative significant improvement on the voice outcome post injection laryngoplasty under local anesthesia. Table 3 shows a comprehensive comparison of the number of patients, approaches adopted, materials used, measurement of voice outcomes and complications of injection laryngoplasty under local anesthesia in various studies.

Table 3. A comprehensive comparison of various studies of injection laryngoplasty (IL) under local anesthesia (LA)

Year	Authors	Technique	Sample size	Injection material	GA/LA	Outcome measurement	Complication
2010	Song et al. (6)	Transthyroid	27 (25- LA 2 - GA)	Crosslinked hyaluronic acid	LA GA	Voice-Related Quality of Life (V-RQOL) survey and the Voice Outcome Survey (VOS) both prior to and at least one month after injection - 87% reported improvement	One subject with collection of resylane at subepithelial space required drainage with suspension microlaryngoscopy
2012	Wang et al. (23)	Thyroid	20	Cross-linked porcine collagen	LA	Pre and 3 months post IL 1. Videolaryngoscopic evaluation for the glottic closure pattern - improved 2. Perceptual grading using the GRB scale (grade, roughness, breathiness) - improved 3. Acoustic analysis - improved 4. Maximal phonation time (MPT) - improved 5. Voice Handicap Index (VHI) questionnaire - improved	Mild vocal fold hematoma - resolved spontaneously in two weeks
2013	Birkent et al. (24)	Cricothyroid membrane	35	Bovine Collagen	LA	1. Voice Handicap Index (VHI)-30 - improved 2. Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) - improved 3. GRBAS - all improved except roughness 4. VAS - investigate patient tolerance to office-based IL (pain score 0-10)	-
2013	Upton et al. (25)	Transoral	27	Juvéderm Ultra Plus hyaluronic acid gel	LA	Analysis on VHI/GFI/DSI pre and 1-month post injection Subjective measures outcome 1. Voice Handicap Index - improved 2. Glottal Function Index - improved Objective measures outcome 1. Dysphonia Severity Index - improved	In one patient temporary glottic inflammation required intravenous steroids for resolution and caused no permanent sequelae. Three patients (10%) were unable to tolerate transoral injection and required conversion to the transcervical route.
2013	Wen et al. (25)	Thyroid or transoral	60 Out of 60 (33 employed porcine collagen) (27 employed Hyaluronic acid)	Cross-linked porcine collagen (PC) Hyaluronic acid (HA)	LA	Compare the outcome of VHI 10 and MPT between porcine collagen and hyaluronic acid. Both outcomes showed no significant differences.	-

Table 3. continued

Year	Authors	Technique	Sample size	Injection material	GA/LA	Outcome measurement	Complication
2014	Lee et al. (27)	Cricothyroid membrane	60	Hyaluronic acid Calcium hydroxyapatite Artificial collagen	LA	<ol style="list-style-type: none"> Voice analysis was performed preoperatively and at 1 month postoperatively The glottal gap using glottal gap index Perceptual Analysis (Grade, Roughness, Breathiness, Asthenia, Strain scale); (all improved except roughness) Acoustic analysis (Jitter for frequency variation, shimmer for amplitude variation, Noise Harmonic Ratio) Aerodynamic study (MPT, Mean airflow rate, Subglottic pressure) MPT improved Mean airflow rate improved significantly after injection Subglottic pressure (remained same) 	-
2014	Clary et al. (28)	Thyrohyoid With laryngeal introducer technique	21	20 with Radiesse voice gel One with Radiesse voice	LA	<p>Assessment:</p> <p>Questionnaires post procedure on the discomfort of the IL under LA with laryngeal introducer technique – well tolerated</p>	-
2014	Halderman et al. (29)	Transthyrohyoid and transoral	64	Restylane (crosslinked hyaluronic acid)	LA	<p>Pre and post video stroboscopic examination</p> <p>No granulomatous/scarring changes</p> <p>Mucosal wave amplitude preserved</p> <p>No foreign body reaction/inflammation</p>	<p>Two patients: injection into subepithelial plane</p> <p>One patient: developed atrial fibrillation</p> <p>One patient: developed shortness of breath with evidence of edema in the false cord and true cord; was resolved with steroid outpatient.</p> <p>One patient: hematoma in the arytenoid, a/e fold and true cord (patient on coumadin therapy)</p>
2014	Powell et al. (14)	Cricothyroid membrane	68	Hyaluronic acid Calcium hydroxyapatite	LA	<p>Outcome measurement pre and 2 weeks post procedure</p> <p>Voice Performance Questionnaire – significant improvement</p> <p>GRBAS – significant improvement</p>	<p>One patient developed persistent haemorrhage on injection site (on warfarin and dual antiplatelet)</p>

Table 3. continued

Year	Authors	Technique	Sample size	Injection material	GA/LA	Outcome measurement	Complication
2015	Pei et al. (30)	Cricothyroid membrane	29 Out of 29, 14 injected with hyaluronates and 15 had conservative management	One group received Hyaluronates (Restylane) One group received conservative treatment	LA	Outcome measurement: Quantitative laryngeal electromyography, videolaryngostroboscopy- (normalized glottal gap area, NGGA) UVFP-related quality of life (Voice Outcomes Survey, VOS) laboratory voice analysis (include Jitter, Shimmer, Noise harmonic ratio) SZ ratio MPT health-related quality of life (SF-36)	
2016	Mohammed et al. (16)	Transthyroid	21	Calcium Hydroxyapatite	LA	VHI - 10 pre 25 VHI - 10 post 16.9 (Improved)	Three patients unable to tolerate procedure Superficial injection
2018	Ricci Maccarini et al. (31)	Transnasal fiberoptic injection laryngoplasty Using a high-pressure injection pistol connected to a flexible injection needle, injecting centrifuged autologous fat	22	Centrifuged Autologous fat	LA	Significant improvements in: videolaryngostroboscopic findings, perceptual evaluation (GRBA), maximum phonation time QoL self-assessment and VHI	No complication reported
2019	Lee et al. (32)	Mainly Cricothyroid approach	617	Calcium hydroxylapatite (Long lasting material)	LA	Measure the complications of IL under LA with CaHA Voice outcome was not analyzed.	Failure 0.52% Superficial injection 0.82% Acute dyspnea 0.21%

Table 3. continued

Year	Authors	Technique	Sample size	Injection material	GA/LA	Outcome measurement	Complication
2019	Choi et al. (33)	Cricothyroid	306	Long-lasting material (ArteSense)	LA	*This study evaluated the outcome of early IL with long lasting material Outcome measurement: aspiration symptom, maximum phonation time (MPT), jitter, shimmer, noise to harmonic ratio (NHR), overall grade (G) and breathiness (B) of GRBAS (grade of dysphonia, roughness, breathiness, asthenia, strain) scale score, and Voice Handicap Index (VHI) were significantly improved after IL	-
2019	Singh and Gupta (17)	Cricothyroid	12	Calcium hydroxylapatite	LA	Stroboscopy (Symmetry of vocal cords, Mucosal wave on both vocal folds, and Glottic closure) Acoustic analysis (Fundamental frequency, Jitter, Shimmer, S-Z ratio, and Maximum phonation time) VHI	-

GA: General anesthesia; QoL: Quality of life; LA: Local anesthesia; VHI: Voice-Handicap Index

To accurately assess the voice outcome post injection laryngoplasty, a multidimensional holistic assessment is undoubtedly essential. To the best of the authors' knowledge, our research is among the very first few that have studied the multidimensional voice outcomes which consist of all subjective, objective, and acoustic analysis post early injection laryngoplasty under local anesthesia with the double-bend needle technique. According to our literature review, there are not many reported multidimensional voice outcome studies on double-bend needle technique injection laryngoplasty. Song et al. (6) reported voice outcomes with double-bend needle technique adopted mainly on subjective voice outcome survey and voice-related quality of life. Our multidimensional voice outcome study with the double-bend needle technique in post early injection laryngoplasty under local anesthesia showed significant improvement of the glottic function in the improvement of the objective and acoustic analysis, and no patients had any complications.

Hippocrates once said, "First, do no harm." Despite the promising multidimensional voice outcomes with reported low rates of complication in injection laryngoplasty under local anesthesia (17,20), safe medical practice is crucial in modern medicine. We advocate injection laryngoplasty under local anesthesia as both a clinically and financially effective modality of treatment for patients with glottal insufficiency. However, it should only be done in a setting where the transfer of patients service and emergency equipment are available at all times should any complications arise (3). The procedure should be terminated if the patient is unable to tolerate it (17). Patients with pathological laryngeal condition, low pain threshold and those who require a concomitant operative procedure with the usage of direct laryngoscope and rigid telescope should avoid injection laryngoplasty under local anesthesia (3,20).

Proper glottic closure is important for generating cough and preventing aspiration during swallowing.

Multiple studies have shown that injection laryngoplasty benefits patients with glottic insufficiency in preventing aspiration (1). EAT-10 is a validated and symptom-specific outcome tool commonly used in clinical practice to measure swallowing difficulties. However, in our study, EAT-10 scoring was not included in view of the incomplete data recruited.

Limitations

Though the multidimensional voice outcomes post injection laryngoplasty under local anesthesia are promising, there are several limitations in our study.

1. We measured the multidimensional voice outcomes up to 3 months. A longer observational period would provide us with more concrete clinical evidence.
2. In all patients we used hyaluronic acid-based material with injection laryngoplasty; therefore, the comparative multidimensional voice outcomes of other injectable materials could not be evaluated.
3. Videolaryngoscopic assessments were not included in the presented study.
4. We adopted only the transthyrohyoid approach. Comparison of the outcomes with transthyroid and transcricothyroid approaches could not be made.
5. A study which includes EAT-10 would be more comprehensive, particularly in assessing the outcome of swallowing ability post injection laryngoplasty under local anesthesia.

The rationale of performing injection laryngoplasty under local anaesthesia as early as one day post recurrent laryngeal nerve (RLN) injury may be questionable as the neck is commonly edematous, inflamed and tender after thyroidectomy. Nevertheless, the injection procedure may be done under general anaesthesia or delayed until the neck is less swollen and tender. The senior author's experience in performing injection laryngoplasty in acutely injured RLN showed benefits to the patients especially in preventing patients from going home from the hospital with nasogastric feeding due to aspiration issues. Future studies also should investigate the safety and efficacy of injection laryngoplasty performed on-table or within few days of iatrogenic injury of RLN.

