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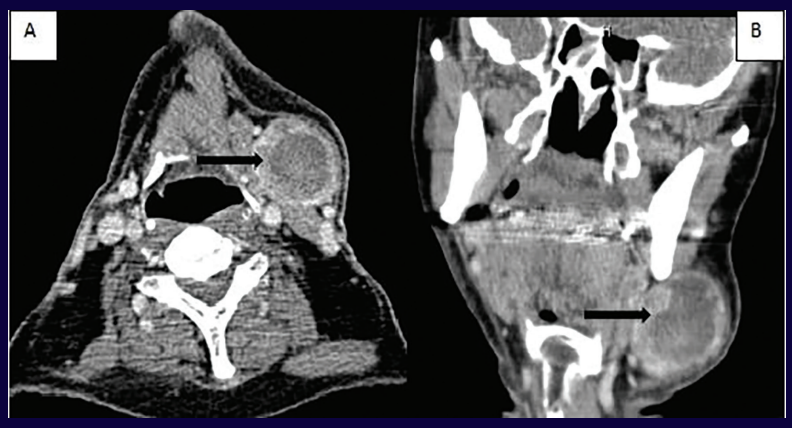

A Rare Case of Mammary Analogue Secretory Carcinoma Localized in the Submandibular Gland

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Original Investigations

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Contents

Turkish Validation and Reliability Study of the Carcinologic Handicap Index for Head and Neck Cancer Patients

Original Investigation

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Abstract

Objective: This study aimed to conduct a Turkish validation study of the Head and Neck Carcinologic Handicap Index (CHI) and investigate its effectiveness in assessing morbidity in head-and-neck tumor patients.

Methods: The original CHI was translated into Turkish after a language validation study based on international standards. The study included 189 patients. Age, gender, primary tumor location, and tumor-node-metastasis stages were recorded. All patients were asked to complete the CHI form. A total of 37 patients completed the CHI form once more within 15 days to examine temporal stability. A control group was also formed to evaluate the validity of the CHI.

Results: The Cronbach's alpha coefficient was 0.898. For temporal validity, the global score showed a statistically significant correlation ($p<0.001$; $r=0.604$). There was a statistically significant difference between the global scores of the patient and the control groups ($p<0.001$). The global score and tumor stage differences were statistically significant ($p=0.012$). Review of the relationship between the tumor location and the scores showed a statistically significant difference in swallowing ($p=0.001$), feeding ($p=0.001$), and hearing ($p=0.015$).

Conclusion: The study adapted the CHI into Turkish and showed that it can be used as a valid and reliable index for the morbidity assessment of head-neck cancer patients. We recommend frequent use of the CHI throughout follow-up.

Keywords: Head and neck cancer, handicap, quality of life, validity study, morbidity

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Introduction

Head and neck carcinomas are among the most common cancer types worldwide (1). A multidisciplinary examination is essential when choosing therapy for head and neck carcinomas because the treatment differs depending on the disease's stage, anatomical location, and surgical accessibility. Along with improvements in standard treatment, such as radiation, surgery, and multimodal therapies brought about by immunotherapy advancements, survival has significantly increased in recent years. The five-year survival rate improved from 55% between 1992 and 1996 to 66% between 2002 and 2006 (2). However, as mortality rates decrease, more individuals have to live with treatment-related sequelae. Disruption of the functions of the affected structures may negatively impact life quality.

The head and neck region has essential functions such as swallowing, respiration, feeding, phonation, and hearing. In malignancies in this region, pain, deformities, functional disorders, and psychosocial problems can be observed due to both the effects of the cancer itself and cancer-directed treatments (3). Focusing only on the oncologic process in the follow-up of patients may cause the effects of treatment sequelae on the patient's daily life to be overlooked. Questionnaires or scales for detailed documentation are needed to monitor post-treatment morbidity in patients regularly. Quality-of-life measurements during patient follow-up are crucial for individualizing and coordinating the treatment strategy offered to patients. In addition to problems related to the primary disease, issues related to the function of the affected structures can be identified and prioritized. For example, swallowing problems in patients can be recognized much earlier and treated before they cause more significant issues. Similarly, physiotherapy support can be provided earlier if the patient has limited neck and shoulder movements.

In 2017, Balaguer et al. (4) introduced the head and neck Carcinological Handicap Index (CHI), designed to evaluate the quality of life for head and neck cancers. The CHI's initial version, which focuses on nine sub-domains, has demonstrated strong psychometric properties, validating its application in clinical assessments (4). Nevertheless, during clinical applications, it was found that the domains of neck-shoulder movements and psychosocial impact of physical appearance were missing, which often posed problems for patients. Therefore, an update was made by the same team in 2021 to cover these two new areas (5). Although the CHI is being used by more and more clinicians today, a validity and reliability study of the Turkish version was yet to be conducted. Our study aimed so to conduct a Turkish validation study of the latest CHI version and investigate the effectiveness of this index in evaluating morbidity in head and neck cancer patients and determining patient priorities.

Methods

The Turkish Adaptation Stage

Research approval was received from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval date: 18.04.2023; approval number: 60116787-020-358580). First, written permission for the Turkish adaptation was obtained from the original CHI authors, Balaguer M. et al. (4,5). Then, the Turkish language adaptation stage of the scale began. In this stage, two researchers independently translated the original scale into Turkish. Then, the same two researchers combined and converted the scale into a single translated text. This Turkish text was back translated into English by another researcher who was fluent in both native languages. Three researchers then reviewed the original, Turkish, and translated scales to decide on the final Turkish index to be used. After the language validation process, the Turkish text was structured according to the original system (Figure 1).

The CHI evaluates 11 domains related to the primary symptoms experienced by patients with head and neck cancer. Four of these domains focus on sensory functions, four on the functions of the upper respiratory and digestive systems, two on the social effects of the disease, and one on neck and shoulder movements. Each domain consists of four questions, with responses scored on a five-level scale: never, very rarely, occasionally, frequently, and always. This scoring system results in a domain score ranging from 0 to 16 points and a global score. As the score from the handicap index increases, so do the difficulty perceived by patients and the impact of the disease on their life quality.

Data Collection

All head and neck cancer patients admitted to the outpatient clinic between April 2021 and July 2024 were included in the study. We explained the study's purpose to the patients and obtained their consent. Age, gender, primary tumor location, and TNM stages at initial diagnosis were recorded. The patients were then asked to complete the CHI form consisting of 11 domains. The aim was to examine the temporal stability (test-retest reliability) by having 37 patients fill out the CHI form again within 15 days.

A control group was also formed to evaluate the validity of the CHI. The control group was composed of people who matched the patient group in terms of age, gender, and socio-economic status and had no oncologic disease. After being provided information about the study, the control group of healthcare workers and patients' relatives was asked to complete the CHI form once.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25 (IBM Corp.; Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation and minimum (min.) and maximum (max.) values. Categorical variables are presented as count and percentage. Internal consistency was assessed using Cronbach's alpha coefficients. The construct validity of the scale was established by confirmatory factor analysis. The Kaiser-Meyer Olkin test was used to determine the adequacy of the sample size, and Bartlett's test was used to assess its suitability. In confirmatory factor analysis, Goodness of Fit Index (GFI), Comparative Fit Index (CFI), Normed Fit Index (NFI), Root Mean Square Error of Approximation (RMSEA), and χ^2/df goodness of fit indices were evaluated. Standardized factor loadings were obtained to examine how appropriate the scale was to the original scale structure. In statistical evaluation, the normal distribution of the parameters was tested with the

Baş Boyun Kanserli Hastalar için Engellilik Ölçeği						
		Hiçbir zaman	Çok nadir	Ara sıra	Sıklıkla	Sürekli
AĞRI	Ağrılarınız için ağrı kesici kullanıyor musunuz?					
	Ağrılarınız geceleri sizi uykudan uyandırır mı?					
	Ağrılarınız günlük aktivitelerinize engel olur mu?					
	Ağrı nöbetleriniz olur mu?					
YUTMA	Yutma zorluğunuz var mı?					
	Yediğiniz ya da içtikleriniz boğazınıza kaçıyor mu?					
	Yemeklerden sonra yediklerinizin boğazınıza geri geldiği oluyor mu?					
	Yiyecekleri çiğnerken zorlanıyor musunuz?					
BESLENME	Yediklerinizi yutabilmek için kıvamını değiştirmek zorunda kalıyor musunuz?					
	Yutma güçlüğüne bağlı olarak yemeğinizi yemeniz uzun zaman alıyor mu?					
	Yemeklerinizi güçlendirmek için ek gıda takviyesine ihtiyaç duyuyor musunuz?					
	Kilo kaybediyor musunuz?					
SOLUNUM	İstirahat halindeyken nefes almakta güçlük çekiyor musunuz?					
	Nefes alma problemleriniz fiziksel aktivitelerinizi kısıtlıyor mu?					
	Kendinizi nefes alırken tıkanmış hissediyor musunuz?					
	Uyumak için yarı-oturur pozisyona ihtiyaç duyuyor musunuz?					
KONUŞMA	Konuşmada zorlanıyor musunuz?					
	Dinleyenler sizin konuşmanızı anlamakta zorlanıyor mu?					
	Ailenizle, arkadaşlarınızla, komşularınızla normalden daha mı az konuşuyorsunuz?					
	Kelimeleri çıkarmakta zorlanıyor musunuz?					
İŞİTME	Anlamadığınız için konuşmaları tekrar ettiriyor musunuz?					
	Gürültülü yerlerde konuşulanları anlamakta zorlanıyor musunuz?					
	Telefon konuşmalarını anlamakta zorlanıyor musunuz?					
	Kulaklarınızda uğultu, çınlama gibi sesler oluyor mu?					
GÖRME	Karanlık ortamlarda görmekte zorlanır mısınız?					
	Uzağı veya yakını görmede zorlanıyor musunuz?					
	Gözlerinizde sizi rahatsız eden kamaşma veya uçuşmalar oluyor mu?					
	Görme alanınızda daralma hissediyor musunuz?					
KOKU-TAT	Kokuları almakta zorlanıyor musunuz?					
	Koku alma zorluğunuz nedeniyle kaza geçirmekten korkar mısınız?					
	Yediklerinizin tadını almakta zorluk çeker misiniz?					
	Koku ve tat alma zorluğunuz sebebiyle kendinizi kötü hissettiğiniz oluyor mu?					
FİZİKSEL GÖRÜNÜM	Fiziksel görünümünüzdeki değişiklikler sizi rahatsız ediyor mu?					
	Fiziksel görünümünüzdeki değişiklikler sebebiyle insanların size bakışlarından rahatsız oluyor musunuz?					
	Fiziksel görünümünüzdeki değişiklikler sebebiyle sosyal hayatınız kısıtlanıyor mu?					
	Hastalığınız nedeniyle özel hayatınız değişti mi?					
BOYUN-OMUZ	Boynunuz, omuzlarınız veya kollarınızda his kaybı fark ediyor musunuz?					
	Başınızı çevirmekte zorlanıyor musunuz?					
	Ağırlık taşırken zorlanıyor musunuz?					
	Kollarınızı kaldırmada zorluk çekiyor musunuz?					
PSİKOSOSYAL	Hastalığınız kişisel ve sosyal hayatınızı kısıtlıyor mu?					
	Hastalığınız diğer insanlarla ilişkilerinizi etkiliyor mu?					
	Hastalığınızı sebep olduğu problemler sizi rahatsız ediyor mu?					
	Hastalığınız yüzünden kendinizi engelli hissediyor musun?					

Figure 1. The Turkish version of the head and neck Carcinologic Handicap Index

Shapiro-Wilk test. Independent group t-tests and one-way ANOVAs were performed on those who showed parametric conformity. The Mann-Whitney U and Kruskal-Wallis tests were performed for those who did not conform. In addition, the Spearman's correlation test was applied to evaluate the relationship between numerical data. The statistical significance level was determined as $p<0.05$ in all analyses. The strength of the "r" coefficient in correlation was interpreted as follows: 0.00 to 0.299, weak; 0.300 to 0.599, moderate; 0.600 to 0.799, strong; 0.800 to 0.999, very strong.

Results

The study included 189 head and neck oncology patients. Of these, 159 (84.1%) were male, and 31 (15.9%) were female, with a mean age of 62.53±11.02 (min. 26-max. 87) years. In terms of tumor location, 111 (58.7%) were in the larynx, 34 (18%) in the oral cavity, 18 (9.5%) in the nasopharynx, 12 (6.3%) in the oro-hypopharynx, and 14 (7.4%) were other head and neck tumors (such as salivary gland, paranasal sinus, thyroid). Regarding the stage at the time of initial diagnosis, 73 (38.6%) patients were stage I, 31 (16.4%) were stage II, 47 (24.9%) were stage III, and 38 (20.1%) were stage IV.

The control group included 123 subjects. Their mean age was 61.35±9.22 (min. 44-max. 86) years; 98 (80.3%) were male, and 24 (19.7%) were female.

Internal Consistency

The overall Cronbach's alpha value of the disability index was 0.898. Cronbach's alpha values obtained in the domains of the index are given in Table 1. Internal consistency results in pain, phonation, hearing, vision, physical appearance, and psychosocial domains were considered satisfactory (>0.7). Cronbach's alpha results obtained in other domains were also within acceptable limits (>0.6).

Construct Validity

When the results of the confirmatory factor analysis were analyzed, it was seen that all fit indices showed a good or acceptable level of fit (χ^2/df=1.675, RMSEA=0.06, CFI=0.819, GFI=0.754, NFI=0.654). Further, when the coefficients obtained from the items were examined, it was seen that only one item had a value below 0.3 (Table 2). In order not to disrupt the integrity and structure of the scale and because it was not a very low value, this item did not need to be removed, and the scale structure was preserved. The Bartlett's test result was p=0.0001, and the Kaiser-Meyer-Olkin value was 0.812. According to this coefficient, it was determined that the sample size was very well-compatible with factor analysis.

Temporal validity (Test-retest reliability)

For temporal validity, the relationship between the results of the scale filled in at two different times by 37 patients was evaluated. According to the results obtained, a statistically significant positive correlation was found for the global CHI score ($p<0.001$; $r=0.604$). In the domains of the handicap

Table 1. Results on Cronbach's alpha test

Domain	Cronbach's alpha values
Pain	0.805
Swallowing	0.614
Feeding	0.680
Respiration	0.687
Phonation	0.853
Hearing	0.789
Vision	0.701
Olfaction-gustation	0.689
Physical appearance	0.769
Neck and/or shoulder movements	0.679
Psychosocial	0.835
Global score	0.898

Table 2. Confirmatory factor analysis results

Domain	Item	Coefficient	Domain	Item	Coefficient
Pain	1st	0.706	Vision	1st	0.592
	2nd	0.804		2nd	0.549
	3rd	0.745		3rd	0.571
	4th	0.667		4th	0.675
Swallowing	1st	0.58	Olfaction-gustation	1st	0.675
	2nd	0.383		2nd	0.63
	3rd	0.492		3rd	0.794
	4th	0.675		4th	0.651
Feeding	1st	0.286	Physical appearance	1st	0.454
	2nd	0.522		2nd	0.467
	3rd	0.8		3rd	0.792
	4th	0.711		4th	0.797
Respiration	1st	0.398	Neck/ shoulder movements	1st	0.673
	2nd	0.755		2nd	0.483
	3rd	0.724		3rd	0.595
	4th	0.644		4th	0.439
Phonation	1st	0.857	Psychosocial	1st	0.742
	2nd	0.58		2nd	0.807
	3rd	0.819		3rd	0.76
	4th	0.858		4th	0.697
Hearing	1st	0.519			
	2nd	0.666			
	3rd	0.809			
	4th	0.83			

index, there was a strong correlation (r>0.6) in the domains of phonation, hearing, vision, olfaction-gustation, and psychosocial, and a moderate correlation (0.4<r<0.6) in the domains of pain, swallowing, feeding, respiration, physical appearance, and neck-shoulder movements (Table 3).

Comparison Between Patient and Control Groups

The mean global score in the patient group was 40.06±26.95, while the mean score in the control group was 21.19±15.80. There was a statistically significant difference between the global scores of the two groups (p<0.001).

When the scale's domain scores were analyzed, no significant difference was observed for pain, hearing, and vision (p>0.05), while significant difference was observed for the other seven domains (Table 4).

Results According to Tumor Stage

The study observed that the mean global score obtained on the handicap index increased as the tumor stage increased (Table 5). The difference between the tumor stage and the global score was statistically significant (p=0.012).

When the relationship between the stage of the tumor and the domains of the index was examined, a significant difference was found in the domains of feeding (p=0.028), phonation (p=0.001), olfaction-gustation (p=0.04), and physical appearance (p=0.001). In contrast, no significant difference was found in the other domains (p>0.05).

Results According to Tumor Location

When the relationship between tumor location and the scores obtained in the handicap index was examined, statistically significant difference was found in the domains of swallowing (p=0.001), feeding (p=0.001), and hearing (p=0.015). No significant difference was found between the other domains and tumor location (p>0.05). The mean scores obtained in the domains with statistical differences are summarized in Table 6. As a result of post hoc analysis (Tukey HSD test), in the domains of swallowing and feeding, oral cavity and oro-hypopharyngeal cancer patients had a statistically significant higher rate of disability compared to laryngeal cancer patients, while in the domain of hearing, nasopharyngeal cancer patients had a higher rate of disability compared to other head and neck cancer patients.

Table 3. Temporal validity (correlation between the results of the scale filled in at two different times)

Domains	"r" coefficient	p-value
Pain	0.531	<000.1*
Swallowing	0.558	<000.1*
Feeding	0.532	<000.1*
Respiration	0.419	<000.1*
Phonation	0.639	<000.1*
Hearing	0.661	<000.1*
Vision	0.652	<000.1*
Olfaction-gustation	0.666	<000.1*
Physical appearance	0.540	<000.1*
Neck and/or shoulder movements	0.564	<000.1*
Psychosocial	0.614	<000.1*
Global score	0.604	<000.1*

* p<0.05 statistical significance level

Table 4. Comparison of patient and control groups

Domains	Patients	Controls	p-value
	Mean±SD	Mean±SD	
Pain	2.36±3.26	2.99±2.67	0.75
Swallowing	4.16±3.79	1.67±2.65	<0.001*
Feeding	4.52±4.51	0.75±1.49	<0.001*
Respiration	2.39±3.23	1.33±2.55	0.001*
Phonation	6.24±5.4	0.74±1.73	<0.001*
Hearing	4.48±4.64	3.84±3.63	0.12
Vision	3.45±3.63	4.63±3.27	0.14
Olfaction-gustation	2.85±3.8	0.88±2.17	<0.001*
Physical appearance	2.42±3.72	0.82±1.75	<0.001*
Neck and/or shoulder movements	3.51±4.09	2.43±2.72	0.005*
Psychosocial	3.66±4.58	1.11±2.73	<0.001*
Global score	40.06±26.95	21.19±15.80	<0.001*

* p<0.05 statistical significance level

SD: Standard deviation

Table 5. The relationship between tumor stage and global score

Tumor stage	Number of patients	Mean±SD
Stage I	73	32.33±24.23
Stage II	31	41.19±29.78
Stage III	47	45.08±27.86
Stage IV	38	47.76±25.53

SD: Standard deviation

Table 6. The relationship between tumor location and domains of index

Tumor location	Swallowing Mean±SD	Feeding Mean±SD	Hearing Mean±SD
Larynx	3.26±3.38	3.65±4.18	3.48±4.16
Oral cavity	6.84±4.23*	6.38±4.48*	5.61±5.45
Nasopharynx	5.50±3.74	4.77±4.58	8.06±5.05*
Oro-hypopharynx	6.25±3.64*	8.16±5.01*	4.01±2.44
Other	5.01±4.16	3.50±4.11	4.50±4.34

* p<0.05 statistical significance level

SD: Standard deviation

Discussion

The term quality-of-life was first defined in 1948 by the World Health Organization as "health is not only the absence of disease but a state of complete physical, mental and social well-being of the individual" (6). Knowing the patient's life quality provides the physician with a better understanding of the patient's life from their perspective. Thus, patient-physician communication is strengthened, cooperation is ensured on a realistic basis, the patient's expectations from the physician can be better understood, and patient compliance can increase. The Head and Neck CHI, validated in Turkish in our study, is a quality-of-life scale defined for evaluating morbidity and disability in head-neck cancer patients, and its validity and reliability have been demonstrated (4). The clinical aim of applying this scale is to differentiate the function-limiting factors and to determine patients' needs regarding disease management.

Scales developed in societies from different languages and cultures must be tested in the community to ensure the equivalence of the content in terms of concept and language, test their measurement properties in the community, and conduct reliability and validity studies before they are applied in the society (7). Reliability shows the stability and consistency of test results. In our study, internal consistency was first evaluated to determine the reliability of the Turkish version of the CHI, and high internal consistency was found with a Cronbach's alpha value of 0.898. Although internal consistency was within acceptable limits in all sub-domains of the scale, the lowest value was found in the swallowing domain. Similarly, low internal consistency was found in the swallowing domain on the original CHI scale. When we look at the questions in the swallowing domain, three follow the swallowing stages: oral preparation, pharyngeal, and esophageal; one evaluates all swallowing phases in scope. The relatively low internal consistency in the swallowing domain may be because the questions assess the different phases of swallowing. The authors of the original CHI reported that the questions in the swallowing domain were included in the original scale because of their clinical importance and ability to discriminate between swallowing phases (4).

The results obtained from a reliable scale should also be reproducible. In other words, if a test is applied to the same individuals more than once, the results of the application should be similar (8). In our study, a strong correlation was observed in the global score between the results of the scale completed by the patients at two different times. Although a statistically significant correlation was found in all index domains, the correlation coefficients were lower than the original CHI. In our study, the domains with relatively low correlation coefficients were the functions most exposed to temporal fluctuations, such as pain, swallowing, feeding, and respiration. Head and neck cancer patients with ongoing treatment were also included in the study. The ongoing treatment of the patients, even within two weeks, may have caused the degree of complaints to change, and therefore, the correlation coefficients may have been relatively low. Nevertheless, statistically significant correlations were found in all domains, indicating that the scale is reliable.

Validity is the ability of a scale or test to measure the feature it wants to measure accurately and without confusing it with other features (9). In our study, when the patient and control groups were compared, a statistically significant difference was found in the global score and in the other domains except for pain, hearing, and vision. This result shows the validity of the scale. In general, people frequently have pain, hearing, and vision problems. Given the average age of the patient and control groups, the lack of notable differences in these domains may be explained by the fact that age-related dysfunctions in the domains of pain, hearing, and vision are common in the general population and that head and neck tumors have a relatively small impact on these three areas. Similarly, the original CHI study indicated no significant differences in pain, hearing, and vision domains between the patient and control groups. (4).

In our study, when the relationship between tumor location and the domains of the scale was examined, statistically significant loss of function was found in the areas of swallowing and feeding in oral cavity and oro-hypopharyngeal cancer patients, and in the area of hearing in nasopharyngeal cancer patients. The locations of tumors in the oral cavity and oropharynx impact both the oral and pharyngeal stages of swallowing. Laryngeal structures have less influence on food transportation. Therefore, swallowing and feeding are expected to be affected more in patients with oral cavity or oropharyngeal tumors (9). Similarly, hearing function is more affected in nasopharyngeal cancer patients due to tumor-related Eustachian tube dysfunction, and the radiotherapy area includes the hearing region (10). These results show us the effectiveness of CHI in determining patient priorities.

The CHI is a scale designed for all head and neck cancer patients. However, the functions affected and the degree to which they are affected will vary according to the site of origin and cancer stage. Considering the diversity of the tumor being evaluated and individual psychosocial dynamics, it would be more appropriate to focus on high-scoring domains rather than using an overall cumulative score. The sub-scores for each domain help identify priority functional losses. While patients' needs can vary based on age, gender, treatment method, cancer stage, or tumor location, this scale allows for personalized assessments based on individual circumstances.

The main limitation of our study is that it was conducted at a single center. Future multicenter studies will better assess the

scale's usability for monitoring patients. Another limitation is that a native English-speaking expert did not evaluate the scale during the language validity phase. However, since the scale is not psychological, it does not account for cultural differences and consists of simple sentences that all patients can easily understand, input from a native speaker was not deemed necessary.

Conclusion

In conclusion, the Turkish version of the CHI demonstrated acceptable psychometric properties regarding internal consistency, temporal validity, and content validity. Based on the results of our study, we recommend the regular use of CHI in the follow-up care of patients with head and neck cancer. Considering the life quality measurements during oncological follow-up of patients will help determine the patient's priorities and coordinate the treatment strategy by revealing problems that may be overlooked.

Ethics

Ethics Committee Approval: Research approval was received from the Pamukkale University Non-Interventional Clinical Research Ethics Committee, (approval date: 18.04.2023; approval number: 60116787-020-358580).

Informed Consent: All participants were informed about the purpose of the study, and written informed consent was obtained prior to their inclusion.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M., C.O.K., Concept: E.M., C.O.K., Design: E.M., C.O.K., Data Collection and/or Processing: E.M., C.O.K., A.Y., Analysis and/or Interpretation: E.M., C.O.K., A.Y., Literature Search: E.M., C.O.K., A.Y., Writing: E.M., C.O.K., A.Y.

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Main Points

- Focusing solely on the oncological aspects in the follow-up care of head and neck cancer patients may result in neglecting the impact of the treatment's side effects on their daily lives.
- The Head and Neck Carcinologic Handicap Index (CHI) is designed to identify the factors that limit function in these patients and assess their disease management needs.
- This study adapted the CHI into Turkish and confirmed its reliability and validity.
- We suggest regularly using the CHI during follow-ups for patients with head and neck cancer.

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Evaluation of BRAF and KRAS Gene Expression in Nasal Polyposis

Original Investigation

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Abstract

Objective: The goal of this study was to investigate the expression patterns and potential relationship of the Kirsten rat sarcoma viral oncogene homolog (KRAS) and B-raf proto-oncogene (BRAF) genes in nasal polyposis (NP).

Methods: Twenty-nine patients were included in the study. Small punch biopsies were collected from nasal polyps during each operation and immediately frozen in liquid nitrogen. Punch biopsies were also taken during surgery from the inferior turbinate or the septum mucosa of the patients as a control group, and these samples were also frozen. Total ribonucleic acid (RNA) was isolated using TRIzol reagent. The gene expression analyses of the KRAS and BRAF genes were performed by the real-time polymerase chain reaction method.

Results: When compared to control subjects, KRAS nasal polyp gene expression increased in 21, but decreased in eight of the 29 patients. This statistical analysis revealed a statistically significant difference between the nasal polyp group and the controls (p=0.023). Like KRAS, a decrease was observed in BRAF gene expression in six, and an increase in 23 patients (p=0.011).

Conclusion: Our findings suggest a potential association between BRAF and KRAS genes expression and NP, but further studies are needed to confirm this relationship. This finding suggests that the genetic background of NP could be a contributing factor, with the BRAF and KRAS mutations playing a role.

Keywords: Nasal polyposis, gene expression regulation, KRAS gene, BRAF gene, mutation, polymerase chain reaction, nasal mucosa, biopsy

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Introduction

Nasal polyposis (NP) is a common, long-term inflammatory condition affecting the sinus and the nasal mucosa. Characterized by widespread semi-transparent, soft, grape-like abnormal mucosal formations of unknown etiology, it can be easily recognized via endoscopic nasal examination (1-3). Nasal polyps are common in the ethmoid sinuses, the middle turbinates, and the meatus. Although NP is a benign disease with a tendency to recur at varying time intervals in each patient, it is a very disturbing

disease with complaints of nasal obstruction, rhinorrhea, postnasal dripping, and smell loss (1). Deformation of intranasal structures and nasal bones can also be detected in long-term, untreated patients with advanced disease. In NP, while predominant Th2-type inflammation is the characteristic feature of the disease that causes eosinophil-dominated inflammatory cells in polyps, the involvement of numerous molecular markers, cytokines, and chemokine molecules in the disease process make it a very heterogeneous complex inflammatory disease (1-3). The central hypothesis of our study was that the expression levels of the B-raf proto-oncogene (BRAF) and Kirsten rat sarcoma viral oncogene homolog (KRAS) genes are significantly altered in the nasal polyp tissue compared to non-polypoidal nasal mucosa (inferior turbinate or nasal septum mucosa) from the same individuals, suggesting a potential role for these genes in the pathogenesis of NP.

The BRAF is an intracellular serine/threonine protein kinase that effects epidermal growth factor receptor signaling via the mitogen-activated protein kinase (MAPK) downstream signaling route (4,5). The BRAF gene mutation has been extensively studied in thyroid malignancies because it is the leading papillary thyroid cancer associated with a worse prognosis and aggressive tumor behavior (6). On the other hand, this mutation has also been studied in malignant diseases other than thyroid cancer, including colorectal, ovarian, and melanoma, with a management effort on BRAF-dependent kinase inhibitor therapy (7). Rarely, BRAF oncogene mutations have also been studied in non-malignant diseases, including NP and Hashimoto's thyroiditis, other than malignant diseases (2,4). KRAS is a member of the Ras family of genes that has an effector role in some signaling cascades regulating gene expression, such as the MAPK pathway (4). KRAS mutation, like BRAF mutation, is commonly found in various malignancies such as those of the pancreas, the colon, the lungs, the uterus, the brain, and the kidneys. However, studies reporting KRAS mutations in non-malignant diseases that were primarily NP are very rare in the literature (1-3). The goal of the presented study was to investigate the relationship between the NP disease and the gene expression of BRAF and KRAS by comparing the BRAF and KRAS gene expression levels of NP specimens, and the nasal septum or the inferior turbinate mucosa specimens as controls, in the same patients using real-time polymerase chain reaction (PCR) techniques. To the best of our knowledge, this is the first study assessing both BRAF and KRAS gene expression by using real-time PCR in human NP disease.

Methods

Patients

This prospective study was conducted in a tertiary university hospital, İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Department of Otorhinolaryngology- Head and Neck Surgery. The study was approved by the Health Sciences İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Board (approval number: 2017/0083, date: 23.03.2023). All participants provided their informed consent to be included in the study. Initially, 32 patients were included in the study. Three patients were excluded, as two were diagnosed with inverted papilloma and one with antrochoanal polyp after histopathologic examination. The study was conducted with 29 cases who underwent endoscopic endonasal surgery due to NP disease. Of the 29 patients, 19 (65.5%) were male and 10 (34.5%) were female, with ages ranging from 18 to 69 years. Their average age was 44.17±13.76, and the median age was 44 years. The duration of the symptoms ranged from one to 15 years, with an average of 5.21±4.12 and a median time of four years. The number of sinuses treated ranged from 1 to 4 (maxillary, ethmoid frontal, and sphenoid sinuses); the average was 2.38±1.29, and the median was two. Only one patient (3.4%) was a smoker. The exclusion criteria were a medical history of head and neck malignancy with or without head and neck radiation therapy, history of chemotherapy due to malignancy, and age younger than 18 years. Patients aged ≥18 years, had proven NP through rigid or flexible endoscopic endonasal examination, and underwent endoscopic endonasal surgery met our inclusion criteria. All patients had undergone paranasal sinus computed tomography (CT) scan before surgery to predict the extent of the disease and detect altered anatomy due to prior surgery.

Patients' Clinical Features

There were complaints of nasal obstruction in 96.6% of cases, loss of smell in 27.6%, pain in 13.8%, and asthma in 20.7%. A previous history of endoscopic endonasal surgery for NP was present in 44.8%. Additional chronic diseases, including diabetes mellitus and hypertension, were present in 17.2%, and six (20.7%) had asthma. While 37.3% of the cases had septum deviation, 58.6% did not, and one (4.1%) had a perforated septum due to prior surgery. Hypertrophy in the lower turbinate was present in 55.2%, and 20.7% had middle turbinate findings (Table 1).

KRAS and BRAF Gene Expression Technique

During the NP procedure, small biopsy specimens were excised, and promptly frozen in liquid nitrogen. In the control group, punch biopsies were collected from the inferior nasal turbinate or the nasal septum mucosa, and the specimens were also subsequently frozen in liquid nitrogen. Total ribonucleic acid (RNA) extractions were conducted utilizing TRIzol reagent. Complementary deoxyribonucleic acids (cDNAs) were synthesized using oligo dT primers with the commercial cDNA synthesis kit. KRAS and BRAF expression studies were conducted via real-time PCR with

particular primers and normalized with the GAPDH gene. The PCR reactions were conducted under the following conditions: initial denaturation at 95 °C for 5 minutes, followed by 40 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 30 seconds, and extension at 72 °C for 30 seconds. The final extension was performed at 72 °C for 5 minutes. Each reaction included 2 µL of cDNA template, 1 µL of each primer, 6 µL of nuclease-free water, and 10 µL of SYBR Green master mix in a total volume of 20 µL. Primer pairs are given in Table 2. Expression calculation was done with the 2-CT method.

Statistical Analysis

Statistical analysis was done using the SPSS 21.0 program with the Wilcoxon signed-rank test, with $p<0.05$ considered as a statistically significant difference. The Wilcoxon signed-rank test revealed statistically significant differences in gene expression for both KRAS ($Z=-2.281$, $p=0.023$) and BRAF ($Z=-2.555$, $p=0.011$). To further support these findings, 95% confidence intervals (CIs) for the median differences were calculated, providing a more robust interpretation of effect size and variability.

Results

KRAS and BRAF Gene Expression Results

We found that eight of the 29 samples showed decreased KRAS expression, while 21 showed different rates of increased expression ($p=0.023$). For BRAF, a decrease in expression was observed in six samples, while KRAS expression increased in 23 samples to varying degrees ($p=0.011$). Both BRAF and KRAS gene expression increments were statistically significant ($p<0.05$) (Table 3).

To better interpret the gene expression data presented in Table 3, raw KRAS and BRAF values were normalized by calculating fold changes relative to the median expression level of each gene. Box-plots were used to visualize the distribution and variability of these fold changes (Figure 1). Statistical comparison using the Wilcoxon signed-rank test revealed no significant difference between KRAS and BRAF fold changes ($p=0.151$). However, both Pearson's and Spearman's correlation analyses indicated a strong, statistically significant positive correlation between KRAS and BRAF fold changes (Pearson's $r=0.765$, $p<0.0001$; Spearman's $p=0.789$, $p<0.00001$). These findings suggest that KRAS and BRAF gene expressions tend to increase or decrease in parallel across the patient cohort, implying a potential co-regulatory or pathophysiological link between the two genes in the studied context.