A future larger comprehensive study should be ideal to elucidate this information. Despite these considerations, the conclusion on the improvement of multidimensional voice outcome post injection laryngoplasty under local anesthesia from this database seems valid.

Conclusion

Early percutaneous transthyrohyoid injection laryngoplasty with the double-bend needle technique under local anesthesia is an effective modality for the treatment of glottic insufficiency with life and voice quality improvements. Hence, with the evidence of significant improvement of multidimensional voice outcome post early injection laryngoplasty, it should be highly considered in selected suitable patients with UVFP.

Ethics Committee Approval: Since this study is a retrospective study, ethics committee approval is not required.

Informed Consent: Retrospective study.

Conflicts of Interests: No potential conflict of interest relevant to this article was reported.

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Main Points

- Injection laryngoplasty under local anesthesia is a prudent and cost-effective treatment of unilateral vocal fold paralysis.
- The double-bend needle technique allows better visualization and access to the endolarynx resulting in a high success rate.
- Significant improvement on the multidimensional voice outcomes was evidenced by our series of subjective and objective evaluations.

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En Bloc Resection of Supraglottic Carcinomas with Transoral Laser Microsurgery

Original Investigation

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Abstract

Objective: Complete en bloc supraglottic tumor excision with transoral laser microsurgery (TLM) can be achieved with good postoperative outcomes. We report surgical feasibility and the postsurgical outcomes of en bloc resection of supraglottic laryngeal squamous cell carcinomas (LSCC) with TLM.

Methods: Seventeen patients who underwent TLM for supraglottic laryngeal cancer were included in the study. Demographic and pathological data, clinic and follow-up outcomes of the patients were reviewed and analyzed.

Results: Type 1 TLM was performed in three patients, type 2a in one patient, type 3b in 12 patients, and type 4b in one patient. Negative surgical margins were achieved in all of the cases. Re-excision or any adjuvant treatment for positive resection margins was not required in any of the cases. Eight patients received adjuvant radiotherapy due to lymph node metastasis. Mean follow-up time was 33.8±15.7 months (range: 10–65 months). None of the patients had recurrence or distant metastasis.

Conclusion: The transoral approach with the use of CO₂ laser and microscopy offers complete tumor excision for treating supraglottic LSCC. The three-dimensional structure of the supraglottis can be achieved with adequate exposure. En bloc resection is possible with safe margins.

Keywords: Larynx carcinoma, partial laryngectomy, supraglottic carcinoma, transoral laser microsurgery, squamous cell carcinoma

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Introduction

The most crucial goals in treating supraglottic laryngeal squamous cell carcinomas (LSCC) involve oncological and functional outcomes. Recently, however, the preservation of laryngeal functions has come to influence the decision of treatment modality. There are

many treatment options, and supraglottic LSCC can be effectively treated with an open partial horizontal laryngectomy (OPHL), transoral laser microsurgery (TLM), transoral robotic surgery (TRS), or radiotherapy (RT).

In 1990 Zeitels et al. (1) published the first LSCC case series treated with TLM.

Thirty years on TLM has proven to be an excellent option, especially for supraglottic and glottic carcinomas (2, 3). Additionally, many studies reported that better functional outcomes were obtained with TLM compared to other modalities (4, 5). In a recent study TLM was reported to be less invasive than OPHL (6).

TLM is a good option for early-stage supraglottic LSCC and offers similar survival rates and decreased morbidity compared to OPHL (7). However, there are still controversies about using TLM for the treatment of advanced stage supraglottic LSCC. In principle, en bloc tumor resection with safe margins is the standard treatment method in the surgery of all laryngeal cancers; however, many surgeons can regard multi-bloc or piecemeal resection of tumors as an option to achieve better visualization (8).

En bloc transoral tumor resection is considered challenging and piecemeal resection is contentious in the surgery of advanced stage supraglottic LSCCs (8-10). This study reports the post-surgical outcomes and surgical feasibility of en bloc resection of supraglottic LSCC with TLM.

Methods

The study was designed as a retrospective one, and all data were retrospectively collected. Data include the medical records of patients diagnosed with supraglottic LSCC and treated with TLM in April 2016 to July 2020. Demographic data, tumor stage, histopathological grade, nasogastric tube (NG) removal and decannulation time, as well as video laryngoscopic records were reviewed and analyzed. The laryngeal cancer staging designated by the American Joint Committee on Cancer was used for tumor staging (11).

Seventeen patients who had undergone TLM for supraglottic laryngeal cancer were included. All patients had biopsy-proven laryngeal squamous cell cancer. Sizes and localizations of the tumors, and the mobility of the vocal folds were noted in preoperative video laryngoscopy examination. Positron emission tomography (PET/CT) or neck and chest computed tomography (CT) scans were done during preoperative oncological evaluation, also to exclude distant metastases.

Procedure and Instrumentation

European Laryngological Society (ELS) classification system was used to classify resections (12). The same senior surgeon (KÖ) performed all tumor excisions under general anesthesia. A carbon dioxide laser (Lumenis Acupulse Duo[®], Yokneam, Israel) was used with AcuBlade equipment. The power was set to 10 watts in the continuous super-pulse mode. Steiner's distending operating laryngoscope obtained laryngeal exposure with a Storz suspension device (Karl Storz[®], Tuttlingen, Germany). The laryngoscope's upper blade

was placed in the vallecula, and the lower blade displaced the endotracheal tube. The en bloc resection technique was successfully performed in all cases.

Medial supraglottic laryngectomy (SGL) with resection of the preepiglottic space was performed for the medially located lesions extending to the infrahyoid epiglottis. Lateral SGL was performed for the tumors located on the lateral or posterior supraglottic space, and aryepiglottic folds, ventricular folds, arytenoids, pharyngo-epiglottic folds or anterior wall of pyriform fossa were resected based on tumor location. Limited excisions were performed only for small T1 tumors located in the free edge of aryepiglottic folds or epiglottis. Resection was started with the dissection of the preepiglottic area from the vallecula until the hyoid bone was reached. The preepiglottic space was dissected, and glossoepiglottic ligament was divided. The aryepiglottic fold was cut, and the false vocal fold was separated from the arytenoid cartilage. Dissection was continued posterior to anterior on each side to release the supraglottic structures and the tumor from the thyroid cartilage. At the end of the procedure, the whole epiglottis, the preepiglottic space, the aryepiglottic folds, the false vocal folds, and the laryngeal ventricles had been resected in en bloc fashion. Figures 1 and 2 show the surgical specimens that were resected with TLM. Super-selective or selective neck dissection was performed in clinically lymph node-negative necks. In clinically lymph node-positive necks, modified radical neck dissection was performed. Tumor positive lymph node and resection margins in postoperative histopathology were indications for adjuvant therapy.

Postoperative follow-up routine was every two months in the first year, every three months in the second year, every four to six months until the fifth year and annually thereafter. Patients underwent full head and neck examination, and ultrasound was performed at every visit, and a chest X-ray or CT was taken annually. CT scan, magnetic resonance imaging, and positron emission tomography were done when necessary.

Ethical Considerations

The study was conducted in line with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki guidelines and its amendments (ethics committee approval IRB no: 20-7.1T/5). Informed consent was obtained from all patients for their respective surgical procedures.

Statistical Analysis

The SPSS computer software (SPSS version 22.0, SPSS Inc. Armonk, NY, USA) was used for statistical analysis. Descriptive statistics of the patients were expressed as mean \pm standard deviation.

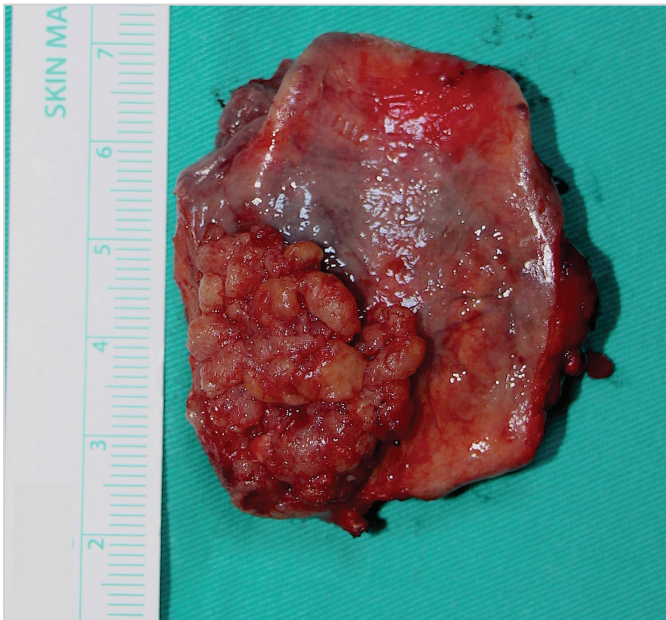


Figure 1. Surgical specimen of patient number 3. The tumor was located on the left side of the infrahyoid epiglottis. Type 3b transoral supraglottic laryngectomy (SGL) was performed



Figure 2. Surgical specimen of patient number 16. The tumor was on the laryngeal surface of the infrahyoid epiglottis, extending to the petiole

Results

Seventeen patients were included in the study. Sixteen were male, and one was female, and their mean age was 66.5 ± 5.7 years (range: 57–79 years). Tumor stage was T1 in four patients, T2 in ten, and T3 in three patients. In all patients, supraglottic LSCC was resected with clear margins.

Resections were type 1 in three patients, type 2a in one patient, type 3b in 12 patients, and type 4b in one patient. Nine patients had bilateral selective and eight had unilateral neck dissection. There were 8 (47%) patients with loco-regional lymph node metastases. Lymph node metastasis with extranodal spread and perineural invasion was found in one patient. The summary of patient outcomes is given in Table 1.

Two patients required prophylactic tracheostomy after extended supraglottic resection. Decannulation times for these two patients were 13 and 16 days, respectively. Three patients suffered from dyspnea during/after adjuvant RT due to laryngeal edema, and one of them required a tracheostomy. One patient developed anterior glottic stenosis and was successfully managed with TLM. All patients were successfully decannulated. There were no early postoperative complications.

Median NG tube removal time was ten days (IQR=7, range: 1–26 days). In three patients who had T1 supraglottic LSCC, oral feeding was started on the second postoperative day without NG tube placement. Mean hospitalization time was 12 days (range: 3–34 days) Gastrostomy tube was used in one patient due to chronic aspiration and dysphagia after adjuvant RT.

Tumor histopathology was well-differentiated LSCC in nine and moderately differentiated in seven patients. Basaloid LSCC was found in one patient. Mean tumor size was 2.8 ± 1.4 cm (range: 1.5–4.5 cm). Negative surgical and pathological resection margins were achieved in all patients. Re-excision or any adjuvant treatment for positive resection margins was not required in any of the cases. Lymph node metastasis was the primary indication for adjuvant treatment. Postoperative RT was performed in eight patients, one with extra nodal tumor extension also received concurrent platinum-based chemotherapy. Mean follow-up time was 33.8 ± 15.7 months (range: 10–65 months). None of the patients had local or regional recurrence, or distant metastasis during this period.

Discussion

Transoral resection of supraglottic tumors by preserving glottic functions has become possible and widespread in the last three decades with the ongoing development of laser and endoscope technology (8). The three-dimensional structure of the supraglottis can create challenges for complete resection of the tumors. In conventional SGL, the horizontal part of the supraglottis above the vocal cords on which the tumor is located is resected. This method is considered a safe and successful oncological surgery in selected patients. It may require initial tracheostomy. Also, dysphagia and aspiration can be problematic in some patients because of the resection of the supraglottic structures (13, 14).

Table 1. Summary of demographic, surgical, pathologic and clinical data of the patients

Patient no	Age/Sex	Surgical treatment		Tumor histopathology		Postoperative pathologic stage [#]	Tumor diameter	Adjuvant treatment	Nasogastric tube removal time (day)
		Transoral supraglottic laser laryngectomy type ^e	Neck dissection						
1	64/Male	3B	Bilateral selective	Well-differentiated LSCC*	T2N0M0	3 cm	-	6	
2	65/Male	2A	Bilateral selective	Well-differentiated LSCC	T1N0M0	3 cm	-	1	
3	69/Male	3B	Bilateral selective	Well-differentiated LSCC	T2N0M0	3 cm	-	6	
4	79/Male	3B	Left modified radical type 3	Moderately differentiated LSCC	T3N2BM0	3 cm	Radiotherapy	15	
5	62/Male	3B	Bilateral selective	Well-differentiated LSCC	T2N0M0	1.5 cm	-	7	
6	58/Male	3B	Bilateral selective	Moderately differentiated LSCC	T2N1M0	3 cm	Radiotherapy	6	
7	63/Male	3B	Bilateral selective	Well-differentiated LSCC	T3N0M0	4.5 cm	-	21	
8	70/Male	1	Left modified radical type 3	Basaloid LSCC	T1N2bM0	3 cm	Radiotherapy	2	
9	75/Male	3B	Right modified radical type 3	Moderately differentiated LSCC	T2N2bM0	3 cm	Radiotherapy	7	
10	57/Male	3B	Left modified radical type 3	Moderately differentiated LSCC	T2N1M0	2.1 cm	Radiotherapy	7	
11	67/Male	1	Bilateral selective	Well-differentiated LSCC	T1N0M0	1.6 cm	-	2	
12	62/Female	3B	Right modified radical type 3	Moderately differentiated LSCC	T2N1M0	2 cm	Radiotherapy	26	
13	63/Male	4B (lesion extends to pyriform fossa)	Right modified radical type 3	Well-differentiated LSCC	T2N0M0	2 cm	-	12	
14	70/Male	3B	Right modified radical type 3	Moderately differentiated LSCC	T2N3bM0	2 cm	Radio chemotherapy (Extranodal tumor extension +)	9	
15	70/Male	1	Bilateral selective	Well-differentiated LSCC	T1N0M0	2 cm	-	7	
16	62/Male	3B	Bilateral selective	Well-differentiated LSCC	T2N0M0	2.3 cm	-	10	
17	59/Male	3B	Left modified radical type 3	Moderately differentiated LSCC	T3N1M0	2 cm	Radiotherapy	8	

*: Laryngeal squamous cell carcinoma

[#]: Laryngeal cancer staging designated by the American Joint Committee on Cancer

^e: European Laryngological Society Classification System for transoral supraglottic laryngectomy

TLM is considered a good option for treating early-stage glottic carcinomas (15). It offers favorable results similar to RT without harming the glottic functions. The anatomy and histology of the glottic site are suitable for transoral procedures. Resection can be made with smaller safe margins, and lymphatic and arterial/venous microvessels are less common compared to the supraglottic site (16).

Early-stage supraglottic LSCCs are also good candidates for TLM. In the classification of the ELS, Type 1 TLM in supraglottic LSCC is described as the limited excision of small superficial lesions with only one supraglottic subsite (11). T1 tumors can be resected safely without harming uninvolved supraglottic structures with a CO₂ laser. Laryngeal functions such as phonation and swallowing can also be protected. In our study, three patients were diagnosed with T1 supraglottic tumor. Tumors were located on the aryepiglottic fold without glottic extension in two patients. The other patient had a small-sized tumor located on the free edge of the epiglottis. En bloc complete tumor resection was performed in these patients, and none of them had disease recurrence, dysphagia, or aspiration.

The extension of the bulky supraglottic tumor to the infrahyoid epiglottis, epiglottic petiole, preepiglottic space, or ventricular fold makes en bloc transoral resection difficult. The accessibility of the inferior margin and the dissected tumor tissue's traction can be hard without resecting a part of the tumor. Piecemeal resection is an option for these tumors. This technique was favored by Rudert et al. (10) who described the laser resection lines in supraglottic structures for bisecting the tumor tissue.

Previous studies reported TLM success combined with neck dissection and/or RT for treating advanced stage supraglottic LSCC (17-19). It offers good functional and oncologic results. Peretti et al. (9) published the results of eighty cases affected by supraglottic LSCC and treated with TLM. They reported that ten patients required re-excision for residual tumor, and two patients with positive surgical margins in histopathological examination had disease recurrence. They stated that better visualization of surgical margins is possible with piecemeal resection of bulky lesions. They did not report the comparison of outcomes with en bloc resection due to limited patient numbers. There is a lack of data in previous studies comparing the piecemeal and en bloc resection of supraglottic LSCC with TLM.

In our series, 12 patients underwent type 3b, and one patient underwent type 4b supraglottic TLM laryngectomy, and en bloc resection was achieved in all. No residual tumor was present in the postoperative histopathological examination. The differentiation between healthy tissue and tumor can be challenging due to inadequate exposure during resection. Also, appearance of the healthy tissue can be affected by

CO₂ laser's hemostatic effect. Piecemeal resection is an option for resection of bulky tumors, but carries the concern of incomplete resection or an increased risk of tumor metastasis (20). Adequate exposure and lighting are essential for optimal microscopic view. Transoral laser resection of the supraglottic tumors in en bloc fashion was feasible and clear margins could be achieved without bisecting the tumor.

Incomplete resections can be catastrophic in the treatment of LSCC (2, 17). Meticulous resection with clear margins is the primary goal of the laryngeal surgery. However, comprehensive pathological examination of the tumor specimen is essential. The orientation of the pathologist to surgical specimens and tumor margins is crucial. Evaluation of all surgical margins may not be possible in the piecemeal technique. This advantage can also be considered a superiority of en bloc resected surgical specimens.

Besides tumor size and patient anatomy, the surgeon's experience in TLM can be another critical factor. In our study, the senior surgeon (KÖ) who operated on all patients has an experience of more than 300 cases in open partial laryngectomy, TLM, and transoral robotic surgery (TORS). The resection of advanced stage supraglottic tumors can be challenging without expertise in oncologic laryngeal surgery. Early-stage supraglottic LSCCs and limited excisions may be more appropriate for inexperienced surgeons.

There are other transoral treatment options, such as TORS, for patients diagnosed with supraglottic LSCC (21). We also have experience in TORS and offer this procedure in our hospital; however, it is not preferred by patients because of its high cost which they have to assume. Primary radio(chemo)therapy as a larynx preservation approach is also an option for the patients with locally advanced disease (22). Comparative studies are mandatory for the best conclusion on the oncologic outcomes. In our study, we mainly focused on the feasibility of the en bloc resection of the tumor and its positive effect on oncologic evaluation. We achieved good clinical and oncological postoperative results in en bloc resection with TLM in supraglottic LSCCs. The small number of patients and the relatively short postoperative follow-up period are the shortcomings of this study. The mean follow-up time was 33.8 months; however, recurrences mostly occur in the first two years in LSCC cases. Prospective controlled studies with larger patient groups and longer follow-up periods are needed to achieve more substantial conclusion.

Conclusion

In this report we presented our results in the en bloc resection of supraglottic LSCC with TLM. In all patients, en bloc tumor resection with safe margins was achieved. The transoral approach with the use of CO₂ laser and microscope offers complete tumor excision for treating supraglottic

LSCC. The three-dimensional structure of the supraglottis can be achieved with adequate exposure. En bloc resection is possible with safe margins without harming healthy laryngeal tissues.

Ethics Committee Approval: The ethics committee approval was received for this study from the Ege University Ethics Committee (IRB no: 20-7.1T/5).

Informed Consent: Informed consent was obtained from all patients for their respective surgical procedures.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Main Points

- This study aims to report the postsurgical outcomes and the surgical feasibility of en bloc resection of supraglottic carcinomas (SGC) with transoral laser microsurgery (TLM).
- En bloc resection with safe margins was achieved in all patients.
- None of the patients developed local or regional recurrence, or distant metastasis during the mean 33-month follow-up period.
- The transoral approach with the use of CO2 laser and microscope offers complete tumor excision.