To enhance the robustness of the statistical findings, 95% CIs were calculated for the median differences in gene expression levels. For KRAS, the Wilcoxon signed-rank test yielded a test statistic of 63.0 with a p-value of 0.021, and the 95% CI for the median difference ranged from -0.025 to 0.086. Although statistically significant, the inclusion of zero in the

Table 1. Symptoms and clinical findings of nasal polyposis patients included in the study

Symptoms and findings		n	%
Nasal obstruction	Yes	28	96.6
	No	1	3.4
Smell loss	Yes	8	27.6
	No	21	72.4
Pain	Yes	4	13.8
	No	25	86.2
Asthma	Yes	6	20.7
	No	23	79.3
Previous FESS surgery	Yes	13	44.8
	No	16	55.2
Additional chronic disease	Yes	5	17.2
	No	24	82.8
Septal deviation	Yes	11	37.9
	No	17	58.6
	Perforated	1	3.4
Inferior turbinate hypertrophy	Yes	16	55.2
	No	13	44.8
Middle turbinate	Not present or partially present	7	24.1
	Present	22	75.9

n: Number of patient numbers, FESS: Functional endoscopic sinus surgery

Table 2. Primer sequences used for gene expression analysis. PCR conditions-including annealing temperature, cycle number, and reagent concentrations-should be provided to enhance reproducibility

GAPDH	F-5'-GGGTGATGCTGGTGCTGAGTATGT-3'
	R-5'-AAGAATGGGAGTTGCTGTTGAAGTC-3'
KRAS	F-5'-TCTTGCCTCCCTACCTTCCACAT-3'
	R-5'-CTGTCAGATTCTCTTGAGCCCTG-3'
BRAF	F-5'-GGCAGAGTGCCTCAAAAAGAA-3'
	R-5'-AACCAGCCCGATTCAAGGA-3'

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase, KRAS: Kirsten rat sarcoma viral oncogene homolog, BRAF: B-raf proto-oncogen, PCR: polymerase chain reaction

Table 3. BRAF and KRAS gene expression results

Patients	KRAS results	BRAF results
1	1.097179246	1.175361666
2	1.001621713	1.030369095
3	1.018120367	1.077038148
5	0.967776972	1.017288726
7	0.970051343	1.045043215
8	1.128866204	1.195048732
9	1.085551034	1.074484002
10	0.96099251	0.969552211
11	1.088569584	1.15297407
12	0.975080824	1.083389811
14	0.947106598	0.943466947
15	1.080471593	1.062976901
16	1.048824264	1.014898646
18	0.983468754	0.90912133
19	0.971429611	0.98634447
20	0.969725294	0.95497642
21	1.1043126	1.22840006
22	1.124316883	1.178283147
23	1.219108282	1.270550481
24	1.189088232	1.779561132
25	1.03379119	1.04301161
27	1.048202537	0.941551158
29	1.005388311	1.002334551

KRAS: Kirsten rat sarcoma viral oncogene homolog, BRAF: B-raf proto-oncogene

CI suggests a relatively modest effect size. In contrast, BRAF expression showed a test statistic of 53.0 with a p-value of 0.008, and the corresponding 95% CI ranged from 0.002 to 0.083. The entirely positive interval for BRAF supports a more consistent and meaningful increase in gene expression. These results strengthen the evidence for altered expression of both KRAS and BRAF in NP, with BRAF demonstrating a potentially stronger association.

Discussion

While NP is a benign disease that does not show malignant transformation, its symptoms, such as nasal obstruction, smell dysfunction, anosmia, and nasal discharge, can disrupt the comfort and quality of life of patients. One of the most challenging aspects of this disease is its tendency to recur despite surgical intervention, and NP shows recurrences at different time intervals that vary in each patient. Although the etiology of the disease is still unclear, the data obtained from the studies show that genetic and environmental factors have a significant effect on the formation of NP (1-3).

Although our study identifies significant changes in BRAF and KRAS gene expression in NP, the precise functional and mechanistic implications of these alterations were not directly investigated. Recent studies shed light on the potential mechanistic roles of these genes in NP pathology. For instance, a recent investigation demonstrated that the activation of the RAS/RAF/MEK/ERK signaling pathway in nasal polyps contributes significantly to the cell proliferation, inflammation, and tissue remodeling characteristics of NP, suggesting that BRAF and KRAS over-expression could exacerbate these processes (8). Furthermore, integrated genomic analyses combining genome-wide association studies and expression quantitative trait loci have highlighted the involvement of multiple genetic loci, including those related to inflammatory pathways and cellular growth, in the development of NP (9). These findings provide a robust foundation for future functional studies aimed at elucidating the specific roles of BRAF and KRAS gene expression in NP pathology.

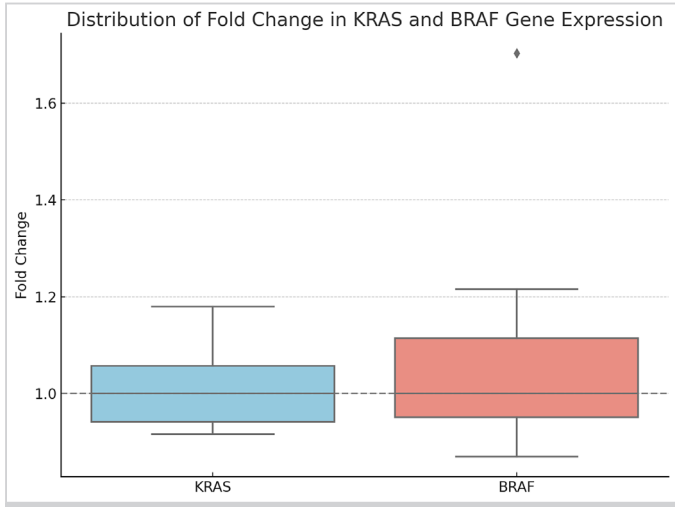

Figure 1. Distribution of fold change in KRAS and BRAF gene expression

KRAS: Kirsten rat sarcoma viral oncogene homolog, BRAF: B-raf proto-oncogene

These molecular alterations may account for the chronicity, recurrence tendency, and resistance to treatment seen in some NP patients, although more longitudinal studies are needed to confirm this.

In short, while our findings do not yet translate into immediate clinical decisions, they support the concept that KRAS and BRAF expression changes may eventually serve as molecular markers for disease severity or treatment resistance in NP. This area holds potential for future therapeutic targeting, especially as MAPK pathway inhibitors are well-characterized in other contexts.

The influence of genetic factors and heredity on the occurrence of NP has been well documented in studies showing that the disease was more common in family members and twins (1,10,11). A multi-centric study with

224 patients found a family history rate as high as 52.66% (10). Additionally, a family history of NP was found as 14% in a smaller group of 50 patients (11). A striking finding in the referred study was the presence of NP in more than one family member in 6% of the patients (11). These results indicate that genetic factors may be contributing to NP occurrence, at least in some cases, associated with possible environmental factors.

The impetus of this study was to determine whether NP has a genetic basis, by performing BRAF and KRAS gene expression via the reverse transcription-PCR (RT-PCR) technique. The detection of these genetic mutations is also likely to be a beacon of hope for possible inhibitory therapy for patients with these mutations. We performed gene expression of BRAF and KRAS genes via the RT-PCR technique, comparing immediately fresh-frozen with liquid nitrogen biopsy samples of NP tissue and control tissue samples from inferior turbinate or nasal septum mucosa in the same patient. Similar to NP, a high incidence of KRAS mutation has also been observed in non-neoplastic hyperplastic colon polyps that did not cause malignant transformation (12). KRAS mutation seems to be related to the pathogenesis of NP. We found that KRAS expression and BRAF expression increased in 21 cases and 23 cases out of 29 cases, respectively, and both increases were statistically significant ($p<0.05$). Lin et al. (13) concluded that tumor necrosis factor alpha stimulates chemokine ligand 2 (CCL2) transcription in NP fibroblasts. The B-Raf/MEK/ERK signaling cascade is in charge of CCL2 expression, which is the key factor for the monocyte chemotaxis modulator in NP fibroblasts, leading to macrophage recruitment in the pathogenesis of NP.

In our study, we also found that BRAF was associated with NP pathogenesis, and BRAF expression was increased in NP tissue compared to normal inferior turbinate or septal mucosal tissue. On the other hand, previous research has reported conflicting results regarding BRAF gene expression in NP. For instance, Zaravinos et al. (3) observed decreased levels of BRAF mRNA in NP tissues compared to adjacent turbinate mucosa, contrasting with our findings of increased BRAF expression. These discrepancies could be attributed to methodological variations, differences in patient populations, tissue sampling techniques, or heterogeneity within NP pathology itself. Variations in inflammatory profiles, presence or absence of comorbid conditions such as asthma or allergy, and differences in prior medication usage (e.g., corticosteroids) could also explain these inconsistencies. Given the scarcity of studies investigating BRAF gene expression in NP, it remains difficult to fully elucidate the underlying mechanisms. Therefore, future research should standardize patient selection criteria and methodological approaches to clarify the role of BRAF expression more accurately in NP.

However, studies regarding BRAF and KRAS mutations in NP in the literature are not presently adequate to clarify their part in the pathogenesis of the disease. On the other hand, the MEK1/2-ERK1/2 pathway, which is closely related to these mutations in NP, is activated (phosphorylated) to lead to NP formation, and research in this area is of great interest to a highly active research community (14-16). Much more genes other than BRAF and KRAS have been detected in NP with micro-assay techniques (1). Hyper- and hypo-methylation of some genes, suppression, and increment of gene expression have been found to be closely related to NP (17,18). These findings showed that the complexity of the disease and NP formation is multifactorial, which includes hereditary, epigenetic, environmental, and individual factors interacting with each other.

Our research has certain limitations. It was conducted with a relatively small sample size of 29 patients, which may limit the statistical power and generalizability of the findings. Therefore, it remains unclear whether the sample size was sufficient to detect clinically meaningful differences in KRAS and BRAF gene expression. Future studies are needed with large samples of cases. The other limitation is that the study did not include or control for potentially influential factors such as allergy, asthma, atopy, prior corticosteroid use, or detailed history of smoking, all of which may affect NP pathology and gene expression outcomes. Future research should consider collecting comprehensive data on these factors and adjusting for them in statistical analyses to enhance the validity and interpretability of findings.

Conclusion

In conclusion, our study identified significant associations between increased BRAF and KRAS expression and the presence of NP, suggesting a potential genetic component to this chronic inflammatory disease. However, these results are correlative and do not establish direct causation. Further experimental studies investigating the causal mechanisms and functional implications of BRAF and KRAS gene expression changes are necessary to clarify their exact roles in NP pathogenesis.

Ethics

Ethics Committee Approval: The study was approved by the Health Sciences İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Board (approval number: 2017/0083, date: 23.03.2023).

Informed Consent: All participants provided their informed consent to be included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö.A., T.Ç., Concept: G.Ö.A., F.Ö., H.İ.Y., O.İ.Ö., T.Ç., Design: G.Ö.A., F.Ö., H.İ.Y., O.İ.Ö., T.Ç., Data Collection and/or Processing: G.Ö.A., F.Ö., H.İ.Y., O.İ.Ö., T.Ç., Analysis and/or Interpretation: G.Ö.A., F.Ö., H.İ.Y., O.İ.Ö., T.Ç., Literature Search: G.Ö.A., F.Ö., T.Ç., Writing: G.Ö.A., F.Ö., O.İ.Ö.

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Main Points

- Nasal polyposis has multifactorial causes and adverse effects on patient comfort and quality of life due to frequent relapses.
- Underlying mechanisms of the disease are still uncertain.
- Some genetic, environmental and individual factors interact in leading to the disease.
- A strong correlation was identified between BRAF and KRAS, elevated gene expression, and the disease.
- These findings may play a guiding role in understanding the underlying causes of this disease, the cause(s) of which have not been fully revealed.

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Post-Pandemic Surge in Complications of Acute Otitis Media

Original Investigation

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Abstract

Objective: Acute otitis media (AOM), a common middle ear infection, can lead to severe complications if not properly managed. The coronavirus disease 2019 (COVID-19) pandemic significantly impacted healthcare delivery and disease management. This study aimed to evaluate the incidence of complicated AOM cases from the pre-pandemic to post-pandemic period.

Methods: A retrospective review was conducted at Necmettin Erbakan University, Department of Otolaryngology, on patients diagnosed with complicated AOM in the period from January 2014 to February 2024. Patients were categorized into three periods: pre-pandemic (2014-2020), pandemic (2020-2022), and post-pandemic (2023-2024). Clinical data, including demographics, types of AOM complications, and treatment methods, were analyzed.

Results: A total of 32 patients (20 females and 12 males) with AOM complications were identified. Mastoiditis was the most common complication, seen in 43.75% of the patients, with increased incidences of 64.3% in the post-pandemic period. Subperiosteal abscess was noted in 12.5 % of the patients, exclusively in the pandemic and post-pandemic periods. Facial nerve paralysis (12.5%) and labyrinthitis (9.3%) were noted only in the post-pandemic period. Meningitis was noted in 15.6% of the patients, with increased incidences in the post-pandemic period. Observed during the post-pandemic period, sigmoid sinus thrombosis was noted in only one patient (3.1%).

Conclusion: Despite the reduced AOM incidence rates during the early pandemic, a surge was seen in complicated AOM cases in the post-pandemic period. This increase could be linked to COVID-19's impact on the immune system, pathogen virulence changes, and disruptions in vaccination protocols. These findings highlight the need for improved surveillance of AOM cases regarding complications in the post-pandemic era.

Keywords: Pandemics, coronavirus disease 2019, otitis media, complications, mastoiditis, facial paralysis

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Introduction

Acute otitis media (AOM) is the infection of the middle ear caused by bacterial or viral pathogens leading to inflammation and fluid buildup behind the eardrum. AOM is one of the most common diagnoses seen in childhood. It affects nearly 750 million people globally and is the most frequent infection that is prescribed with antibiotics in pediatric patients (1). Although it is accepted as a benign condition with treatment and preventive options, it can progress to complications, particularly if left untreated

or inadequately managed. The complications of AOM have a broad range, from intratemporal to intracranial, and could result in life threatening conditions. The most common intratemporal complication is mastoiditis, while the most commonly seen intracranial complication is meningitis (2). Accessibility to antibiotics and generalized application of vaccination has dramatically decreased the frequency of these complications of AOM. Whereas a shortage of specialists in underdeveloped countries and long waiting lists in developed countries are of public health concern in preventing these complications.

The emergence of the coronavirus disease 2019 (COVID-19) pandemic led to significant disruptions in healthcare systems worldwide, profoundly affecting the epidemiology and management of infectious diseases. Non-pharmaceutical interventions such as social restrictions, universal masking, social distancing, and national lockdowns were implemented to reduce COVID-19-related morbidity and mortality. These social restrictions also contributed to a noticeable decrease in hospital admissions for AOM, acute tracheitis, and acute laryngitis which are caused by other microorganisms (3). However, during the post-pandemic period with the relaxation of the social restrictions, there was a subsequent increase in severe upper respiratory infections which led to complications that required surgical intervention (2). Infections, which decreased throughout the pandemic, began to reappear in increasing numbers, revealing more complicated consequences in the post-pandemic period.

The increase in complicated infections observed in the post-pandemic period is believed to be linked to the effects of the pandemic itself, as well as to the changes in the virulence of the causative microorganisms. One key factor is the disruption of the immune system caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. A study by Hopkins et al. (4) has shown that SARS-CoV-2 could impair the development of long-term immune responses, potentially weakening the body's ability to effectively combat infections, including AOM, and increasing the risk of complications.

Another significant consequence of the pandemic has been the interruption of routine vaccination programs, even in developed countries. The reduction in well-child visits during the pandemic led to fewer opportunities for administering essential vaccinations, which may have contributed to the observed rise in infections caused by microorganisms other than SARS-CoV-2 (5). Moreover, changes in the virulence of pathogens during this period resulted in weaker immune responses and reduced the efficacy of medical treatments, including antibiotics, thereby increasing the incidence of secondary complications.

In this context, we aimed to investigate the effect of the COVID 19 pandemic on the incidence of complicated AOM cases from the pre-pandemic to the post-pandemic period.

Methods

We retrospectively analyzed the records of AOM patients who were diagnosed based on the American Academy of Pediatrics, 2013 AOM Clinical Practice Guideline and the American Academy of Otolaryngology-Head and Neck Surgery, 2016 OME Clinical Practice Guideline (6,7). Patients who were admitted to Department of Otolaryngology, Necmettin Erbakan University, Turkey between January 2014 and February 2024 with complicated AOM were included in the study. A total of 4,207 AOM cases were analyzed. The inclusion criteria for complicated otitis media were based on the presence of complications such as mastoiditis, facial nerve paralysis (FNP), meningitis, indicating that the infection did not remain confined to the middle ear but spread to the surrounding tissues, affecting intracranial and extracranial areas.

In patients who developed complications after AOM, physical examination, laboratory findings, and imaging methods such as computed tomography (CT) and magnetic resonance imaging were used during the diagnostic process. Acute mastoiditis was diagnosed based on physical examination findings such as redness and swelling behind the ear, forward displacement of the auricle, otalgia, and high fever, along with temporal CT findings showing loss of mastoid bone aeration and increased soft tissue density. Grading of FNP in patients performed according to House-Brackmann grading scale. The diagnosis of meningitis was established by analyzing the cerebrospinal fluid obtained through lumbar puncture in patients presenting with symptoms such as high fever, neck stiffness, headache, and altered consciousness. The diagnosis of subperiosteal abscess was established in patients with clinical findings such as prominent swelling, redness, tenderness behind the ear, and anterior displacement of the auricle. The diagnosis was confirmed by contrast-enhanced temporal CT, demonstrating mastoid bone destruction and fluid accumulation in the periosteal space. The diagnosis of labyrinthitis was established based on the clinical evaluation in patients with sudden-onset vertigo, hearing loss, and tinnitus, confirmed by audiological tests revealing hearing impairment.

Patients whose information was not available, or incomplete, were excluded from the study. Patients who had genetic disorders with immune dysregulation, patients who were using immune suppression drugs were excluded from the study.