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Management of a Spontaneous Thyroid Nodule Hemorrhage Causing Acute Airway Obstruction

Case Report

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Abstract

Spontaneous intrathyroidal hemorrhage (ITH) causing airway obstruction is relatively rare. We report a case with no known history of a thyroid disease that presented with an ITH causing severe airway obstruction as a life-threatening situation. A 57-year-old female patient presented to the emergency department with sudden onset of swelling of the anterior neck, severe dyspnea, and unconsciousness. Computerized tomography scan after intubation revealed a 6.2x5.3 cm mass originating from the right thyroid lobe and compressing the airway. Drainage of hematoma with right lobectomy was done. When the patient was extubated one day after the surgery the vocal cords were found to be mobile. She was discharged after two days and there was no need for further intervention during the one-month follow-up. Spontaneous life-threatening ITHs are rare entities. Immediate assessment of airway obstruction and achieving a secure airway are crucial. Besides drainage of hematoma, thyroidectomy may also be necessary.

Keywords: Airway obstruction, thyroidectomy, goiter, hematoma, spontaneous hemorrhage, emergency, case report

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Introduction

Thyroid gland hemorrhage is a life-threatening situation if not managed promptly and correctly. Spontaneous intrathyroidal hemorrhage (ITH) causing airway obstruction is relatively rare and different causes are reported in the literature (1-4). Spontaneous hemorrhage of the thyroid gland usually occurs in cases with thyroid nodules and cysts; however, the reason for rupture is still not clear (2, 4-6). We report a case with no known history of a thyroid disease that presented with an ITH causing severe airway obstruction as a life-threatening situation.

Case Presentation

A 57-year-old female patient presented to the emergency department with sudden onset of swelling of the anterior neck, severe dyspnea, and unconsciousness. The patient was intubated to secure the airway and referred to our department. The larynx had shifted to the left however; the vocal cords were visible. She had no history of any disease. According to her relatives' statement, dizziness and nausea had started 12 hours ago and swelling began to appear on the right side of her neck in the meantime. She had forced herself to vomit to feel better and then slept. After

few hours, her relatives were unable to wake her up fully. The size of the swelling was rapidly increasing, and dysphagia and severe dyspnea ensued the enlargement of the swelling. They brought her to the emergency service.

Blood gas analysis and computerized tomography (CT) of the neck were done in emergency setting. Blood gas analysis revealed severe acidosis with a pH of 6.3. Right after securing the airway, the patient was transported to the intensive care unit and treatment of acidosis was administered. CT scan revealed a 6.2x5.3cm mass originating from the right thyroid lobe and compressing the trachea; and rupture of a cystic thyroid nodule was suspected (Figure 1).

An urgent surgery for drainage of the hematoma was decided because of tracheal compression, active bleeding, and rapid enlargement of the size of hematoma. Intraoperatively, a huge mass was seen to compress the trachea and shift it to the left side. Careful sharp dissection with coagulation was performed and blood clots were removed from inside the cyst. However, there was still bleeding in the surgical area and despite massive cauterization, there was a risk of a recurrent hematoma. Thus, the removal of the right lobe of the thyroid was deemed necessary. After identifying and preserving the recurrent laryngeal nerve (RLN) and parathyroid glands, lobectomy was performed (Figure 2). The patient was not extubated immediately after the operation, but on the next day; and the vocal cord movements and thyroid function tests were normal. After two days, she was discharged with oral antibiotics. During the one-month follow-up there was no need for further intervention. Histopathologic report revealed a multinodular goiter with a hemorrhage of cystic nodule. The patient was referred to the endocrinology department for further follow-up.

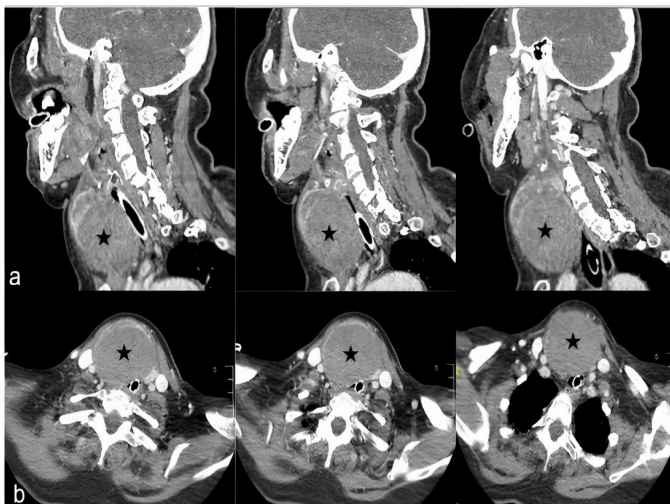


Figure 1. Computerized tomography scan showing a. Sagittal sections: a huge hematoma compressing the airway b. Axial sections: hematoma arising from the right thyroid lobe compressing the trachea and causing a shift to the left side. (★) indicates right thyroid lobe

Discussion

ITH is relatively rare and the mechanism causing the hemorrhage is unknown. Some of the factors reported in the literature may be grouped as traumatic and nontraumatic causes (1, 2, 4, 5). Blunt trauma to the anterior neck region or fine needle aspiration biopsy are responsible for most of the cases. Use of anticoagulants, bleeding diathesis are other reasons for ITH. Even though increased intravascular pressure such as Valsalva maneuver, choking, constipation could be accepted as the etiological factors of spontaneous ITH, there is no consensus as to why hemorrhage occurs (3). Increased vascularization of the gland and more specifically arteriovenous shunting inside the nodule are thought to be the causal factors (2, 4, 6, 7). In the presented case, increased intravascular pressure caused by vomiting could be the reason for ITH. Yang et al. (2) found that abundant blood supply and spongiform internal content of the nodule revealed by ultrasound were associated with ITH of their patients with partial cystic thyroid nodule.

The symptomatology of ITH ranged from asymptomatic to life-threatening airway compromise. Dysphagia, swelling of the anterior neck, dyspnea are the main symptoms of ITH depending on the size of the hematoma (2). The overall condition and vital parameters of the patient must be assessed before any radiological imaging. Flexible nasolaryngoscopy of those with symptoms is the fastest way to evaluate the

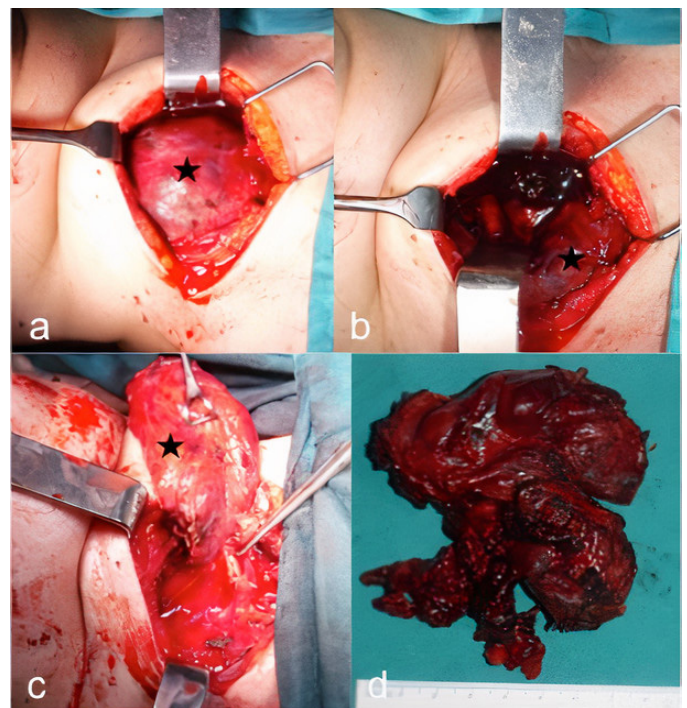


Figure 2. a. Right thyroid lobe b. Hematoma arising from right thyroid lobe c. Identifying the recurrent laryngeal nerve and view of the right thyroid lobe intranodular vessels d. Specimen. (★ indicates right thyroid lobe)

airway. An urgent neck CT with contrast or ultrasound can show the size of hematoma and enable to assess airway obstruction (2, 4, 5, 8-10). However, as with our case, it may not be possible to wait for a CT scan and immediate intubation becomes of vital importance.

The most critical stage in the management of ITH is ensuring a secure airway. If intubation is not performed in a prompt and timely manner, airway impairment may occur rapidly, severe morbidities may develop, and emergency intervention may be needed. Venous congestion and edema may cause dyspnea in case of active bleeding even when the airway is not compressed.

In most cases, patients with ITH do not need an urgent thyroidectomy. After urgent drainage of hematoma, elective thyroidectomy with neuromonitoring guidance will be the best option (2, 6, 7, 9, 10). In some cases, however, it can be challenging to stop the bleeding and an urgent subtotal thyroidectomy can become necessary. In our case, right after surgical drainage, it was not possible to stop bleeding from the thyroid tissue and we decided to perform a lobectomy in the same session. Although we prefer to perform all kinds of thyroid surgeries under neuromonitoring guidance, this method was not possible in this case given the high risk of reintubation failure with a neuromonitoring endotracheal tube. Subtotal thyroidectomy may be an option to reduce the risk of re-bleeding; however, it should be kept in mind that benign nodules can also cause ITH as well as malignant nodules (6, 7). We preferred lobectomy for this case because we did not have a clear sign that the patient had a kind of a malignant thyroid disease.

ITH with mild symptoms can be followed with serial ultrasound examinations, administering steroid and antibiotic therapy to prevent edema and abscess formation (5). Cases with ITH due to anticoagulant therapy are usually treated with conservative methods. It is associated with nodular thyroid disease and generally suspension of anticoagulant therapy and changing treatment to low molecular weight heparin helps to avoid worsening of symptoms (2, 4).

Conclusion

Spontaneous life-threatening ITH is a rare entity. Immediate assessment of airway obstruction and achieving a secure airway are crucial. If bleeding cannot be stopped after drainage or surgical exploration, thyroidectomy can become imperative in the same session.

Informed Consent: This is a retrospective case study.

Peer-review: Externally peer-reviewed.

Author contributions

Conception: H.B., L.Y., Design: H.B., A.H., Supervision: S.B., Data Collection and/or Processing: H.B., L.Y., A.H., Analysis and/or Interpretation: H.B., L.Y., Literature

Review: H.B., L.Y., A.H., S.B., Writing: H.B., Critical Review: H.B., L.Y., S.B.