The pandemic period in Türkiye began in March 2020 with the arrival and rapid spread of the first COVID-19 case. The years 2020-2022 were considered the COVID-19 pandemic period, during which lockdowns, online education, travel restrictions, and a nationwide vaccination campaign were implemented. After 2022, with the complete removal of the mask mandate in indoor spaces and the lifting of other

restrictions, Türkiye transitioned into the post-pandemic period. Therefore, in our study, the periods were divided into three phases: the pre-pandemic (January 2014-February 2020), the pandemic (March 2020 - December 2022), and the post-pandemic (January 2023 - February 2024). Demographic data, clinical findings of the patients, their complications, treatment modalities, and clinical outcomes were noted.

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Necmettin Erbakan University (approval no: 2024/4910, date: 05.04.2024). Clinical observation was conducted in accordance with the principles of good clinical practice.

Statistical Analysis

Data was analyzed using SPSS 22.0 software. The normality of data distribution was studied using the Kolmogorov-Smirnov test. Depending on the normality assumption, the distribution of patients' demographic characteristics was presented as mean ± standard deviation or median (minimum-maximum). Categorical variables were expressed as absolute frequencies and percentages.

No inferential statistical tests were performed, and data was presented descriptively to provide an overview of the patient population, complications, and trends across the pre-pandemic, pandemic, and post-pandemic periods.

Results

The study results have revealed that 32 patients were diagnosed with complications secondary to AOM in the study period. These complications included mastoiditis, subperiosteal abscess, FNP, meningitis, labyrinthitis, and sigmoid sinus thrombosis. The cohort had a mean age of 27.5±26.7 years, ranging from two months to 75 years. Of the 32 patients, 20 (62.5%) were female and 12 (37.5%) were male. Eighteen of the patients were in the pediatric age group under 18 years, while 14 were over 18 years. The predominant presenting symptom was otalgia, reported in 85% of the cases. The distribution of diagnoses along with the years are shown in Table 1 and Figure 1.

During the pre-pandemic period (2014-2020), the number of AOM cases admitted to our hospital was 2,998, while the number of complicated AOM cases was four During the pandemic period (2020-2022), the number of admitted AOM cases was 856, with six cases of complicated AOM. In the post-pandemic period (2023-2024), the number of admitted AOM cases was 353, while the number of complicated AOM cases had risen to 22. A significant rise in the proportion of complicated AOM cases among total AOM cases was observed, particularly during the pandemic and post-pandemic periods. The number of total AOM and complicated AOM cases by years are shown in Figure 2. Additionally, while all complicated AOM cases presenting to our hospital during the pre-pandemic period were adult patients, the majority of complicated AOM cases during the pandemic and post-pandemic periods consisted of pediatric patients. Among the six complicated AOM patients in the pandemic period, four were in the pediatric age group, whereas among the 22 complicated AOM patients in the post-pandemic period, 14 were in the pediatric age group. Compared to the pre-pandemic period, the incidence of complicated AOM cases in the pediatric patient population had significantly increased.

Mastoiditis was the most common complication affecting 14 patients (43.75%). Analysis revealed a notable shift in the incidence across periods: one patient (7.1%) in the pre-pandemic period, four patients (28.6%) during the pandemic, and a substantial increase to nine patients (64.3%) in the post-pandemic period. Treatment protocols for mastoiditis predominantly included antibiotic therapy, with additional surgical interventions such as mastoidectomy (three patients), local drainage (three patients), and ventilation tube placement (one patient). All patients diagnosed with

Table 1. Number of patients with complications of AOM across pre-pandemic, pandemic, and post-pandemic periods

Acute otitis media complications	Pre-pandemic (2014-2020)	Pandemic (2020-2022)	Post-pandemic (2023-2024)
Mastoiditis	1	4	9
Subperiosteal abscess	0	1	3
Facial nerve paralysis	0	0	4
Meningitis	2	1	2
Labyrinthitis	1	0	3
Sigmoid sinus thrombosis	0	0	1
Total	**4**	**6**	**22**

AOM: Acute otitis media

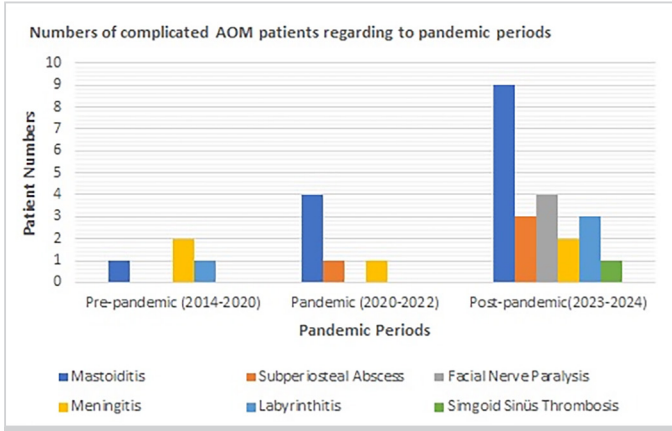

Figure 1. Numbers and trends of complicated AOM cases across pre-pandemic, pandemic, and post-pandemic periods
AOM: Acute otitis media

mastoiditis recovered without any sequelae after medical and surgical treatments.

Subperiosteal abscesses were identified in four patients (12.5%). These abscesses were distributed as follows: one patient (25%) in the pandemic and three patients (75%) in the post-pandemic period. Management encompassed both antibiotic therapy and surgical procedures, including local drainage (three patients) and mastoidectomy (one patient). The physical examination findings of a left-sided subperiosteal abscess in a 2-year-old girl are illustrated in Figure 3. Additionally, Figure 4 presents the CT scan of a 3-year-old patient with acute mastoiditis complicated by a subperiosteal abscess in the right ear (axial plane). All patients diagnosed with subperiosteal abscess recovered without any sequelae after treatments.

FNP was observed in four patients (12.5%), and all cases were detected in the post-pandemic period. Three patients had grade 3 FNP, and one patient had grade 4 FNP. Treatment strategies included antibiotic treatment, ventilation tube placement and steroid therapy. One patient, who also had mastoiditis, required a mastoidectomy. Of the FNP patients, three achieved complete recovery, while one experienced persistent grade 2 facial paralysis at 6-month follow-up.

Meningitis was diagnosed in five patients (15.65%). The distribution of meningitis cases across the periods was two patients (40%) in the pre-pandemic period, one patient (20%) during the pandemic, and two patients (40%) in the post-pandemic period. All patients received antibiotic therapy, and one patient also underwent ventilation tube placement. Notably, the most recent addition was an 18-year-old male diagnosed with meningitis in the post-pandemic period, who was managed with antibiotic therapy. He was diagnosed with bilateral AOM and was started on oral antibiotic therapy. Even though early antibiotic treatment was initiated-one day after the diagnosis-the case progressed to clinical meningitis, and the disease was brought under control after hospitalization and broad-spectrum antibiotic treatment. All patients diagnosed with meningitis recovered without any sequelae with treatments.

Labyrinthitis was observed in four patients (12.5%). The distribution of labyrinthitis cases was one patient (25%) in the pre-pandemic period and three patients (75%) in the post-pandemic period. All individuals who were affected developed sensorineural hearing loss. Treatment for labyrinthitis varied; two patients with concurrent mastoiditis underwent mastoidectomy in addition to medical treatment, while one patient received myringotomy and ventilation tube placement along with medical management. After

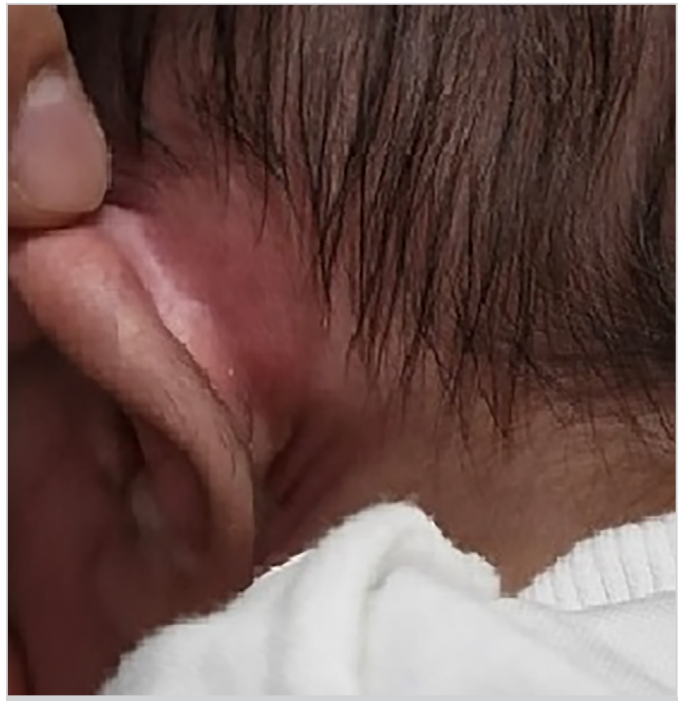

Figure 3. Physical examination showing left subperiosteal abscess in a 2-year-old girl

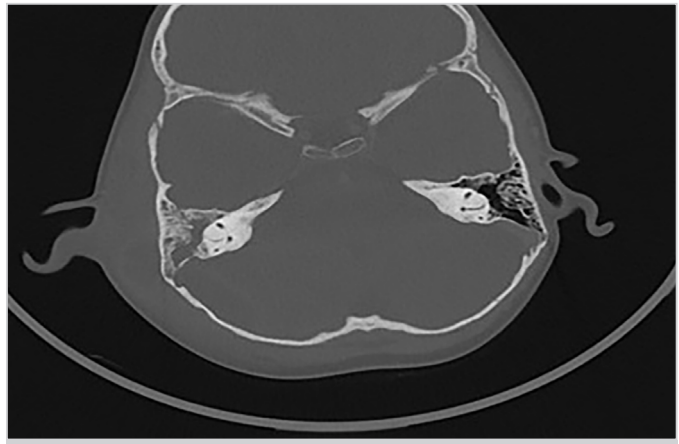

Figure 4. CT scan of a 3-year-old patient with acute mastoiditis complicated by a subperiosteal abscess in the right ear (axial plane)
CT: Computed tomography

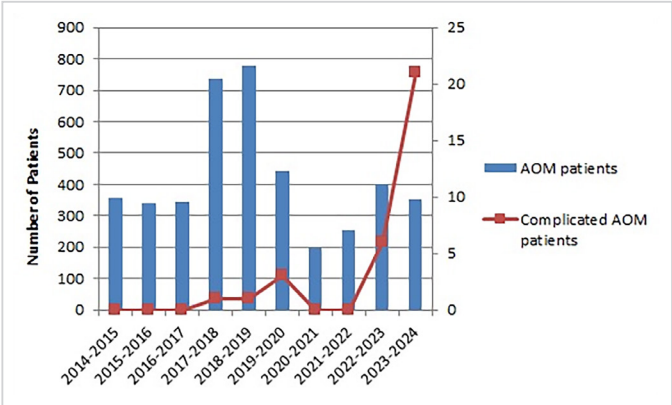

Figure 2. Annual distribution of total AOM and complicated AOM cases, illustrating the increase in complications post-pandemic
AOM: Acute otitis media

completing the treatment of patients with labyrinthitis, the sensorineural hearing loss that occurred in the patients continued as moderate to severe in the control audiograms.

Sigmoid sinus thrombosis was noted in one patient (3.1%), identified during the post-pandemic period, and managed with both antibiotic therapy and ventilation tube placement. In the patient's long-term follow-up, no sequelae were observed.

Discussion

Our study highlights a significant increase in the number of AOM-related complications during the pandemic and post-pandemic periods, although they define a shorter period of time. More severe complications such as mastoiditis, subperiosteal abscesses, FNP, and meningitis, were seen particularly in the post-pandemic period. These results reveal a potential impact of the pandemic on AOM cases and related complications. Previous studies in the literature have investigated the effects of COVID-19 on the development of otitis media and its association with an increased incidence of acute mastoiditis (8-10). However, unlike other studies, our study aimed to contribute to the literature by comprehensively evaluating the increase in other complications, alongside acute mastoiditis, associated with AOM, specifically in the post-pandemic period. Additionally, our study is the first on this topic conducted in Türkiye, and its findings serve as a valuable contribution to and support for studies conducted in the other regions worldwide.

AOM typically arises from the ascent of pathogens from the nasopharynx through the Eustachian tube, leading to inflammation and fluid accumulation in the middle ear. While most cases of AOM resolve spontaneously or with appropriate medical management, complications such as mastoiditis, subperiosteal abscess, labyrinthitis, FNP, and meningitis can occur. These cases necessitate prompt recognition and intervention to prevent serious sequelae. In general, with the introduction of antibiotics, the rate of complications after AOM had decreased significantly (11). Complications after AOM were limited to areas where access to antibiotics is difficult and in cases where antibiotics are not used properly. However, as our results have revealed this has changed with the COVID-19 pandemic.

The COVID-19 pandemic had a significant impact on respiratory infections overall. A greater incidence of complex upper respiratory tract infections may have resulted from the relaxation of COVID-19-related limitations (2). SARS-CoV-2 infection has been shown to induce prolonged changes in the immune system, including impaired T-cell response, dendritic cell depletion, and alterations in myeloid surface markers (4,12). These alterations are suggested to contribute to long-term immune dysfunction, which may increase susceptibility to infections such as AOM. Although these alterations are not directly assessed in our study, they represent potential mechanisms that could contribute to the increased incidence of complicated AOM cases during the post-pandemic period. Apart from the immune dysregulation caused by the COVID-19 infection, several other factors may have contributed to the rise in complicated AOM cases. These include a weakened immune system due to reduced exposure to pathogens and slower immune maturation (12-15). Additionally, changes in pathogen virulence may also play a role. Furthermore, during the pandemic, access to well child visits was limited, potentially leading to disruptions in vaccination programs (15-17). These factors are believed to be the key reasons for the increase in complicated AOM cases, especially among pediatric populations, in the post-pandemic period.

Non-pharmaceutical interventions during the pandemic reduced the spread of respiratory pathogens, including AOM. However, the lifting of these restrictions led to a rebound effect, with a marked increase in AOM cases, likely due to sudden re-exposure to pathogens (13,14). According to Cohen et al. (15) extended periods of low microbial exposure raise the likelihood of subsequent epidemics because of the population's induced immunity debt and the number of vulnerable people. The idea of trained immunity refers to a long-term, pathogen-stimulated functional reprogramming of innate immune cells that would result in a reinforced response after sustained exposures. The host defense would greatly benefit from this procedure (16). Due to the pandemic's hygienic efforts, there were fewer infectious contacts, which may have weakened children's immune systems and increased their vulnerability to infections.

Before the pandemic, infant and young children vaccination coverage rates were acceptable in our country and many other countries owing to national vaccination programs. The COVID-19 pandemic affected vaccine coverage rates across the board, with some seeing a severe decline, especially during the lockdown periods, and a partial recovery after that (17). A significant decline in doctor visits, including well-baby visits, was noted during the initial lockdown that began in March 2020. Paker et al. (18) revealed that the most common causative agent of AOM changed over time and there was a significant improvement in the antibacterial sensitivity of antibiotics after the vaccination program. Global coverage of vaccines such as diphtheria-tetanus-pertussis 3, measles-containing vaccines (MCV1 and MCV2), and meningococcal groups A, C, W, and Y saw substantial decreases during the pandemic (19). These reductions left many children unprotected against severe complications from preventable diseases. Notably, pneumococcal conjugate vaccines and Haemophilus influenzae type b vaccinations, which are critical in preventing respiratory infections and AOM, were particularly impacted. Although our study did

not include individual patient-level vaccination data, recent studies have demonstrated that reductions in pneumococcal vaccination rates during the pandemic were associated with increased incidences of AOM and its complications (20). These findings indicate that maintaining high vaccination rates is critical for preventing otitis media and its related complications in pediatric populations. Therefore, while the observed surge in complicated AOM cases may align with disruptions in vaccination programs, further studies incorporating patient-specific vaccination records are required to confirm this association and understand its impact on disease severity.

Virulence, the degree to which a pathogen harms its host, is dynamic and context-dependent, making it challenging to predict its impact on host proliferation and population spread (21). Depending on this evolution in the virulence of the pathogen, the response of the host's immune system to the pathogen and the effectiveness of the antibiotics and other medical treatments change. Recent studies suggest that the increase in complicated AOM cases observed after the pandemic may be linked to the shifts in the subtypes of pathogens responsible for AOM, as well as the changes in host response and treatment efficacy, potentially driven by pathogen virulence dynamics (20). Shifts in the serotype distribution of *Streptococcus pneumoniae* and increased oxacillin resistance during the pandemic may have altered the microbiological profile of AOM (22). These findings indicate that the pandemic may have changed the pathogen subtypes of upper respiratory tract infections, potentially altering clinical outcomes and complication rates of AOM in the post-pandemic era. Although our study did not include microbiological evaluations to confirm these alterations, the observed rise in complicated AOM cases highlights the necessity for future research to explore these mechanisms in depth and to assess pathogen dynamics in the post-pandemic era.

Previous studies in the literature have investigated the effects of COVID-19 on the development of otitis media and its association with an increased incidence of acute mastoiditis (8,9). In this research, the results showed that there was an increase in complications during the post-pandemic period and this research gives you an idea that AOM cases, which are considered innocent, may become complicated due to changes in the immune system, disruptions in vaccination programs during the pandemic, and changes in the virulence of pathogens. Considering the increase in complications, especially in the post-pandemic period, it is important to treat AOM cases more effectively and seriously. Our study gives an idea about this increase and future research is necessary to elucidate the underlying reasons for this trend.