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

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

Main Points

- Thyroid gland hemorrhage may be a life-threatening situation if not managed promptly and correctly.
- Increased vascularization of the gland and more specifically arteriovenous shunting inside the nodule and abundant blood supply are the factors thought to be the underlying reasons.
- The most critical stage in the management of ITH is ensuring a secure airway.
- In most cases, urgent thyroidectomy is not needed.
- In cases when bleeding cannot be controlled with drainage and surgical exploration, thyroidectomy may become imperative.

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Retropharyngeal Abscess in a Neonate After Extravasation Injury: To Drain or not to Drain?

Case Report

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Abstract

Neonatal retropharyngeal abscess (RPA) is a rare and life-threatening entity. Most of the cases are idiopathic in nature. We encountered a case of RPA in a newborn secondary to extravasation injury. The presence of neck swelling with clinical deterioration following extravasation of total parenteral nutrition (TPN) infused via a peripherally inserted central catheter at the right upper limb raised the suspicion of neck abscess. This was later confirmed to be RPA based on magnetic resonance imaging of the neck. She was treated with prolonged intravenous antibiotics in the Neonatal Intensive Care Unit (NICU). Her condition gradually improved, evidenced by resolution of the collection on serial imaging. Early recognition and prompt management are crucial to reduce the morbidity and mortality from RPA.

Keywords: Retropharyngeal abscess, neonatal, extravasation of diagnostic and therapeutic materials injury, non-invasive treatment, case report

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Introduction

Deep neck space infections in the pediatric age group are not frequently seen and are misdiagnosed at a rate of up to 61.8% (1). Neonatal retropharyngeal abscess is extremely rare and accounts for only 10% of all the cases in the paediatric age group (2). Nevertheless, it is an important clinical entity because of its rapid onset and life-threatening complications such as airway obstruction, jugular vein thrombosis, mediastinal involvement, pericarditis,

pneumonia, and arterial erosion (3). We report a case of retropharyngeal abscess (RPA) that occurred secondary to extravasation of total parenteral nutrition in a neonate and was successfully treated with intravenous antibiotic therapy alone. Our clinical experience with this patient highlights the benefit of the conservative antibiotic approach for RPA and the importance of multi-disciplinary team management. Though deep neck abscesses are uncommon in pediatric age group, it

should always be considered as an important differential diagnosis in neck swelling.

Case Presentation

A female infant was delivered premature at week 32 of the gestation period with a birth weight of 1100 grams. She was born with emergency lower cesarean section due to maternal pre-eclampsia. Antenatally, her mother had history of being a Group B streptococcus (GBS) carrier. The infant was admitted to Neonatal Intensive Care Unit (NICU) from birth and was given intra-tracheal surfactant for treatment of respiratory distress syndrome (RDS). She developed necrotizing enterocolitis (NEC) on her seventh day of life and was treated with intravenous antibiotic. She was kept nil per orally and total parenteral nutrition (TPN) was commenced.

A peripherally inserted central catheter (PICC) was inserted at the right cubital fossa on day 16 of her life. After starting TPN, there was immediate right neck swelling with facial edema. Chest radiograph (CXR) showed the catheter tip at the junction of right subclavian and brachiocephalic vein, and there was no evidence of distal migration of the catheter (Figure 1). This incident was treated as extravasation of TPN and PICC was removed. The neck swelling and facial edema gradually subsided after one week of intravenous antibiotic therapy. Coagulase-negative staphylococci (CoNS) was isolated from the PICC tip.

However, the right neck swelling recurred after completion of intravenous antibiotic therapy. The non-fluctuant, non-tender swelling was seen mainly over the right submental and submandibular area with normal skin color. There was no subcutaneous emphysema palpable. She had developed multiple apneic episodes requiring Bi-level Positive Airway Pressure (BiPAP) support. She also had fever of 37.9 degree Celsius and her heart rate was persistently tachycardic ranging from 180-200 beats per minute during this period.

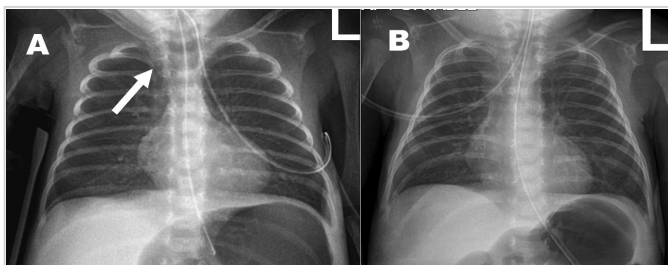


Figure 1a. Chest radiographs (CXR) taken post-right percutaneous insertion of peripherally inserted central catheter (PICC). The white arrow shows the tip of the PICC at the junction of right subclavian vein and right brachiocephalic vein with no fracture of PICC or pneumothorax. Tip of nasogastric tube was seen in the stomach. b. CXR taken when patient developed right neck swelling. The PICC was removed prior to CXR. There was no abnormality in the CXR to suspect retropharyngeal collection

However, there were no hypotensive episodes. Her blood investigations showed a white cell count of $27.3 \times 10^9/L$ which was neutrophils predominant (92.9%) and an increased C-reactive protein level of 3.52mg/dl. As the repeat chest radiograph did not reveal any obvious abnormality, an ultrasound of the right neck was performed. The ultrasound showed presence of a hypoechoic collection seen posterior to the right carotid sheath, with presence of echogenic debris suggestive of an RPA (Figures 2a and b). The collection had crossed the midline retropharyngeally to the left, posterior to the left carotid sheath. Anteriorly, the collection had also displaced the right internal jugular vein (IJV) and the common carotid artery which remained patent. Magnetic resonant imaging (MRI) of the neck confirmed the findings of the ultrasound examination. The collection was seen as hypointense signal on T1W1, hyperintense signal on T2WI and rim enhancement on post contrast (Figures 3a and b). A diagnosis of RPA was made, and intravenous antibiotic therapy was re-commenced. Blood culture then grew CoNS which was sensitive to teicoplanin and rifampicin.

She was referred to the Otolaryngology team in view of the possibility that the RPA may cause upper airway obstruction. A repeat ultrasound performed one week after commencement of treatment showed non-resolution of the collection. It partially compressed the right IJV and displaced the oesophagus to the left (Figures 2c and d).

Though there was a soft diffuse right submandibular swelling, she did not have any symptoms of upper airway obstruction. There was no stridor and no bulge seen at the posterior

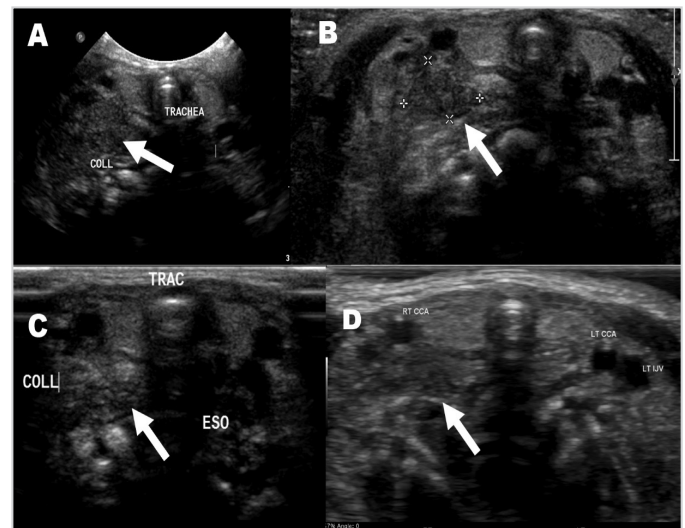


Figure 2. Neck ultrasound: a-b. white arrow, there was a heterogeneous hypoechoic collection in the right neck region posterior to the right internal jugular vein (IJV) and lateral to the oesophagus measuring 1.0x2.5x1.6 cm (APxWxCC); c-d. white arrow, repeated ultrasound of the right neck region one week following treatment showed non-resolution of the previously seen collection. This collection did not cause airway or vascular compression

pharyngeal wall. She remained well with satisfactory weight gain. The workup for primary immunodeficiency which included T and B cell and natural killer cell profiles were unremarkable. In view of the clinical improvement, a multidisciplinary team decision was made to continue the medical therapy with serial imaging and blood parameter monitoring. A neck ultrasound which was performed three weeks after the antibiotic therapy revealed presence of phlegmon at the previous collection site with suspicion of right IJV thrombus formation. An MRI/Magnetic resonance venography (MRV) after six weeks of therapy (combination of intravenous teicoplanin and rifampicin) showed resolution of the retropharyngeal abscess and right IJV thrombosis with presence of collaterals (Figures 3c and d).

She was discharged at corrected gestation of 42 weeks and weight of 2670 grams. A repeat ultrasound performed six weeks after completion of intravenous antibiotic therapy revealed resolution of collection with short segment right IJV stenosis.

Discussion

While deep neck infections can be difficult to diagnose and treat, they are more challenging among the pediatric age group. Deep neck infections can be categorized based

on their anatomical site; namely as retropharyngeal, parapharyngeal, and peritonsillar abscesses. RPA is the most common, constituting 66.7% of deep neck infections in the pediatric age group (4).

The retropharyngeal space is a potential space between the visceral layer and deep layer of the cervical fascia. This space contains large numbers of lymph nodes, especially in children under five years of age. The retropharyngeal space lymph nodes drain the nasal cavity, the nasopharynx, the paranasal sinuses, as well as the soft palate. Therefore, upper respiratory tract infections are the leading cause of RPA in the pediatric age group (2). Dental infections or congenital anomalies may also be a source of RPA formation. On the other hand, trauma and foreign body ingestion are more likely in adult patients. *Staphylococcus aureus* is the most common microorganism isolated in pediatric RPA (1, 3). It is also important to note that children from lower socioeconomical background are more at risk as they may not be able to seek treatment in time and might need more invasive approaches (4).

As for neonates, deep neck abscesses are rare. Male neonates are more at risk, with a male to female ratio of 2:1 (3). Though most of the cases are idiopathic, there are some known predisposing factors, such as history of intubation, nasopharyngeal CPAP, multiple laryngoscopies and even application of suction catheter (3). Presence of congenital abnormalities such as remnant of third branchial arch or cystic hygroma should also be investigated and treated if a patient develops recurrent deep neck abscesses (3).

Clinical presentation in neonates may differ from older children. Though fever is common in childhood RPA, it is usually absent in the neonate. The dangers of a RPA are airway obstruction and spread of infection to involve the carotid sheath and/or the mediastinum (3). As a result, the affected neonate may develop stridor and/or respiratory distress, poor feeding, hoarseness, and weak cry (3). Trismus, drooling, retropharyngeal bulge, and acute respiratory compromise are less common and require immediate medical attention. It may be misdiagnosed as up to 40% of pediatric patients may have no visible neck swelling or restricted neck movement on presentation (1, 5). In our case report, our patient was a preterm neonate with a predisposing factor of nasal CPAP use. Nevertheless, extravasation of TPN was more likely to have caused the neck swelling which later got infected.

Extravasation injury is caused by non-intentional leakage of infused intravenous fluid into the surrounding soft tissue, leading to local tissue reaction or damage (6). Extravasation has been shown to occur in up to 70% of neonates, although tissue damage and skin necrosis is much less common (7). Intravenous lines are often needed for long periods in neonates as a means to provide nutrition and medication. As neonatal veins are small and fragile, this increases their susceptibility to extravasation injury (7). Parenteral nutrition

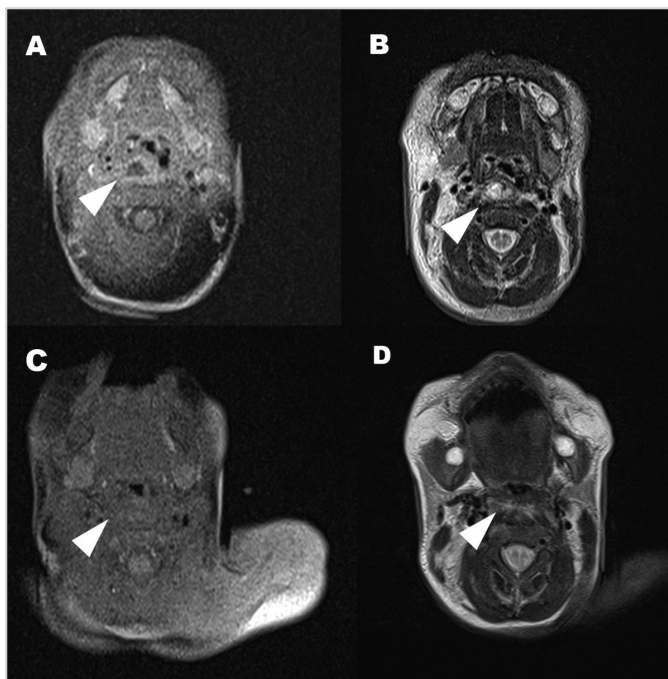


Figure 3. Magnetic resonant imaging (MRI) of the neck: a-b. white arrowhead, the initial MRI of the neck showed the previous collection seen on ultrasound. It showed (b, white arrowhead) T2WI hyperintense signal and (a, white arrowhead) rim enhancement measuring approximately 0.5x 2.0x 1.3 cm (APxWxCC) in widest diameter in post contrast in the right retropharyngeal space. Repeat MRI one month after treatment showed resolution of the collection. There was no longer (c) rim enhancing collection or (d) T2WI hyperintense signal

has been one of the most common implicated causes of extravasation injury (7). Total parenteral nutrition is a vesicant and hyperosmolar solution that is rich in lipids, amino acids, dextrose, vitamins, electrolytes and trace elements, and has the potential to cause varying degrees of deep tissue damage (7). If extravasation of this hyperosmolar solution occurs, it can cause severe damage, such as skin necrosis, skin infections with abscess, or even necrotizing fasciitis. Although the exact mechanism of tissue injury is unclear, the proposed mechanism has been suggested to be related to the hyperosmolarity, acidic pH and toxic effect of local ions in parenteral nutrition (6, 7). Extravasation injury can be treated conservatively by local topical application and antidote administration, or with the saline washout technique (6). There is no consensus on the best treatment for extravasation injury and the importance of prevention has not been sufficiently emphasized.

As deadly complications may arise from deep neck abscesses, urgent surgical drainage has been advocated by many surgeons (8, 9). This is true in adults, as the infection can spread easily along the fascial plane. In children, however, infection is usually confined to the lymph node and spreads only when the lymph node ruptures. With this clinical relevance, studies were done to challenge the conventional method of surgical drainage (5, 10). The wait and watch method with high dose intravenous antibiotics has been shown to be as effective as the drainage method without increasing morbidity and mortality rates or without increasing the length of stay in the hospital (5, 10). It is also worth noting that no pus in up to 21% of the patients who were admitted for surgical management (8).

In cases with airway complications, severe neck movement restriction, bulging of pharyngeal wall, or mediastinitis with significant medical co-morbidities, surgical drainage of the RPA, transoral or transcervical, is more advisable (5). Page et al. (8) proposed positive predictive factors, such as duration of illness of more than two days, history of antibiotic usage and computed tomography of the lesion of more than 2 cm², for advocating surgical drainage.

Conclusion

Early recognition of neonatal RPA is important, and appropriate investigation should be carried out promptly to prevent severe life-threatening complications. RPA secondary to extravasation of TPN is relatively unusual but may cause infection as illustrated in this case report. Fortunately, early recognition and radiologic examination, together with the administration of high dose intravenous antibiotics halted the progression of the disease with complete resolution without any surgical intervention.

Authorship Contributions

Conception: N.J.J., G.B.S., Design: N.J.J., G.B.S., Supervision: N.J.J., G.B.S., E.Y.H., S.I., Data Collection and/or Processing: N.J.J., G.B.S., M.I.A., Analysis and/or Interpretation: N.J.J., G.B.S., M.I.A., E.Y.H., S.I., Literature Review: N.J.J., G.B.S., M.I.A., E.Y.H., S.I., Writing: N.J.J., G.B.S., M.I.A., S.I., Critical Review: N.J.J., G.B.S., M.I.A., E.Y.H., S.I.

Informed Consent: Consent was obtained from the patient's parents. Her anonymity was preserved throughout the case report.

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

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Main Points

- Extravasation of total parenteral nutrition in the neonate is one of the rare causes of neonatal retropharyngeal abscess.
- Early recognition of the disease and early administration of high dosage of antibiotics will halt the progression of the disease without surgical intervention.
- The wait-and-watch approach with intravenous antibiotics is as effective as the surgical drainage method without increasing the risks of morbidity and mortality in selected cases.

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A Rare Tumor in the Neck of a Child: Plexiform Neurofibroma

Case Report

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Plexiform neurofibroma represents an uncommon variant of neurofibromatosis type 1, constituting only 5%–30% of all cases. Plexiform neurofibroma is usually diagnosed during childhood and arises from multiple nerves, manifesting as bulging and deforming masses that can also involve connective tissue and skin folds. We report a case of a two-year-old girl who presented with worsening stridor since birth and later exhibited progressively increasing left neck swelling at the age of 10 months old. Ultrasound and magnetic resonance imaging (MRI) showed a lobulated solid mass in the left deep neck space extending to the midline and having a mass effect on the airway with involvement of the supraglottic region. Tracheostomy was done, and a biopsy of the supraglottic lesion revealed a plexiform neurofibroma. The patient was conservatively managed after a discussion with her parents concerning the associated potential of operative morbidity. The patient's parents had learned about tracheostomy care, and the patient was scheduled for yearly MRI surveillance. MRI was performed again three months after the initial diagnosis and showed stable lesion. Plexiform neurofibroma is a slow-growing tumor. A treatment decision must consider the benefits of surgery and the morbidity of the progressing disease. Hence, airway management is crucial prior to the final decision of such cases.

Keywords: Plexiform neurofibroma, neck, larynx, airway, rare diseases, tracheotomy, case report

Introduction

Plexiform neurofibroma (PN) is an uncommon variant of Neurofibromatosis type 1, representing only 5%–30% of all cases (1). Neurofibromatosis type 1 (NF-1) is a rare autosomal dominant genetic condition that occurs in 1 in 3,000–5,000 births (1). PN is the major cause of

morbidity and disfigurement (2). There are few cases of PN reported in the neonatal period making the diagnosis difficult and unexpected in neonates with stridor (2). In this work, we highlighted a case of PN in a toddler who presented stridor since birth and neck swelling when the child was one year old.

Case Presentation

A born term two-year-old Chinese girl presented with worsening noisy breathing since birth. The child had a good cry and no history of aspiration. She was treated for laryngomalacia by a clinician up to the age of six months old. The mother then noted a painless but progressively increasing swelling on the left side of the child's neck when the child was ten months old. There was no sign of inflammation. She failed to thrive, as her weight was only at the fifth percentile. Her developmental history was up to age. The child's maternal grandfather had been diagnosed with Neurofibromatosis type 1.

Upon examination, the child was seen to have biphasic stridor with no other signs of respiratory distress. Pectus excavatum was observed. There were multiple firm, lobulated masses (levels II and III, sized 4×4 cm) on her left neck, with no skin changes. She had nine café-au-lait spots.

Flexible nasopharyngolaryngoscopy (FNLPS) showed a mass on the left supraglottic region that was obstructing the laryngeal inlet. The mass was also partially obscuring the view of the glottis.

An ultrasound showed a lobulated hypoechoic mass with echogenic debris within the mass (Figure 1). The mass was similar in repeated scans. Hence, magnetic resonance imaging (MRI) was performed to evaluate the lesion's character and extension. MRI showed that a lobulated heterogeneous "bag of worms" lesion occupied the left lateral neck and extended superiorly into the parapharyngeal region, posteriorly into the posterior cervical space and inferiorly up to the retrosternal and superior mediastinum. It encased the carotid vessels inferiorly. The lesion displaced the airway to the right. MRI findings were suggestive of plexiform neurofibroma with airway compromise (Figure 2).