Our study has some limitations that should be acknowledged. First, the retrospective nature of the study and its reliance on existing data may introduce selection bias, potentially affecting the validity of the results. Second, as the study was conducted at a single tertiary referral center, the findings may not be generalizable to other regions or healthcare settings. Third, the observed increase in complicated AOM cases may be linked to decreased vaccination rates during the pandemic, which could have altered pathogen distribution and antibiotic sensitivity. However, it is important to note that our study did not include microbiological evaluations, individual vaccination data, or detailed immunological assessments. Due to these limitations, while our proposed mechanisms are supported by existing literature, further validation through well-designed prospective studies is necessary. Additionally, to better evaluate the effect of COVID-19 on the development of complicated otitis media, it is essential to document the history of COVID-19 infection and vaccination status in future studies. Our study did not include definitive, objective data regarding the patients' retrospective vaccination status or whether they had contracted COVID-19. Including such data in future research would enhance the accuracy and generalizability of the findings.

Despite these limitations, our study provides valuable insights into the post-pandemic increase in complicated AOM cases, highlighting the importance of maintaining vigilant clinical practices and conducting more comprehensive studies to elucidate the underlying mechanisms.

Conclusion

The significant rise in complicated AOM cases during the post-pandemic period highlights potential lasting impacts of the COVID-19 pandemic. Factors contributing to this increase may include the long-term immune dysregulation induced by SARS-CoV-2, shifts in pathogen virulence, and the interruption of routine vaccination programs. These findings suggest a need for continued research into the pathophysiology of complicated AOM and underscore the importance of comprehensive treatment strategies and vigilant public health measures to prevent severe outcomes. Addressing these challenges requires a collaborative effort from healthcare providers, public health officials, and researchers to improve patient care and outcomes in the post-pandemic era. Additionally, studies incorporating microbiological evaluations, presenting the COVID-19 infection and vaccination status of patients, and covering broader geographic and demographic samples are needed for a more comprehensive understanding of this phenomenon.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of Necmettin Erbakan University (approval no: 2024/4910 , date: 05.04.2024).

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., F.C.E., M.A.E., H.A., Concept: M.K., H.A., Design: M.K., M.A.E., H.A., Data Collection and/or Processing: M.K., M.A.E., H.A., Analysis and/or Interpretation: F.C.E., H.A., Literature Search: M.K., F.C.E., Writing: M.A.E.

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

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Main Points

- A significant increase in complicated acute otitis media (AOM) cases was observed in the post-pandemic period compared to pre-pandemic years, despite an overall reduction in AOM incidence during the pandemic.
- Mastoiditis, subperiosteal abscess, facial nerve paralysis, meningitis, and labyrinthitis became more prevalent in the post-pandemic era, especially among pediatric patients.
- The surge in complications may be associated with immune dysregulation caused by severe acute respiratory syndrome coronavirus 2, interrupted vaccination schedules, and increased pathogen virulence following the coronavirus disease 2019 pandemic.

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A Comprehensive Study of Combined Approach Sialendoscopy in Managing Salivary Gland Sialolithiasis

Original Investigation

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Abstract

Objective: Obstructive salivary gland diseases were traditionally managed conservatively, with surgical treatment reserved for refractory cases only. These surgeries, ranging from papillotomy to sialadenectomy, often involved numerous complications. In the past two decades, sialendoscopy, a minimally invasive technique, has made tremendous progress due to its advantages. This study aims to describe the efficacy of combined approach sialendoscopy as a minimally invasive option for large-sized sialolithiasis that is not amenable to sialendoscopy alone.

Methods: It is an ambispective study of 12 patients over a span of 3.5 years at a tertiary care center conducted with all consenting patients who were treated with combined approach sialendoscopy. Ultrasonography and computed tomography of the patients was done. Therapeutic intervention in the form of combined approach sialendoscopy was done at the same sitting as diagnostic sialendoscopy and postoperative follow-up was conducted for a duration of six months.

Results: In this study of 12 patients undergoing sialendoscopy, glandular swelling was a universal presenting symptom, with 80% patients exhibiting meal-stimulated exacerbation and post-massage relief. Submandibular involvement predominated (83%), with parotid cases comprising the remainder. All patients had sialoliths >6 mm and underwent combined approach sialendoscopy, yielding a 100% immediate symptomatic resolution rate. Recurrence occurred in 16%, successfully managed with repeat sialendoscopy.

Conclusion: As endoscopy is integral to otorhinolaryngology, sialendoscopy represents the evolution of minimally invasive salivary gland surgery. This study highlights the different methods of combined approach sialendoscopy in managing larger as well as distally placed sialoliths, thus reinforcing its role as a superior gland-preserving modality.

Keywords: Sialolithiasis, sialendoscopy, salivary glands, minimally invasive surgical procedures, combined modality therapy

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Introduction

Obstructive salivary gland diseases represent one half of the benign salivary gland diseases. Sialolithiasis is the most common cause of obstruction, affecting almost 1.2% of the general population (1). The other causes of obstruction include strictures/stenosis of duct, juvenile recurrent parotitis or, post-radiotherapy duct stenosis, radioactive

iodine-induced stenosis, Sjögren's syndrome, ductal polyp, and foreign body. Prolonged ductal obstruction results in obstructive sialadenitis, characterized by symptoms such as pain and swelling around the involved gland, which worsen during meals and alleviate with massage. Other symptoms include pus discharge or passage of gritty substance in saliva. Recurrent attacks of sialadenitis can also be present (1,2).

Sialendoscopy is a minimally invasive technique which enables direct visualization of the duct lumen with a mini semi-rigid 0-degree sialendoscope as well as the management of the pathology in the ductal system. All major complications of traditional gland excision like facial or marginal mandibular nerve paralysis, Frey's syndrome, risk of salivary fistula are avoided and thereby morbidity rates are reduced greatly (1-4).

Combined approach sialendoscopy is the treatment of choice for larger sialolithiasis when other methods of stone fragmentation fail. In the case of the submandibular gland, the combined approach involves intraoral duct slitting, while for the parotid gland, it requires an external incision for stone retrieval after stone localization using sialendoscopy. While it tremendously increases the efficacy of sialendoscopic stone removal, it aids the functional recovery of the gland. This study aims to assess the efficacy of combined approach sialendoscopy as a minimally invasive, gland-preserving technique for the optimal management of large sialoliths that are not amenable to sialendoscopy alone.

Methods

An ambispective observational study was conducted at the department of ear, nose and throat (ENT) of a tertiary care center from January 2019 to June 2022 with all consenting patients with symptoms of obstructive sialadenitis and treated with combined approach sialendoscopy. The study received approval from the Institutional Ethics Committee (IEC)-III Relating to Biomedical and Health Research (BHR). [IEC (III)/OUT/39/2022] on 12 January 2022 with project number EC/100/2021 and was conducted in compliance with ethical standards. Informed consent was obtained from the patients using the format approved by the ethics committee.

Inclusion criteria: Patients clinically suffering from obstructive salivary gland disease and confirmed on radiology with a large sialolith (>6 mm in size) or a distally placed sialolith requiring a combined approach sialendoscopy.

Exclusion criteria: Acute sialadenitis, mumps, history of surgically treated salivary gland disease, salivary gland malignancies involving ductal parenchyma, other causes of obstructive salivary gland diseases like ductal strictures, stenosis, or mucous plugs, and previous treatment with conventional sialendoscopy.

After detailed ENT examination all patients underwent pre- and post-sialogogue ultrasonography followed by computed tomography (CT) scanning to identify the location of the sialolith. They were given a course of antibiotics preoperatively and then taken for sialendoscopic stone removal under general anaesthesia. Local infiltration was done using 2% lignocaine + 1:200000 adrenaline solution.

For sialendoscopy, the ostia of Wharton's duct or Stensen's duct was visualized under the operating microscope and serial dilation of the ostia was done using a conical dilator, followed by serial dilators gradually. A guide wire of 0.4 mm was introduced through the dilated ostia and a 1.3 mm diagnostic channel threaded over the guidewire, and then the guidewire was removed. Then the Marchal's semi-rigid sialendoscope was inserted and sialendoscopy was performed using continuous irrigation with diluted steroid solution. It has two channels (0.25 mm rinsing channel and 0.65 mm working channel). If a sialolith that is intractable to sialendoscopy alone was visualized, then the decision for a combined approach was taken.

Surgical Technique of Combined Approach Sialendoscopy

Submandibular duct sialolith: Localization of the sialolith is done via sialendoscopy followed by the insertion of a ductal dilator for continuous localization of the duct. External pressure is applied to elevate the gland towards the oral cavity. An intraoral incision is taken over the floor of the mouth at the localized site of the sialolith. The lingual nerve is identified and preserved during the dissection. Another

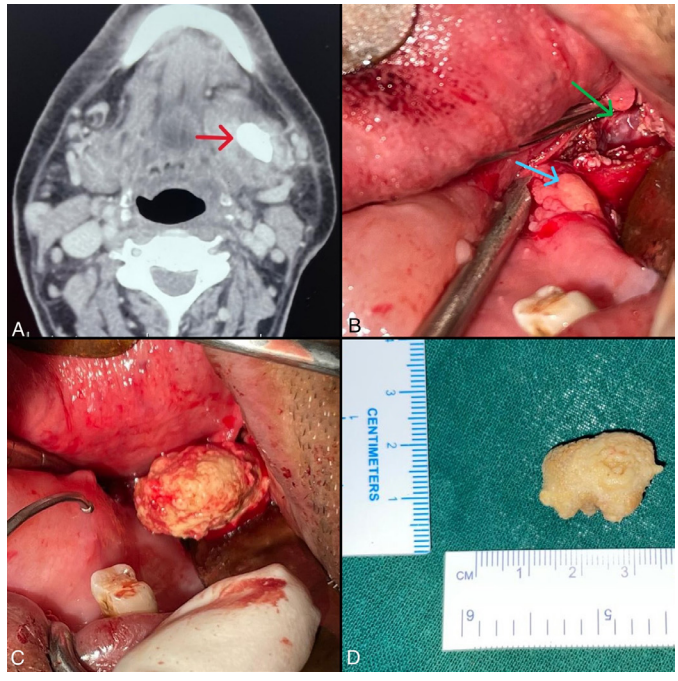

Figure 1. Combined approach submandibular duct sialendoscopy A. Red arrow: sialolith shown in proximal submandibular duct B. Green arrow: duct slitting incision, Blue arrow: lingual nerve C. Stone delivered through intraoral incision D. Calculus (2.5x1.5 cm)

incision is made over the duct, directly above the sialolith, to extract the stone (Figure 1). Subsequent distal sialendoscopy is performed to ensure complete removal of any additional stones or remnants. Repair of the Wharton's duct is done using Vicryl 3-0 round body sutures and followed by stenting of the duct. In some cases, duct marsupialization can also be done for proper salivary drainage, using Vicryl sutures as shown in Figure 2.

Parotid duct sialolith: Sialendoscopy is done using the Marchal sialendoscope to locate the stone, followed by the placement of a guide wire which is taped in-situ. A Modified Blair incision is made, and the flap is elevated until the parotid duct is visible. The scope is then advanced over the guide wire to enable external transillumination over the duct. An incision is made over the duct externally, and the stone is carefully extracted to avoid injuring facial nerve branches. Repeat sialendoscopy is performed to ensure complete removal of any additional stones or remnants. Stensen's duct is repaired using 3-0 (round body) Vicryl sutures through the external wound, and intraoral irrigation is done via the parotid duct papilla to check for leaks from the duct at the external site. After confirming the duct repair's integrity, the external skin incision is sutured, and a Minivac drain is placed for 7-10 days (Figure 3). In addition, intraoral stenting of the parotid duct is kept in place for 4-6 weeks to ensure proper healing.

All patients were postoperatively followed up for a duration of six months with history taking and clinical examination which were recorded in the case record forms.

Figure 2. Duct marsupialization of submandibular duct post sialendoscopic sialolith removal with duct slitting

Results

The patients had a mean age of 30 years with the majority being male (66.6%). Ten out of 12 patients had submandibular gland involvement whereas two had parotid sialolithiasis.

The presenting complaints of the patients were mostly swelling that increased in size when eating food and getting relieved with massage. A few patients (16.6%) complained of recurrent attacks of sialadenitis associated with acute pain, fever, and pus discharge from the duct papilla. The presenting symptoms of patients are summarized in Table 1.

Ultrasonography and CT scans were done in all patients for a comparative analysis of their sensitivity in detecting sialolithiasis. This revealed that CT scans exhibited a superior sensitivity in detecting calculi. Ultrasonography could diagnose 75% of the sialolithiasis patients while CT scan proved to be beneficial in all of the cases. Figure 4 shows a sialolith as seen on ultrasonography and CT scan.

In our study, a combined approach was employed for patients with larger stones (more than 6 mm), for whom fragmentation and sialendoscopic extraction of the stone was not feasible. The technique of combined approach followed in each case is given in Table 2.

In one patient with submandibular sialolithiasis with two calculi, the distal sialolith was successfully extracted in toto, while the proximal sialolith underwent strategic fragmentation and was meticulously cleared through saline irrigation.

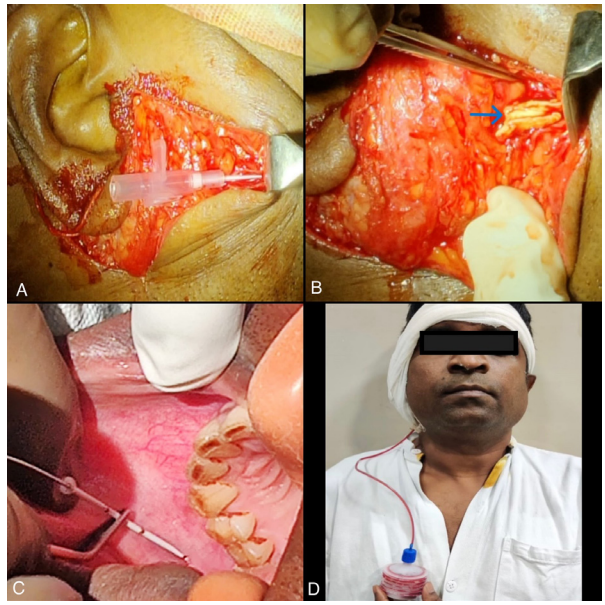

Figure 3. Combined approach parotid sialendoscopy A. Modified Blair incision with flap elevated and localization of duct (pink intravenous cannula was inserted in the parotid duct as a marker) B. Blue arrow: stone visualized through external incision C. Stenting of parotid duct D. Postoperative picture of patient with Minivac drain *in situ*

Table 1. Presenting symptoms in patients with sialolithiasis of submandibular or parotid duct

Presenting symptoms	Submandibular		Parotid	
	No. of patients	Percentage	No. of patients	Percentage
H/o* swelling	10	100	2	100.00
Increase with meals	8	80	2	100
Decrease on massage	8	80	2	100
H/o pain	8	80	2	100
Recurrent attacks of sialadenitis	1	10	1	50
Passage of gritty material	1	10	1	50
Pus discharge in saliva	2	20	2	100

H/o*: History of

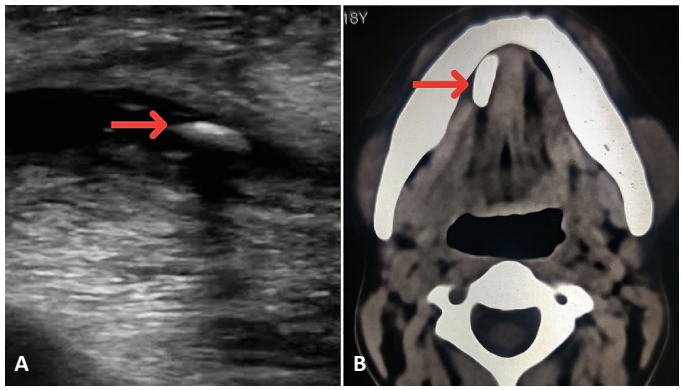

Figure 4. A. Sialoliths seen on ultrasonography with a dilated duct B. Sialolith seen in submandibular duct on CT scan

CT: Computed tomography

Post procedure stent was placed to maintain proper salivary flow in seven of the submandibular duct patients and the rest underwent duct marsupialization while in case of parotid duct all patients were stented. Almost all patients complained of mild pain and swelling in the first postoperative 24 hours that subsequently subsided with analgesics. Postoperative complications like long standing swelling, false passage, duct extirpation requiring emergency gland removal were not seen in any of the patients.

Following initial surgical intervention for submandibular sialolithiasis, recurrence of symptoms occurred after five months in one patient. This was managed with anti-inflammatory medication and antibiotics, followed by a repeat diagnostic sialendoscopy which revealed a mild ductal stenosis that was not diagnosed during the first procedure and no residual sialolith. Subsequently, the patient received weekly intraductal steroid injections for four weeks that lead to resolution of symptoms. On following up the patient for the next six months there was no further recurrence noted.

Another patient with parotid sialolithiasis experienced symptomatic recurrence six months post procedure. Repeat sialendoscopy unveiled residual intraductal debris, which was meticulously cleared through targeted irrigation with a diluted steroidal solution. The intervention resulted in substantial symptomatic relief, reaffirming the efficacy of endoscopic management in recurrent sialolithiasis.

Discussion

Our study of 12 patients included chronic obstructive sialadenitis due to sialolithiasis which were all managed by sialendoscopy with a combined approach.

The age distribution of the patients in our study was highly variable without any specific pattern but the mean age was 30 years. Capaccio et al. (2), similarly, reported to have found the incidence peaks of obstructive salivary gland diseases to occur between 30-60 years of age. The most common indication for sialendoscopy in our study was sialolithiasis which is consistent with the study by Hald and Andreassen (3). The predominant clinical presentation among our patients was swelling of the affected gland region and intermittent pain exacerbated by food intake, referred to as "meal-time syndrome" (4).