We proceeded with a tracheostomy, direct laryngoscopy, tracheoscopy and ultrasound-guided biopsy of the neck and left arytenoid mass under general anesthesia. Direct laryngoscopy showed that the supraglottic structures had been pushed to the right by a left arytenoid mass (Figure 3). The true vocal cords, subglottis and trachea were normal.

Ophthalmology and neurology assessments were done and showed normal results. A brainstem evoked response showed normal bilateral hearing.

Histopathological assessment showed fragments of fibrocollagenous tissue composed of loosely arranged small wavy spindle cells interspersed with wisps of collagen in myxoid stroma. The spindle cells displayed uniform, round ovoid nuclei, inconspicuous nuclei, and scanty eosinophilic cytoplasm. There were few mitosis and ganglion cells, and there was no cellular atypia or necrosis, indicating the benign features of the mass (Figure 4). Immunohistochemistry

showed that the spindle cells were positive for S-100 and negative for SMA and desmin (Figure 5). These findings concluded the diagnosis of plexiform neurofibroma.

Because surgery would hypothetically cause more morbidity to the patient and because it was a slow-growing tumor, she was put under yearly MRI surveillance. A year later, the patient was well, as the MRI surveillance showed no progression of the tumor.

Discussion

PN is a benign, slow-growing tumor which arises from superficial peripheral nerves that could be only superficial or an extension of a deeper, massive plexiform tumor (1, 3).

While around 25%–48% of PN cases are reported above the neck, symptoms are based on the sites of manifestation and present themselves early in childhood (4–6). There is a case reported in the literature of a six-year-old child who presented with emergency upper airway obstruction and was diagnosed with PN in a left deep parotid mass (5). In adults,

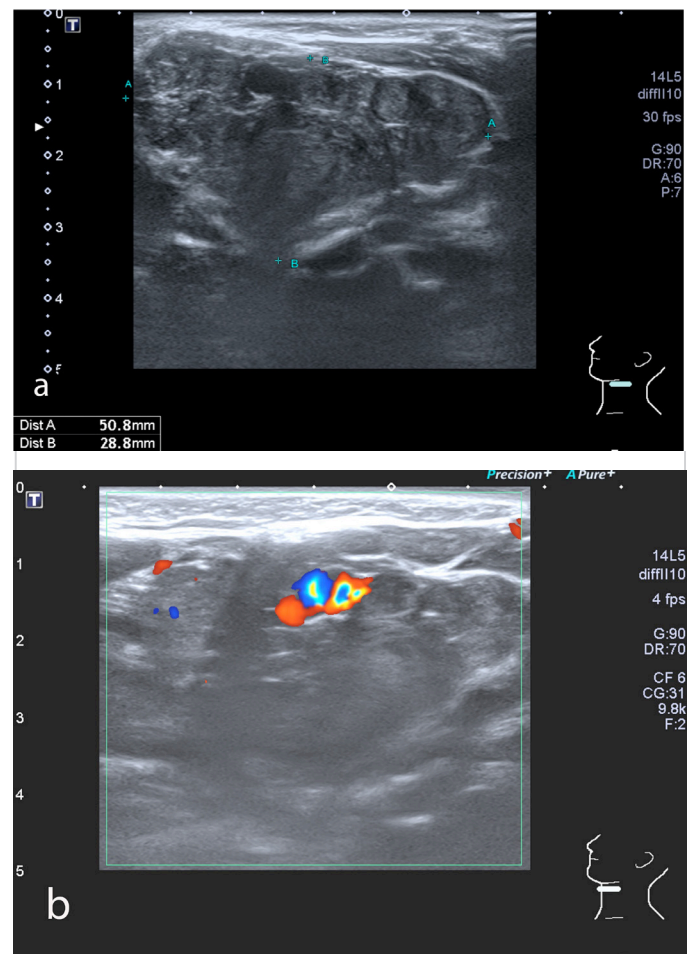


Figure 1. Ultrasound neck scan in B-mode (a) and color doppler (b) show a lobulated solid mass with internal echoes within (not compressible) and no color doppler within, respectively

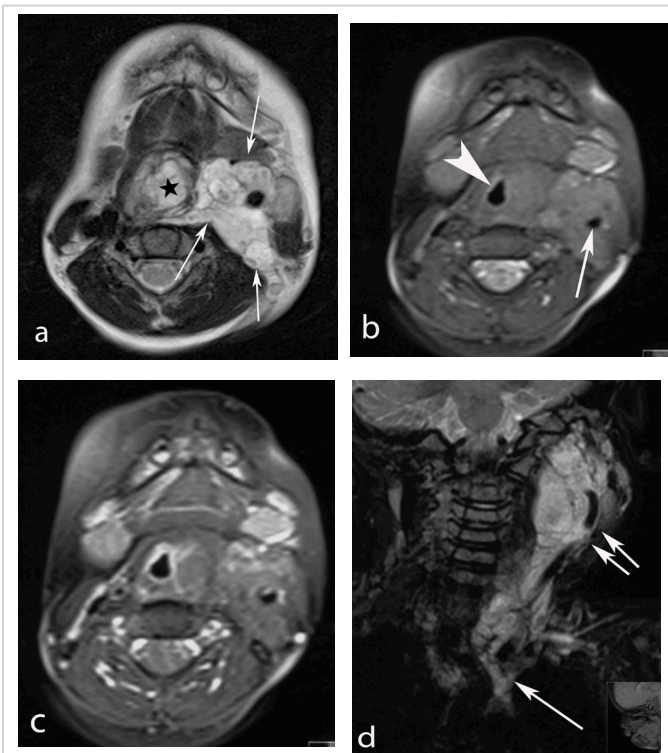


Figure 2. MRI neck scan of the patient: (a) axial T2-weighted image, (b) axial T1-weighted image, (c) axial T1-weighted post-gadolinium image and (d) coronal T2 fat-saturated image. The images show a lobulated mass occupying the left lateral neck space (arrows in a and d) with medial extension to the vocal cord region, which narrows the airway (star in a and arrowhead in b). This demonstrates minimal post-gadolinium enhancement. The mass extends caudally into the region of the superior mediastinum (single arrow in d)

MRI: Magnetic resonance imaging

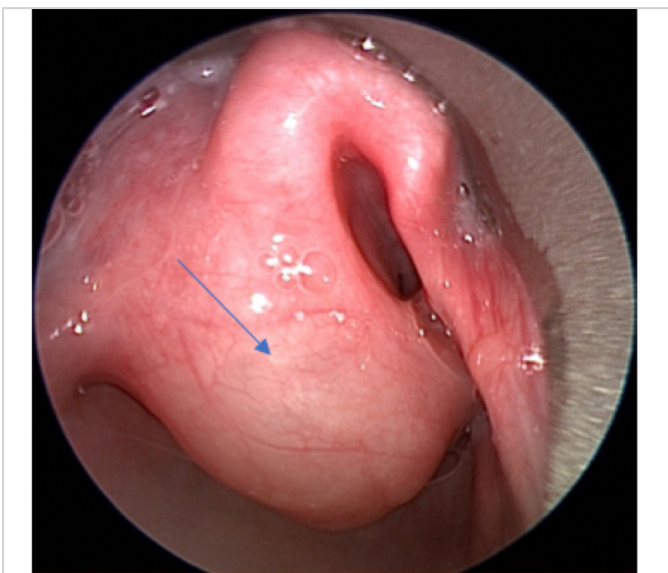


Figure 3. Picture of patient’s larynx on direct laryngoscopy. Supraglottic structures were pushed to the right by a left arytenoid mass (the arrow indicates the mass)

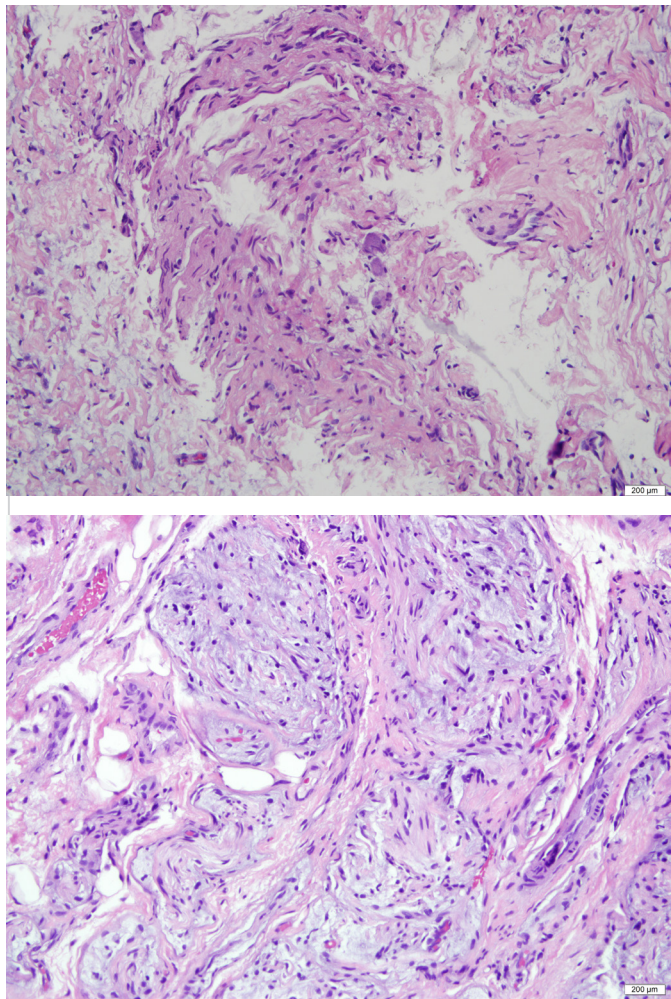


Figure 4. Histopathology of (a) the left neck mass and (b) the left arytenoid (×200)

Fragments of fibro-collagenous tissue composed of loosely arranged small, wavy spindle cells were interspersed with wisps of collagen in myxoid stroma. The spindle cells display fairly uniform, round ovoid nuclei, inconspicuous nuclei, and scanty eosinophilic cytoplasm

the main complaint is a slow-growing mass since childhood that later became infected or bothersome (4, 6). Patients tend to have a first degree relative diagnosed with NF-1 (1-6).