Ultrasonography serves as a primary investigative tool for obstructive sialadenitis, accurately diagnosing most cases, including sialolithiasis (5). However, owing to its superior spatial resolution and sensitivity to calcification, CT is advantageous in acute sialadenitis and for detecting very small calculi. Unlike conventional sialography, which necessitates contrast dye injection, often associated with patient discomfort and potential sialolith dislodgement, CT imaging offers a non-invasive alternative that typically obviates the need for contrast agents, thereby enhancing patient safety (6) A preoperative CT was also helpful in surgical planning in cases where a combined approach would be required as it gives the exact location and orientation of the calculus (7). Magnetic resonance sialography is reserved for cases in which ultrasonography and CT yield inconclusive results in ductal pathology detection, offering excellent delineation of the ductal system (8). When radiology is inconclusive for chronic sialadenitis, diagnostic sialendoscopy is an excellent

Table 2. Technique of combined approach undertaken for each case

Sl/no	Duct/Gland involved	Size of calculi	Location of calculi	Approach	Stenting
1	SMG	15x6 mm	Distally	Duct slitting and marsupialization	No
2	SMG	6.7x5 mm	Proximally	Duct slitting	Yes
3	P	12x5 mm	Distally	External incision	Yes
4	SMG	7x6 mm 3x2 mm	Distally Proximally	Duct slitting	Yes
5	SMG	7x3 mm	Distally (near ostium)	Duct slitting and marsupialization	No
6	SMG	6.5x3 mm	Proximally	Duct slitting	Yes
7	SMG	25x15 mm	Proximally	Duct Slitting	Yes
8	SMG	10x6 mm	Distally	Duct slitting	Yes
9	SMG	20x5 mm	Distally	Duct slitting and marsupialization	No
10	P	8x3 mm	Distally	External incision	Yes
11	SMG	14x5 mm	Distally	Duct slitting	Yes
12	SMG	8x4 mm	Distally	Duct slitting	Yes

SMG: Submandibular duct, P: Parotid duct

option. It allows for both identification and treatment of pathology in one procedure.

The traditional approach to obstructive salivary gland diseases that included sialadenectomy was associated with several postoperative complications like nerve injury, and loss of salivary gland function and was aesthetically unsatisfactory. Our minimally invasive approach of sialendoscopy prevented all such complications. Various instruments like burr, forceps, and Dormia's basket can be used for fragmentation and retrieval of the calculus during sialendoscopy. Alternative modalities such as extracorporeal or laser intraductal lithotripsy are often very costly, time-intensive, and carry a significant risk of residual stone fragments, rendering them suboptimal for the management of large sialoliths as encountered in our study (9).

In our study, the combined approach proved to be beneficial for the larger stones as they were not suitable for removal with conventional sialendoscopic intraductal techniques. Intraoral submandibular duct slitting is a viable option for submandibular duct calculi, with careful dissection to preserve the lingual nerve (10). Post procedure, the duct can be either stented or marsupialized. For larger calculi in the parotid duct, after localizing the calculus with sialendoscopy, an external incision is made, and a preauricular flap is raised to expose the parotid duct, facilitating external retrieval of the calculus. Such a technique of localizing the stone before external incision was described by McGurk et al. (8), a modified version of Nahlieli et al.'s (11) technique. The indications for the use of an external approach in cases of parotid duct stones were previously described by Nahlieli et al. (11) for stones positioned in the proximal one-third of Stensen's duct, in ducts with narrow diameter, stones larger than 5 mm, and for intraparenchymal stones (12). The use of a combined approach sialendoscopy helps in preserving the salivary glands and is thus superior to gland removal (13).

The success rate of combined approach sialendoscopy in our study was 100% with resolution of symptoms in the postoperative period, which can be compared to the 95% success rate in the review article on efficacy of combined approach submandibular sialolithiasis by Askoura et al. (14).

The two postoperative sequelae seen in most of our patients were swelling and pain within the initial 24 hours of surgery. Notably, swelling persisted beyond this timeframe in 50% of cases for which frequent self-massage was advised (15). It gradually resolved in all cases over the subsequent week. Other major complications like false passage or duct extirpation requiring emergency removal of the gland were not encountered in any of our patients.

Recurrence of symptoms was noted in two patients-one with submandibular and one with parotid sialolithiasis-who subsequently underwent successful repeat sialendoscopy at postoperative five and six months, respectively. This underscores the procedure's reproducibility without any contraindications (16).

Sialendoscopy is a minimally invasive surgery and greatly preferred over conventional sialadenectomy. It is a functionally superior procedure with lesser chances of neurological damage and much less morbidity.

The major drawbacks of this procedure are the high learning curve and the expensive setup it requires. Despite these limitations, sialendoscopy should be regarded as the primary approach for managing obstructive salivary gland diseases whenever it is available.

The strengths of this study lie in its comprehensive, stepwise protocol for performing combined approach sialendoscopy, offering valuable procedural guidance. However, a notable limitation is the relatively small sample size, attributable to the paucity of patients presenting with large sialoliths exceeding 6 mm in size.

Conclusion

In the modern era of advanced endoscopic techniques, sialadenectomy for obstructive salivary gland pathology is obsolete. Sialendoscopy, being a minimally invasive technique, is functionally much superior and prevents major complications related to sialadenectomy. A combined approach sialendoscopy further broadens the scope in cases of larger and proximal sialoliths and is also helpful in cases where newer technologies like laser/lithotripsy are not feasible.

Ethics

Ethics Committee Approval: The study received approval from the Institutional Ethics Committee (IEC)-III Relating To Biomedical And Health Research (BHR). [IEC (III)/OUT/39/2022] on 12 January 2022 with project number EC/100/2021 and was conducted in compliance with ethical standards.

Informed Consent: Informed consent was obtained from the patients using the format approved by the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.N., M.S., A.S., Concept: M.N., Design: M.N., M.S., Data Collection and/or Processing: A.S., M.J., P.S., A.J., Analysis and/or Interpretation: M.S., A.S., M.J., P.S., A.J., Literature Search: M.S., M.J., P.S., A.J., Writing: M.S.

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

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Main Points

- Obstructive salivary gland diseases represent half of the salivary gland diseases and sialolithiasis is the most common.
- Sialendoscopy has replaced conventional sialadenectomy in the management of sialolithiasis cases.
- Combined approach sialendoscopy broadens the scope of sialendoscopy manifold.
- This ambispective study describes the advantages of combined approach sialendoscopy achieved in 12 patients in a tertiary care center.

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Retrospective Analysis of Hemorrhage After Pediatric Tonsillectomy

Original Investigation

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Abstract

Objective: This study was conducted to retrospectively analyze pediatric tonsillectomy in patients aged <18 years treated over the past five years, focusing on factors such as sex, surgical method, season of occurrence, transfusion requirement, and surgical intervention in patients presenting with post-tonsillectomy hemorrhage.

Methods: Tonsillectomies performed in the Otorhinolaryngology Clinic of the Kayseri City Training and Research Hospital between June 2019 and June 2024 were retrospectively analyzed using the hospital information management system. Patients re-admitted for post-tonsillectomy secondary hemorrhage were identified, including those managed conservatively, requiring surgical intervention, and/or needing blood transfusion. Hemorrhage incidents were categorized by season (warm: March-August; cold: September-February), and hemorrhage rates were calculated. Surgical methods and the first surgical techniques in patients presenting with hemorrhage were recorded.

Results: In total, 4,994 tonsillectomies had been performed in the study period. Sixty patients (1.20%) were re-admitted and hospitalized due to postoperative hemorrhage, of whom 22 (0.44%) were reoperated and 38 (0.76%) were managed conservatively. Ten patients (0.20%) needed transfusion. Of the patients presenting with hemorrhage, 39 (65%) were admitted during the warm season, and 21 (35%) during the cold season. The cold dissection technique was used in 95.03% of the cases, with a hemorrhage rate of 1.2%.

Conclusion: Tonsillectomy is a common procedure worldwide and post-tonsillectomy hemorrhages are a frequent complication. Reducing morbidity and mortality through preventive strategies is crucial. Patients presenting with post-tonsillectomy hemorrhage should be hospitalized, monitored closely, and evaluated with hemogram and coagulation tests to assess hemorrhage volume and transfusion needs.

Keywords: Palatine tonsil, pediatrics, postoperative hemorrhage, seasons, tonsillectomy

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Introduction

Tonsillectomy is the most common surgery performed by otolaryngologists worldwide. In the United States, more than 500,000 children undergo tonsillectomy each year (1). Although these procedures are generally performed as day surgeries, the management of complications varies depending on the case. Hemorrhages following tonsillectomy are classified as early (primary hemorrhages) if they occur within the first 24 hours after surgery and as late (secondary hemorrhages) if they occur after 24 hours. Post-tonsillectomy hemorrhages are typically seen in 2% to 5% of the cases and remain the most common complication, causing concern for patients and their families and often necessitating hospitalization (2-4).

Numerous studies in the literature have examined various factors influencing postoperative hemorrhage after tonsillectomy, but there is still no universally accepted guideline for managing patients with postoperative hemorrhage (5). Depending on the patient's clinical condition, management may involve hospitalization, bedside procedures (chemical or electrocauterization), topical vasoconstriction (such as ice mouthwash with adrenaline), or in some cases, interventions under general anesthesia. The presented study was conducted to retrospectively analyze the incidence and characteristics of pediatric patients who experienced hemorrhage after tonsillectomy.

Methods

Pediatric patients who underwent tonsillectomy between June 2019 and June 2024 at the, University of Health Sciences Türkiye, Kayseri City Training and Research Hospital were retrospectively studied. Late (secondary) hemorrhage cases were included in the study. The number of hemorrhages, number of reoperated patients, season of occurrence, transfusion requirements, surgical methods used (cold dissection, bipolar electrocauterization, thermal welding), and hemorrhage rates according to surgical methods were analyzed. The season of the occurrence was categorized into two groups: warm season (March to August) and cold season (September to February). Patients with known preoperative or postoperative bleeding disorders or missing data were excluded from the study. Ethics approval was obtained from the Local Ethics Commitee of the, University of Health Sciences Türkiye, Kayseri City Training and Research Hospital (decision no: 153, decision date: 30.07.2024). Written informed consent was obtained from patients' parents. Tonsillectomies were performed using cold dissection, bipolar electrocauterization or thermal welding methods.

Statistical Analysis

Descriptive statistical methods were used to summarize the data. Categorical variables such as sex, surgical technique, hemorrhage status, and season of operation were presented as frequencies and percentages. Continuous variables including age were expressed as mean values with accompanying ranges. Hemorrhage rates were calculated as proportions relative to the total number of surgeries and were further stratified according to surgical technique and season. These descriptive statistics provided a clear overview of patient demographics, procedural distributions, and hemorrhage patterns.

Results

Paediatric tonsillectomy surgeries were performed in 4,994 patients in the Otorhinolaryngology Clinic of the, University of Health Sciences Türkiye, Kayseri City Training and Research Hospital between June 2019 and June 2024. Of these, 2,179 (43.64%) were female and 2,815 (56.36%) were male. Their mean age was 6.33 years. The average age was 6.52 years in females and 6.18 years in males, with an overall age range of 2 to 17 years. Sixty (1.20%) of the patients who had undergone surgery were readmitted to the clinic and hospitalized because of postoperative hemorrhage. Of these, 22 (0.44%) needed reoperation for hemorrhage control, while 38 (0.76%) were managed conservatively (observation only, topical vasoconstriction, or chemical cauterization with silver nitrate sticks). The data is summarized in Table 1. The most commonly used surgical method was cold dissection (95.03%), followed by bipolar electrocauterization (3.26%) and thermal welding (1.70%). The hemorrhage rate was 1.2% with cold dissection, 1.22% with bipolar electrocautery and 1.17% with thermal welding (Table 2). In addition, 10 of the 60 patients (16.66%) who presented with hemorrhage after tonsillectomy needed transfusion, and all of these patients underwent reoperation for hemorrhage control. In the study, 0.20% of the total patients received a transfusion. A total of 50.84% of the surgeries were performed in the warm season, and 49.15% in the cold season. Among the 60 patients with postoperative hemorrhage, 39 (65%) were admitted during the warm season, and 21 (35%) during the cold season (Table 3). The hemorrhage rate was 1.53% in the warm season and 0.85% in the cold season.

Discussion

Postoperative hemorrhage is one of the most common complications of tonsillectomy (6). While it can be managed conservatively in some cases, postoperative hemorrhage can also be severe enough to require surgical intervention (7). Numerous studies have investigated the effect of surgical techniques on hemorrhage rates (8-10). For instance, intracapsular tonsillectomy, performed using the coblation technique in a study with 730 patients, has been reported to have a lower hemorrhage rate than traditional extracapsular tonsillectomy, with an estimated rate of 0.28% (11). In another study comparing the cold dissection, thermal welding, and bipolar electrocauterization methods, no significant differences

Table 1. Demographic details and hemorrhage rates

Parameter	Count	Percentage (%)
Total tonsillectomies	4,994	-
Sex (female/male)	2,179/2,815	43.64/56.36
Average age (all patients)	6.33	-
Average age (female/male)	6.52/6.18	-
Overall age range (years)	2-17	-
Female/male age range (years)	2-17/2-17	-
Total hemorrhages	60	1.2
Conservative management	38	0.76
Reoperation	22	0.44
Blood transfusion	10	0.20

Table 2. Surgical technique and hemorrhagic outcomes

Surgical method	count	Percentage (%)
Cold dissection	4,746	95.03
Thermal welding	85	1.7
Bipolar electrocautery	163	3.26
Surgical method	**Hemorrhage cases**	**Bleeding rate (%)**
Cold dissection	57	1.20
Thermal welding	1	1.17
Bipolar electrocautery	2	1.22

Table 3. Seasonal distribution of hemorrhage occurrences (warm vs. cold season)

Season	Total surgeries, percantage (%)	Hemorrhage casesv	Hemorrhage rate (%)
Warm season (March-August)	2,539 (50.84)	39	1.53
Cold season (September-February)	2,455 (49.15)	21	0.85

in hemorrhage rates were observed (10). The heterogeneity in study numbers, patient ages, and methodologies has led to differing opinions on which surgical method is the safest. In another study, retrospective data from 15,734 patients obtained from the Swedish National Tonsil Surgery Register were analyzed, demonstrating that tonsillectomy performed using the cold technique with cold hemostasis had the lowest hemorrhage rate compared to all hot techniques in terms of post-tonsillectomy hemorrhage (12).

A national study conducted in England and Northern Ireland with 33,291 individuals demonstrated that the use of hot surgical techniques during both tonsil dissection and hemostasis increased the risk of hemorrhage threefold compared to the cold dissection method. On the other hand, in operations where bipolar or monopolar cautery was used for hemostasis following cold dissection, the risk of hemorrhage was found to be approximately 1.5 times higher compared to cold dissection operations in which sutures or packing were used. The results emphasized the presence of a "dose-response relationship" between cautery use and hemorrhage rate (13).

In our study, while hemorrhage rates were similar in tonsillectomies performed using cold dissection, thermal welding, and bipolar electrocauterization, cold dissection was the most used method. In our clinic, where the cold technique is taught as a basic technique in resident training, the cold dissection method is the most frequently used approach and has the lowest bleeding rates, which is consistent with the literature.

In our retrospective study, post-tonsillectomy hemorrhage rate was 1.20%. In the literature, this rate can be as high as 12.3%, with 4.2% of these patients needing reoperation for hemorrhage control (14). Hemorrhage rates reported in the literature are heterogeneous. For example, Blakley (15) reported a rate of 5%, while Tolska et al. (16) reported 14.5%. In a study conducted by Çelikal et al. (17), three surgical techniques were compared in pediatric groups (infant, early childhood, preadolescent, and adolescent). In this study the overall hemorrhage rate was found to be 3.7%.

Öcal et al. (18) reported a 3.4% secondary hemorrhage rate following tonsillectomy in pediatric patients. The variability in these rates can be attributed to several factors. There is no consensus in the literature on which findings should be classified as post-tonsillectomy hemorrhage. In our clinic, we recommend hospital admission if blood is observed even in saliva. Although Walner and Karas (19) proposed a classification system for hemorrhage after tonsillectomy, no universally accepted system currently exists. The significant differences in reported rates could result from variations in the criteria used to define hemorrhage. For instance, Windfuhr et al. (20) considered only hemorrhages requiring surgical intervention as post-tonsillectomy hemorrhages in both pediatric and adult groups, reporting a rate of 5.2%. Conversely, hemorrhage rates in the pediatric age group are generally lower than those in adults (21). Another factor contributing to the heterogeneity in hemorrhage rates is the surgeon's level of experience. Studies indicate an inverse relationship between surgical experience and post-tonsillectomy hemorrhage rates (22,23). For example, a study by Kim et al. (21) showed that postoperative hemorrhage rates were lower for surgeries performed by specialists than for those performed by residents.

Mortality rates after tonsillectomy vary between studies. In general, the mortality rate after pediatric tonsillectomy is quite low, with rates ranging from 1/500,000 to 7/100,000 reported in the literature (24,25). In our retrospective study, no major mortal complications were seen among the 4,994 patients. Additionally, 50.84% of tonsillectomies were performed in the warm season and 49.15% in the cold season. The hemorrhage rate was 1.53% in the warm season and 0.85% in the cold season. Seasonal factors are deemed to influence tonsillectomy hemorrhage rates, as some studies have reported higher rates during the winter months (26). Conversely, other studies have shown higher hemorrhage rates in both winter and summer months, suggesting a bimodal pattern (27). These findings indicate that seasonal infections and weather conditions can increase the risk of hemorrhage after tonsillectomy. For instance, the higher prevalence of upper respiratory tract infections during winter months can increase the risk of tonsil tissue infection and subsequent postoperative hemorrhage.

The management of tonsillectomy hemorrhage typically begins with conservative measures, but severe cases can necessitate surgical intervention or blood transfusion. The study conducted in England and Northern Ireland highlighted that approximately 1.3% of patients experienced complications that necessitated blood transfusion (13). In our study, 0.20% of the patients received transfusion, and all of them needed hemorrhage control under operating theater conditions. The decision to transfuse is influenced by factors such as the volume of blood loss and the patient's hemodynamic status, with timely transfusion being potentially life-saving in cases of significant blood loss (28).

Our study has some limitations. These include its retrospective design, the reliance on data from a single tertiary care hospital, and the unbalanced distribution of surgical methods. Additionally, the impact of seasonal variations and the surgeons' experience levels on hemorrhage rates could not be analyzed in detail.

Conclusion

In this study, we retrospectively analyzed hemorrhage following pediatric tonsillectomy, examining the effects of factors such as the surgical methods used and the season in which the surgery was done. Our findings showed that the hemorrhage rate was higher in tonsillectomies performed in the warm season, and the hemorrhage rates were similar across the different surgical techniques. When patients were classified according to the surgical methods, statistical comparison was not performed due to the unequal distribution of patients between the groups. Among the surgical techniques, cold dissection was the most commonly used method.

Patients presenting with hemorrhage after tonsillectomy should be hospitalized, transfusion preparations should be made as necessary, and vital signs should be closely monitored. However, multicenter prospective studies are required to further evaluate factors such as seasonal variations due to geographical differences and the influence of the surgeon's experience level, and the impact of surgical techniques on hemorrhage rates.

Ethics

Ethics Approval: Ethics approval was obtained from the Local Ethics Commitee of the, University of Health Sciences Türkiye, Kayseri City Training and Research Hospital (decision no: 153, decision date: 30.07.2024).

Informed Consent: Written informed consent was obtained from patients' parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.Ü., E.H.B., S.B.Ç., Y.K., A.K., M.Y., İ.Ö., A.B., Concept: N.Ü., İ.Ö., Design: N.Ü., E.H.B., Data Collection and/or Processing: N.Ü., E.H.B., Analysis and/or Interpretation: Y.K., Literature Search: N.Ü., E.H.B., Writing: N.Ü., E.H.B., S.B.Ç., Y.K., A.K., M.Y., İ.Ö., A.B.

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Main Points

- Post-tonsillectomy hemorrhage rates were higher during the warm season (1.53%).
- Hemorrhage rates were similar across different surgical techniques; however, cold dissection was the most commonly used and considered the safest method.
- Patients with post-tonsillectomy hemorrhage should be closely monitored with surgical intervention and blood transfusion applied when necessary, emphasizing the need for standardized management protocols and consideration of seasonal factors.

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Can Dizziness Be Related to Insomnia Severity and Sleep Quality in Young Adults?

Original Investigation

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Abstract

Objective: Despite the many medical problems arising from sleep disturbances, few studies have been conducted on vestibular disorders. In this study, we aimed to investigate the relationship between dizziness, sleep quality, severity of insomnia and duration of sleep, in young adults with dizziness.

Methods: Forty-nine individuals aged 20-40 years, with normal hearing and complaints of dizziness with an unknown origin were included. The Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), and the Dizziness Handicap Inventory (DHI) were used.

Results: There was a very strong positive correlation between the PSQI and the ISI (r=0.838, p<0.001). Strong positive correlations were observed between PSQI and the total DHI scores (r=0.660, p<0.001), as well as between ISI and DHI scores (r=0.673, p<0.001). In addition, both PSQI and ISI showed strong positive correlations with the physical subscale of the DHI (r=0.673 and r=0.662, respectively; p<0.001 for both). A significant positive correlation was also found between the daytime dysfunction component of the PSQI and the total DHI score (r=0.640, p<0.001). Moreover, sleep duration was moderately and negatively correlated with the emotional subscale of the DHI (r=-0.454, p=0.001), indicating that shorter sleep duration was associated with greater emotional impairment related to dizziness.

Conclusion: Our study showed a high correlation between sleep quality, insomnia severity and dizziness in young adults with dizziness. With inventory, clinicians can contribute to improving people's quality of life by detecting dizziness associated with sleep disorders.

Keywords: Sleep disorders, vestibular diseases, dizziness, insomnia, sleep quality, surveys and questionnaires

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Introduction

Dizziness is a common symptom seen in neurology and ear, nose and throat (ENT) clinics and generally follows a chronic course (1). In large population studies, dizziness is reported to affect approximately 15-20% of adults (2,3).

Patients with dizziness can experience both physical and mental effects. Some deterioration in the quality of life may

occur, especially with the effect of psychosocial factors (1). In a study of the social and individual impact of dizziness, 40% of the participants with dizziness indicated that the condition interrupted their daily activities, 41% took sick leave and 19% avoided leaving home (4). The severity of dizziness and its effect on quality of life can be measured using scales or questionnaires (5).

One of the complaints associated with dizziness is insomnia, and studies have shown that patients with dizziness have a high rate of sleep disturbance and sleep quality affects dizziness (6-9).

Although the meaning of sleep quality varies from person to person, it is defined as an individual's subjective assessment of their sleep experience, integrating aspects of sleep onset, sleep duration, sleep maintenance, and well-being upon awakening (10). However, the severity of insomnia is related to the degree of insomnia symptoms (11).

Sleep imbalance can affect people's quality of life by causing physical and psychological effects (12,13). Sleeping less than seven or eight hours have been associated with some diseases, traffic accidents, and work failures (14,15). Differences in sleep duration may be due to various factors such as age, socio-economic level, and general health status (12).

Human studies suggest a relationship between sleep and vestibular function. The vestibular system is responsible for the perception of head position. It has been hypothesized that the system could play a role in its onset and duration of sleep (16). In particular, it has been shown that sleep deprivation in humans can lead to changes in the posterior parietal cortex, a region that plays a crucial role in processing vestibular data regarding spatial representation (17). Animal studies indicate that the vestibular system modulates circadian rhythms, working in conjunction with input from somatosensory and visual systems (18,19).

Decreased sleep quality or sleep deprivation can affect physical functions, including postural balance, with reduced ability to adapt and selective attention (20,21). Conversely, in patients with chronic dizziness, sleep disturbances can further complicate the severity of dizziness and handicaps caused by dizziness (8).

Despite the many medical problems arising from sleep disturbances, few studies have been conducted on vestibular disorder cases (7,8).

Dizziness and sleep problems are believed to be two conditions that trigger and influence each other. This situation creates a vicious circle (22). Fewer variables can affect sleep quality or intensity in young adults than in older adults (23). Therefore, to eliminate the age effect, the study group of this study consisted of individuals aged between 20-40 years.

Accordingly, we aimed to study the relationship between the quality of sleep, the severity of insomnia, and the duration of sleep and dizziness among young adults. Furthermore, no study comparing subgroups of young people with subjective tests has been found in the literature. Therefore, sleep-related correlations of the subgroups of the Dizziness Handicap Inventory (DHI) were also examined in the study. The study is based on the hypothesis that dizziness may have an impact on sleep quality and insomnia severity in young adults, and further on the postulate that dizziness can affect sleep duration.

Methods

This work was approved by the Non-Interventional Clinical Research Ethics Committee of İstanbul Aydın University (approval no: 2019/114, date: 19.06.2019) and all participants included in the study signed an informed consent form.

Inclusion Criteria

Forty-nine participants (21 female and 28 male) between the ages of 20-40 years with normal hearing and complaints of dizziness of unknown origin for at least one month were included in the study.

ENT and neurological examinations, and audiovestibular assessments were done. Participants with neurological, systemic, psychiatric, and otologic diseases and regular medication use were excluded from the study.

After ENT and neurological examinations of the participants who applied to İstanbul Aydın University Audiology Laboratory between January and May 2019, pure tone audiometry evaluations were performed in a soundproof booth using a clinical audiometer (Interacoustics AC40, Interacoustics A/S, Middelfart, Denmark) with supra-aural headphones between 500-4000 Hz. Hearing thresholds ≤25 dB HL were considered normal. Acoustic immitancemetry (Interacoustics Titan Tympanometer, Interacoustics A/S, Middelfart, Denmark) was used for the middle ear and acoustic reflex evaluation of the participants. Type A tympanogram (peak is between -100 and +50 daPa; compliance from 0.3-1.6 mL) and the presence of acoustic reflexes were defined as inclusion criteria in the study.

Vestibular system examinations were performed using videonystagmography (VNG) [Otometrics International Clinical Systems (ICS) Chartr 200, Natus Medical Incorporated, Middleton, USA] and the Video Head Impulse Test (vHIT) (Otometrics ICS Impulse, Natus Medical Incorporated, Middleton, USA). Spontaneous nystagmus, gaze, saccade, smooth pursuit, and optokinetic eye movements were evaluated with VNG. The presence of pathological nystagmus in the absence of gaze fixation was defined as nystagmus with a velocity of at least 6 degrees per second. For the saccade test, accuracy of <80%, latency of

>280° ms, and peak velocity of <300° were accepted abnormal. Furthermore, a gain of less than 70% was indicative of impairment in smooth pursuit.

A minimum of 20 impulses were performed for each canal. The vHIT analysis is contingent on VOR gain and the occurrence of refixation saccades. The normal range for gain values is 0.80-1.20 for horizontal semicircular canals, 0.70-1.20 for vertical ones.

Since no pathological condition was detected in vestibular evaluation, patients with a history of dizziness of unknown cause were evaluated.

Data Collection Tools

The following questionnaires were administered to the participants by the face-to-face method.

Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index (PSQI) is a 24- item scale developed by Buysse et al. (24), to assess sleep-related disorders and sleep quality over a one-month period. Nineteen questions scored on the scale are calculated to comprise seven components, namely, sleep duration, sleep latency, use of sleeping medications, sleep disturbances, habitual sleep efficiency, daytime dysfunction, and subjective sleep quality. Every component is scored between 0 and 3, with a total score between 0 and 21. A high total score is indicative of poor sleep quality. A PSQI total score ≥5 defines poor sleep quality (24).

Insomnia Severity Index

Insomnia Severity Index (ISI) was developed by Bastien et al. (11) to assess the severity of insomnia. Scale items consist of seven questions. Every item is evaluated within a range of 0-4, with a total score between 0 and 28. ISI comprises items designed to evaluate the sleep maintenance difficulties, severity of sleep onset, interference with daily functioning, satisfaction with current sleep patterns, degree of distress or concern resulting from sleep problems and noticeability of impairment attributed to sleep problems. With the scores obtained, the insomnia level results are: 0-7=no clinically significant insomnia, 8-14=subthreshold insomnia, 15-21=clinical insomnia (moderate severity), 22-28=clinical insomnia (severe) (11).

Dizziness Handicap Inventory

DHI was developed in 1990 by Jacobson and Newman (5). It consists of 25 items that determine emotional and functional outcomes in vestibular system diseases, as well as factors that aggravate dizziness and impaired balance. Sub-inventories are aimed at determining the physical, emotional, and functional effects of vestibular system diseases. Each question answered either "yes" (4 points), "sometimes" (2 points), or "no" (0 points) (5). In this study, DHI scores were categorized into the following ranges: 0-30 (mild handicap), 31-60 (moderate handicap), and 61-100 (severe handicap) (25).

Statistical Analysis

Pearson correlation analysis was performed to study the relationship between scores obtained from questionnaires and the relationship between sleep duration and DHI and its subscales. A p-value ≤0.05 was accepted as significant. SPSS v.23 software was used for statistical analysis. The correlation analysis evaluated according to Evans's classification (26).

Results

Twenty-one female and 28 male participants between the ages of 20-40 years (mean: 30.14±6.29) were included in the study and administered the PSQI, ISI, and DHI questionnaires. The mean of all three questionnaires is shown in Table 1. The patients were asked about their average sleep duration (hours) at night in the last month in their anamnesis and added to Table 1.

As seen in Table 1, DHI is 22.2±19.52, which means the participant group has an averagely mild dizziness handicap (61.22% of the participants had a mild handicap, 38.78% a moderate handicap).

Participants' mean PSQI scores were 7.89±4.01. In our study according to PSQI normal values-22.44% of the participants

Table 1. Descriptive statistics for DHI, PSQI, ISI, age, and sleep duration (n=49)

	Mean±SD
DHI	22.2±19.52
PSQI	7.89±4.01
ISI	11.14±7.11
Age (year)	30.14±6.29
Sleep duration (hrs)	6.12±1.50
Components of PSQI	
Subjective sleep quality	1.38±0.99
Sleep latency	1.89±0.94
Sleep duration	1.32±1.08
Habitual sleep efficiency	0.56±0.84
Sleep disturbances	1.26±0.63
Use of sleeping medications	0.28±0.70
Daytime dysfunction	1.18±0.99
Components of DHI	
Physical (P)	8.65±7.97
Emotional (E)	5.55±5.9
Functional (F)	8±7.3

DHI: Dizziness Handicap Inventory, ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index, SD: Standard deviation

had normal sleep quality, but 77.56% had poor sleep quality. That is, all participants with mild and moderate handicaps had 77.56% poor sleep quality.

The mean score obtained from the ISI scale is 11.14±7.11. These results indicate that the group was on subthreshold insomnia according to normal ISI values. Of the participants, 38.77% had no clinically significant insomnia, 26.53% had subthreshold insomnia, 26.53% had clinical insomnia (moderate severity), and 8.17% had clinical insomnia (severe).

The average sleep duration reported by participants in their anamnesis is 6.12±1.50 hours. This result is below the ideal sleep time (7 hours) (27). While 63.26% of our participants indicated to sleep less than 7 hours, the remaining 36.74% indicated to sleep more than 7 hours.

In the PSQI subgroups, the participants with dizziness complaints were most affected by sleep latency and least affected by sleeping medications. Among the DHI subgroups, physical exposure was found to be the most affected, and emotional impact the least (Table 1).

Error bars of DHI and PSQI subgroups, ISI, and sleep duration are given in Figure 1.

The correlations between the results of the questionnaires DHI, PSQI, and ISI were calculated (Table 2).

A significantly positive and strong correlation was found between DHI and PSQI (r=0.660, p<0.001) and between DHI and ISI (r=0.673, p<0.001) scores. And, as expected, a significantly positive and very strong correlation (r=0.838, p<0.001) was seen between PSQI and ISI scores (Table 2). Correlation curves are given in Figure 2.

A moderately significant negative correlation was found between DHI-Emotional (DHI-E) and sleep durations

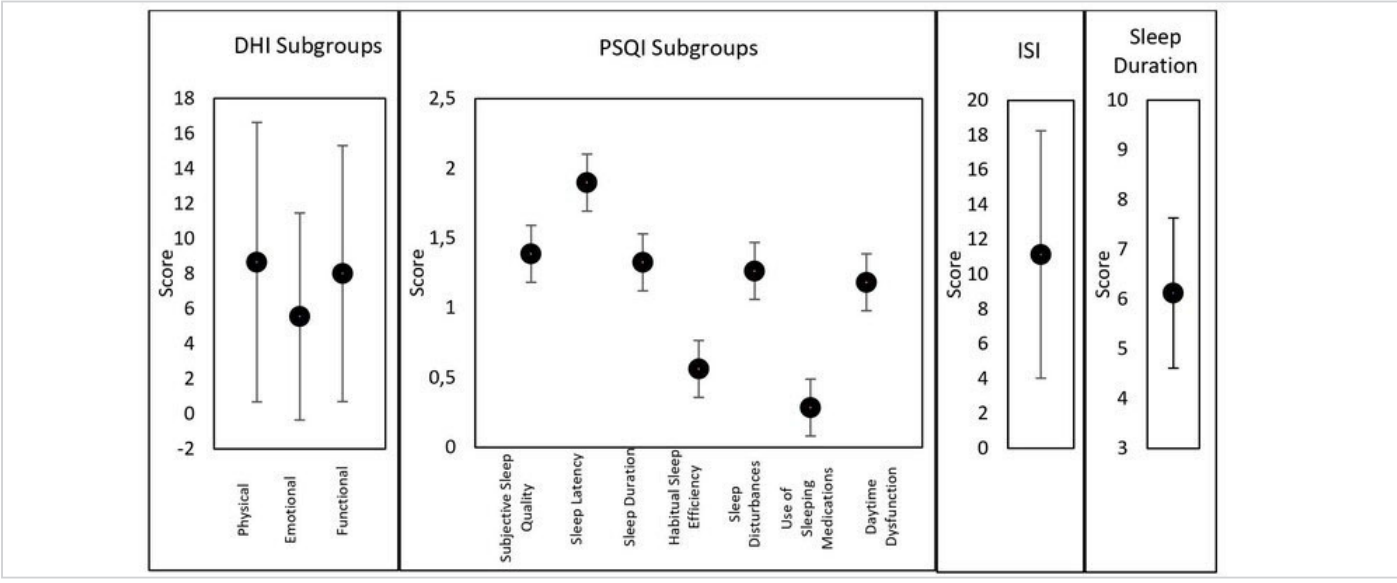

Figure 1. Error bars of DHI and PSQI subgroups, ISI, and sleep duration
ISI: Insomnia Severity Index, DHI: Dizziness Handicap Inventory, PSQI: Pittsburgh Sleep Quality Index

Table 2. Correlation and significance values of DHI, PSQI, and ISI questionnaires and DHI and sleep duration (hrs) relationship (n=49)

	Pearson correlation (r)	p-value
DHI*PSQI	0.660**	<0.001
DHI*ISI	0.673**	<0.001
PSQI*ISI	0.838**	<0.001
DHI*Sleep duration (hrs)	-0.390**	0.006
DHI-P*Sleep duration (hrs)	-0.312*	0.029
DHI-E*Sleep duration (hrs)	-0.454**	0.001
DHI-F*Sleep duration (hrs)	-0.335*	0.019

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), DHI: Dizziness Handicap Inventory, DHI-P: Dizziness Handicap Inventory-Physical, DHI-E: Dizziness Handicap Inventory-Emotional, DHI-F: Dizziness Handicap Inventory-Functional, ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index

(r=-0.454, p=0.001). A significantly weak and negative correlation was found between DHI and the sleep durations (hrs) of the participants (r=-0.390, p=0.006), between DHI-Physical (DHI-P) and sleep durations (r=-0.312, p=0.029), and between DHI-Functional (DHI-F) and sleep durations (r=-0.335, p=0.019).