Our patient presented with stridor since birth. She was therefore treated for laryngomalacia, as it is the most common congenital cause of stridor (7). Other common causes for noisy breathing among babies are congenital subglottic stenosis, vallecular cysts, and congenital unilateral vocal fold paralysis (7). She later developed a neck mass that exacerbated the stridor symptoms and was referred to our center. We felt that the stridor symptoms would warrant earlier management and employed an endoscopic assessment to aid the early diagnosis.

MRI was used to determine the morphology, type of lesion and extent of disease (8). PN displayed high signal intensity on T2-weighted MRI, and most of the borders

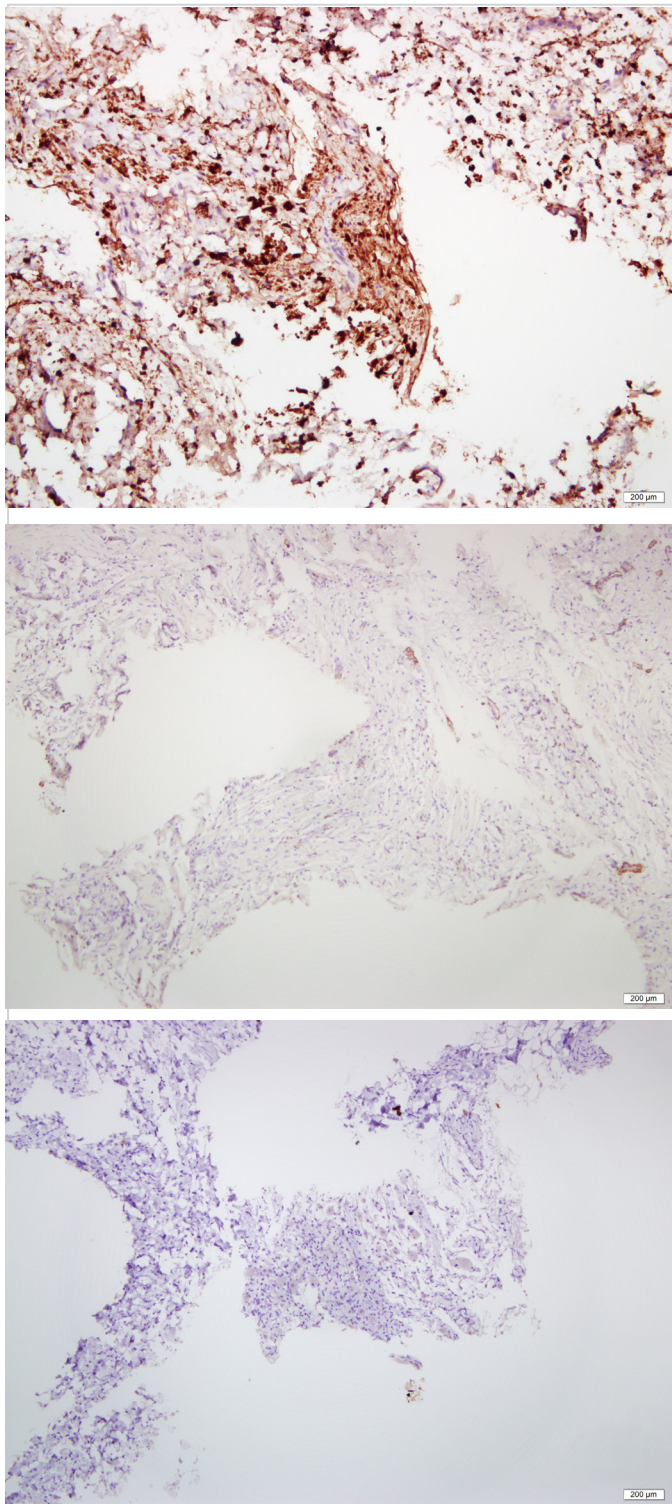


Figure 5. Immunohistochemistry of the left neck mass ($\times 100$)
(a) S-100 protein, **(b)** SMA, **(c)** Desmin
The spindle cells were positive for the S-100 protein and negative for SMA and desmin. Hence, the diagnosis of plexiform neurofibroma was concluded.
SMA: Smooth muscle actin

branched in many directions (8). The lesion was diffuse, which made it difficult to measure objectively (8). However, MRI was adequate for determining volumetric changes, and interobserver variability was less than 10% (8).

Histopathologically, the cells in the nerve sheath proliferated along a significant length of a major nerve and multiple nerve fascicles (3, 9). PN was mostly immunoreactive to the S-100 protein (3, 9). Similar findings in the biopsy of our patient concluded the diagnosis of PN.

Surgical treatment was the main treatment for PN, as no successful cases of medical therapy have been reported in PN patients (3, 9, 10). The decision to perform surgery is typically based on debilitating symptoms and aesthetic problems (5, 6, 9, 10). It might be possible to achieve subtotal or total resection for superficial PN that remains in the upper layer of the skin with a low morbidity risk (9). Invasive PN involving multiple tissue planes with no clear margins was impossible to resect (9). The rate of recurrence recorded for near total tumor resection was 20% (6, 9, 10). The rate of complications of neurological deficits in patients with head and neck PN tumors approached 10% (6, 9, 10). A case was reported of a 12-year-old who had facial nerve palsy grade IV post debulking of PN (6).

Conclusion

We declare that stridor symptoms in infants warrant early management via endoscopic assessments to assist early diagnosis. In our patient, a tracheostomy was done to secure the airway as PN had a mass effect on the airway. Major debulking was not done as it could cause more morbidity to the patient and the PN was a well-known benign slow growing tumor. Yearly MRI surveillance was deemed the best option for the patient.

Informed Consent: The mother of the patient provided the informed consent for the writing and publication of her child's case.

Peer-review: Externally peer-reviewed.

Authorship contributions

Conception: G.B.S., S.S.M.R., Design: G.B.S., S.S.M.R., Supervision: G.B.S., Data Collection and/or Processing: G.B.S., F.M.Z., S.H.M.P., S.S.M.R., M.F.A., Analysis and/or Interpretation: G.B.S., F.M.Z., S.H.M.P., S.S.M.P., M.F.A., Literature Review: F.M.Z., S.H.M.P., S.S.M.R., Writing: G.B.S., Critical Review: G.B.S., F.M.Z., S.H.M.P., S.S.M.R.

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Main Points

- Persistent stridor in a child need full endoscopic assessment.
- Plexiform Neurofibroma is an uncommon tumor but may present with common symptoms of stridor.
- In a patient with café-au-lait spots and family history of Neurofibromatosis Type-1, it would be helpful to assess head and tumor which is associated with Neurofibromatosis.
- Stridor with neck swelling require imaging prior to endoscopic assessment as it may guide us for the site of biopsy.
- Treatment of plexiform neurofibromatosis is challenging as it may cause more morbidity in a child.
- Total resection of invasive plexiform neurofibroma may be delayed as it is a slow growing tumor but require surveillance.

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Preliminary Planning for Mucormycosis in Developing Countries During COVID-19 Pandemic

Letter to the Editor

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Dear Editor,

The coronavirus pandemic was formally declared a public health emergency of international concern (PHEIC) on 30th January 2020. In India, an upsurge of rampant opportunistic infection of coronavirus disease-2019 (COVID-19) associated mucormycosis (CAM), along with the skewed second wave of the COVID-19, has been an issue of concern from May to July 2021. Suppressed immunity due to COVID-19 and its management has created more opportunities for invasive fungal coinfections in immunocompetent individuals.

India is said to be the world capital of both diabetes and mucormycosis and accounts for 40% of the global burden of mucormycosis (1). Diabetes mellitus is the single most common risk factor for mucormycosis in India. Various authors have reported more than 70% of cases of CAM are attributed to India (2, 3).

The sudden increase of mucormycosis in India specifically might be the result of an

unfortunate triad of uncontrolled diabetes (high prevalence), injudicious use of corticosteroid, and COVID-19 infection.

Like other resource-constrained countries, we tried hard to overcome the shortage of protective equipment, and antivirals. Now we have reached a stage with a scarcity of antifungals. Surgical debridement of mucormycosis in the absence of adequate antifungals is a futile exercise. The decline in the surge can be seen with the combined efforts of public and healthcare professionals. Preventive measures and early detection will potentially bend the curve.

Preventive measures

1. The primary measure will be the prevention of the outspread of the COVID-19 and the promotion of vaccination against it.
2. High-risk patients with poor immunity and uncontrolled glycemic state should be advised to be extra cautious. All attempts to avoid inhalation of fungal spores through the nose should be made.

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3. Avoidance of hot humid climate, which might have high environmental spore count, air purifiers may be beneficial.
4. Judicious use of corticosteroids and antifungals should be a practice to step-down the incidence of CAM and to reduce antifungal resistance.
5. Strict glycemic control during the management of COVID-19 and after recovery is paramount.
6. Immunosuppressive drugs like monoclonal antibodies and others which target the immune system should be discouraged.
7. Swab sticks for potassium hydroxide calcofluor white mount (KOH) should be sterile and not spread cross-infection.

Measures for early detection

1. Comprehensive examination of COVID-19 patients and detecting early warning symptoms can identify CAM at the earliest. Nasal obstruction in the form of crusting or discharge are the most common initial symptoms. Blackening of any facial part suggests fungal angioinvasion. Unilateral facial numbness and pain indicate the involvement of the trigeminal nerve. Toothache, loosening of tooth, palatal eschar, facial palsy, and headache are other characteristic findings. Ptosis, periorbital swelling, diplopia, blurred and reduced vision, proptosis indicates orbital involvement. Focal seizures indicate intracranial extension (4).
2. Diagnostic nasal endoscopy and biopsy should be a practice in high-risk patients with high inflammatory markers, on poor glycemic control, on mechanical ventilation, and who have spent more than 50 days in the ICU (5).
3. High-risk patients should be planned for contrast magnetic resonance imaging of paranasal sinuses, orbit, and brain.

To conclude, developing countries are vulnerable to the spread of pandemic. Stringent healthcare infrastructure and public awareness are paramount to recover from this human crisis. We are all in this together and shall evolve in a better way.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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