Correlations between the participants' PSQI and ISI scores and the DHI subgroups were calculated and are shown in Table 3.

A significantly positive and strong correlation was found between DHI-P and PSQI scores (r=0.673, p<0.001), a significantly positive and moderate correlation between DHI-E and PSQI (r=0.562, p<0.001), and between DHI-F and PSQI (r=0.575, p<0.001) scores.

There was a positive and strong correlation between DHI-P and ISI (r=0.662, p<0.001) and between DHI-F and ISI (r=0.654, p<0.001) scores, and a significantly positive and moderate correlation between DHI-E and ISI (r=0.522, p<0.001) scores. Correlation curves are shown in Figure 3.

Correlations between the participants' DHI scores and PSQI subgroups were calculated and are shown in Table 4.

A significantly positive and strong correlation was found between DHI and daytime dysfunction subgroup scores (r=0.640, p<0.001), and a significantly positive and moderate correlation between DHI and sleep disturbances subgroup (r=0.521, p<0.001), between DHI and subjective sleep quality subgroup (r=0.514, p<0.001), and between DHI and sleep duration subgroup (r=0.440, p=0.002) scores, and a significantly positive and weak correlation between DHI and sleep latency (r=0.353, p=0.013) scores.

Discussion

Symptoms of insomnia can range from mild to severe and even lead to mortality. Moreover, many individuals may be at risk of falling due to dizziness (28). While the relationship between sleep quality and dizziness in older adults has been widely studied-partly due to the presence of more confounding factors-fewer variables are known to affect both in young adults, and this population has been studied less. Therefore, this study focused on young adults with dizziness, investigating the relationship between sleep quality, insomnia severity, and dizziness.

Our study, inconsistent with literature, showed a significantly positive and strong correlation between the DHI and PSQI

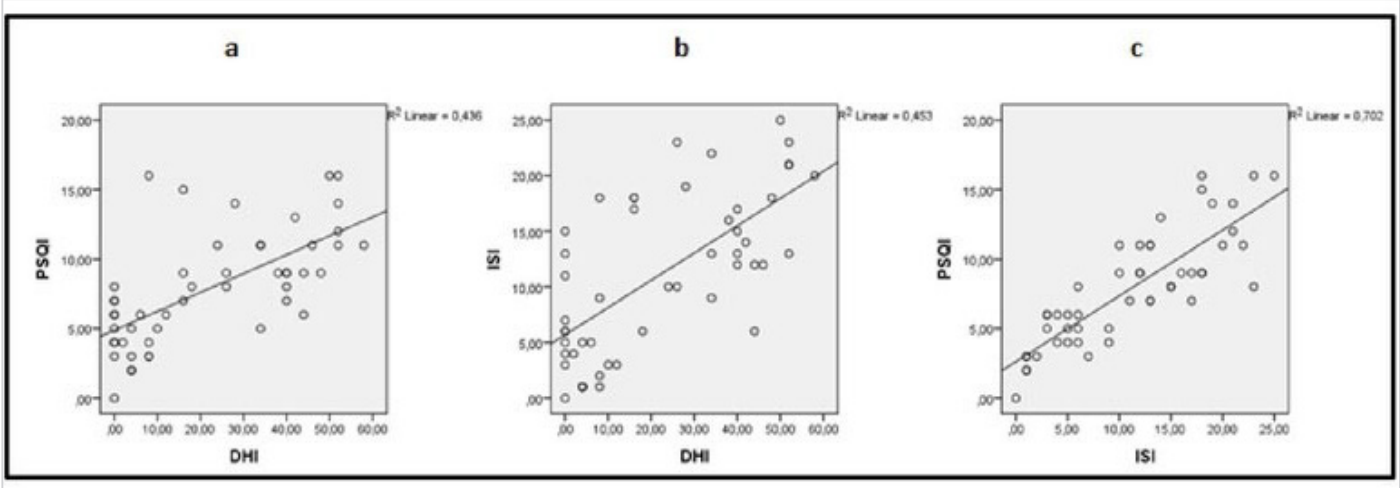

Figure 2. Correlation curves (a- DHI and PSQI, b- DHI and ISI, c- PSQI and ISI)
ISI: Insomnia Severity Index, DHI: Dizziness Handicap Inventory, PSQI: Pittsburgh Sleep Quality Index

Table 3. Correlation and significance values of PSQI and ISI questionnaires with DHI subgroups (n=49)

	PSQI		ISI	
	Pearson correlation (r)	**p-value**	**Pearson correlation (r)**	**p-value**
DHI-P	0.673**	<0.001	0.662**	<0.001
DHI-E	0.562**	<0.001	0.522**	<0.001
DHI-F	0.575**	<0.001	0.654**	<0.001

**Correlation is significant at the 0.01 level (2-tailed), DHI: Dizziness Handicap Inventory, DHI-P: Dizziness Handicap Inventory-Physical, DHI-E: Dizziness Handicap Inventory-Emotional, DHI-F: Dizziness Handicap Inventory-Functional, ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index

scores in young adults. As the sleep quality score increased, the DHI score also increased, which means increasing complaints of dizziness highly impairs sleep quality (7,9). Studies have emphasized that an increase in anxiety about insomnia should be taken into consideration as it may in turn increase the feeling of dizziness (7). Few studies have examined sleep quality in patients with dizziness. The findings of Kim et al. (9) demonstrated that these two problems are also associated with poor quality of life and emotional stress. Vestibular function and sleep quality can affect each other like a vicious circle, causing the symptoms to exacerbate (6-8).

Table 4. Correlation and significance values of DHI and PSQI subgroups (n=49)

	DHI	
PSQI	**Pearson correlation (r)**	**p-value**
Subjective sleep quality	0.514**	<0.001
Sleep latency	0.353*	0.013
Sleep duration	0.440**	0.002
Habitual sleep efficiency	0.209	0.154
Sleep disturbances	0.521**	<0.001
Use of sleeping medications	0.246	0.088
Daytime dysfunction	0.640**	<0.001

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), DHI: Dizziness Handicap Inventory, ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index

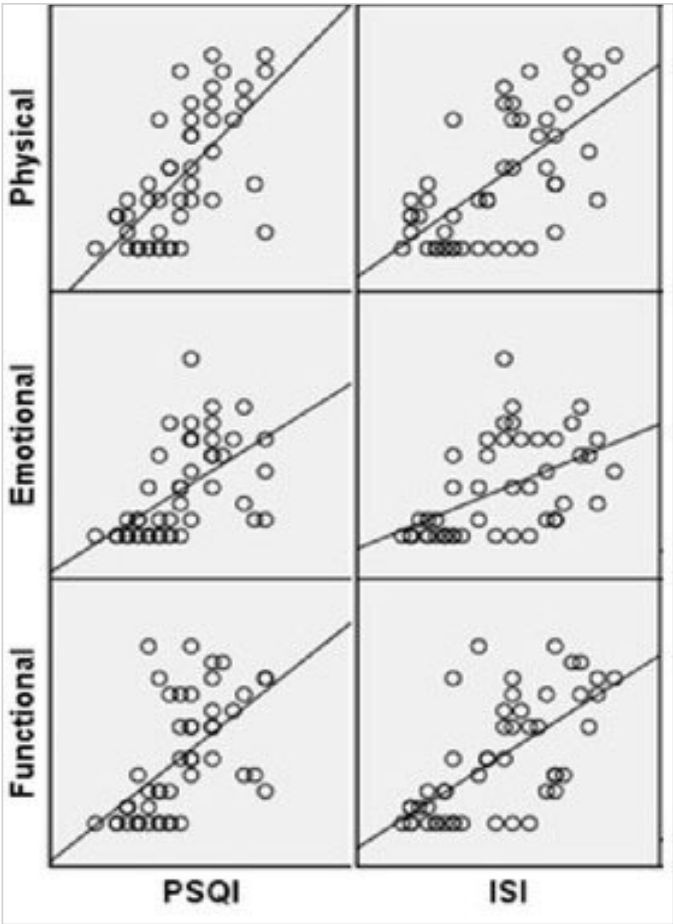

Figure 3. Correlation curves of PSQI and ISI with DHI subgroups ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index

The findings of this study revealed that the ISI and DHI scores are significantly positive and strongly correlated. According to these findings, the impact of dizziness on quality of life and the severity of insomnia increase parallelly. In another study, DHI and ISI results showed a significant correlation in all evaluated vestibular diseases like vestibular migraine, benign paroxysmal positional vertigo in participants aged 11-78 years (9).

In our study, the correlations between DHI subscales and PSQI and ISI were also analyzed. The correlations of the DHI-P subscale with the other two were significantly stronger than the other DHI subscales. In one study, it was observed that only DHI-Physical scores were significantly increased in patients with more severe obstructive sleep apnea (OSA) in the 23-70-year age range (29). PSQI and ISI were thought to be more related to the physical domain, as sleep problems in patients with dizziness directly affect the essential needs in daily life (21).

All these studies have examined patients with dizziness in the elderly group or in a wide range of ages with etiology, like vestibular disorders and OSA. Our study investigated dizziness, sleep quality, and insomnia severity from two different perspectives: one is that our study group, referred to our clinic with major dizziness symptoms, includes young adults aged 20-40 years. Second is that unknown origin was seen in this group. To the best of our knowledge, there is no other study in the literature that has studied a group with unknown cause of dizziness.

The correlation between PSQI subscales and DHI was also analyzed in our study. The correlation between the daytime dysfunction subscale with DHI was significantly stronger than the other PSQI subscales. DHI was developed by Jacobson and Newman (5) to measure the effect of dizziness on daily activities, therefore, given the content of the DHI questionnaire this correlation was expected.

Albathi and Agrawal (16) studied the relationship between vertigo and sleep duration with 20,950 participants aged 18-85 years. The authors found that these two conditions were correlated with each other, and sleep durations were shorter in individuals with vertigo. Another study found that patients with bilateral vestibular loss had shorter sleep durations and abnormal sleep patterns compared to the control (30). In our study, consistent with the literature, significantly negative

and weak correlations were found between sleep durations and the DHI total score. It was observed that individuals with high DHI scores had shorter sleep durations.

However, when correlations were examined separately for the subscales of DHI, the DHI-E subscale was found to have a negative moderate correlation with sleep duration. Unlike other DHI subscales, better correlations with DHI-E indicate that short sleep duration has an emotional impact on individuals. Research has indicated a correlation between sleep duration and depression (31,32). The correlations regarding the subscales that we examined in our study were not found in the literature. Knowing which of the DHI subscales affects patients more gives us information about the need for support in that area.

In our study, PSQI and ISI scores were significantly positive and very strongly correlated with each other. Our results are consistent with the literature where PSQI and ISI scores were found to be correlated with each other, especially in studies on the validity and reliability of the tests (33,34). The comparable results of the referred studies, which evaluate sleep quality and insomnia severity, also indicate that the participants in the study responded carefully and consistently during the measurement.

In the presented study, no evaluation was conducted for mental fatigue, attention, or stress factors that could affect the test results. This constitutes a limitation of the study.

Conclusion

To conclude, insomnia can occur as a result of dizziness or trigger dizziness in young adults. The problems brought about by dizziness affect people's quality of life. As sleep problems are not addressed in DHI, questioning sleep problems may be clinically effective in patients who present to vestibular clinics with the complaint of dizziness. It can provide a new perspective on the etiology of dizziness by helping in the diagnosis and treatment of dizziness in young adults. It can also be a guide for the rehabilitation of patients by facilitating a multidisciplinary approach. In addition, the evaluation made with DHI subscales helps to reveal the complaints of patients that are more closely related to sleep problems. Studies with larger samples and different age groups are needed to further investigate the relationship between dizziness and sleep.

Ethics

Ethics Committee Approval: This work was approved by the Non-Interventional Clinical Research Ethics Committee of İstanbul Aydın University (approval no: 2019/114, date: 19.06.2019).

Informed Consent: All participants included in the study signed an informed consent form.

Footnotes

Authorship Contributions

Concept: Ö.K., Design: Ö.K., Y.S., A.K.C., Data Collection and/or Processing: Y.S., A.K.C., Analysis and/or Interpretation: Ö.K., Y.S., Literature Search: Y.S., A.K.C., Writing: Ö.K., Y.S., A.K.C.

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

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Main Points

- Young adults with moderate dizziness handicaps are likely to have poor sleep quality.
- Individuals with a high dizziness handicap score may often have shorter sleep durations.
- Sleep problems can occur in young adults with dizziness of unknown origin.
- Sleep can affect the dizziness handicap subscales in different sizes.

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Compliance of ORL-HNS Journals in Türkiye with the Principles of Transparency

Original Investigation

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Abstract

Objective: Principles of transparency and best practice in scholarly publishing is one of the important standards for the functioning and publishing quality of peer-reviewed scientific journals. The aim of this study is to evaluate Turkish otorhinolaryngology, head and neck surgery (ORL-HNS) journals according to these principles and to point out the areas that need improvement.

Methods: This descriptive study is based on the evaluation of website contents of eight Turkish ORL-HNS journals according to the 16 principles of transparency criteria. The number of scientific papers published in 2020 and 2021 were retrieved from the respective websites of the journals. The impact factors were calculated by analyzing the citations in 2022 via Google Scholar. The probable relationship between impact factor and compliance with transparency principles was investigated. Impact factor and transparency principles were studied to draw attention to the international standards which can contribute to journals for international scholarly publishing.

Results: The journals highly comply with website publishing, ethics, access, and ownership criteria; however, most of them do not comply with advisory council, advertising, other income, and business practices criteria. While the first three journals with the highest impact factors comply with 12 to 14 of the 16 criteria, the last three comply with five to 12.

Conclusion: The journals with high transparency criteria scores and high impact factors suggest that these criteria are important in terms of the reliability and validity of the information, and citation. Moreover, the websites of Turkish scientific ORL-HNS journals were seen to need improvement according to the transparency criteria, especially regarding financial issues such as business, financial status, and advertising.

Keywords: Otorhinolaryngology, peer review, journal article, journal impact factor, scholarly publishing, best practice

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Introduction

Peer-reviewed scientific journals have made great contributions to the development of science. There are many scientific journals in many fields of expertise where scientific research results are revised and published with peer evaluation. Criteria for the functioning of these journals have been developed and published by various international organizations. One of these resources, the principles of transparency and best practice in scholarly publishing

was developed and first published in 2013 and revised in 2022 by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishing Association (OASPA), and the World Association of Medical Editors (WAME). The principles of transparency consist of 16 criteria related to publishing standards, such as name, website, publication calendar, archive, and license, which should be stated on the website of the journals (1).

Journals that meet the principles of transparency can be indexed by DOAJ. Especially in recent years, due to the increasing number of predatory journals, authors have begun to be more careful about not publishing in predatory journals. WAME developed a guide to identify predatory journals (2). One of the most important criteria of this guide for choosing a journal to submit a manuscript is whether the journal is indexed by DOAJ. Therefore, it has become important for journals to comply with the transparency principles developed by these four important international publishing organizations under the leadership of DOAJ. Studies have shown that this compatibility is related to publishing quality (3).

Regarding the advancements about scientific publishing, the publishing quality of journals in the field of otorhinolaryngology, head and neck surgery (ORL-HNS) continues to improve in Türkiye. A study examining case reports in Turkish ORL-HNS journals, mentioned that case reports that adopted various principles such as complying with ethical standards and being easily accessible would be very supportive of moving Turkish journals to more preferred indices (4). In our study, the compliance of ORL-HNS journals published in Türkiye was studied based on the principles of transparency. The aim was to investigate and analyze whether the journals complied with these principles and thereby inform journals by pointing out the aspects that needed improvement. Also, principles that are more likely to be incompatible with this field were examined and a possible relationship between journal citation numbers and the index of compatibility with transparency principles was evaluated to draw attention to global standards that could be useful in international scholarly publishing.

Methods

Data Collection

COPE, DOAJ, OASPA, and WAME are important scientific organizations. In 2013, they published 16 criteria under the title Principles of Transparency and Best Practice in Scholarly Publishing. These criteria were revised, and the 4th version was published in 2022. The 16 criteria are the name of the journal, its website, publishing schedule, archive, copyright, licensing, publication ethics and related editorial policies, peer review, access, ownership and management, an advisory body, editorial team-contact information, author fees, other revenue, advertising, and direct marketing. In addition, these 16 criteria are grouped under four main headings: journal content, journal practices, organization, and business practices (1).

In this sub-analysis, the statuses of eight ORL-HNS journals published and registered in Türkiye were scored as 1 for compliance and 0 for non-compliance with a range of minimum 0 and a maximum 16 points, as shown in Table 1 and 2. Accordingly, the compatibility scores of the journals with the transparency criteria were calculated. The conditions required for the conformity with the criteria are explained in Table 1. Journals that met more than half of the conditions for a criterion were considered to meet that criterion.

The Turkish Archives of Otorhinolaryngology, the European Journal of Rhinology and Allergy, The Turkish Journal of Ear, Nose and Throat, the KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery, the Journal of Ear Nose Throat and Head Neck Surgery, the Praxis of Otorhinolaryngology, the ENT Updates, The Journal of International Advanced Otology were included in the analysis which was carried out by examining the websites of the journals (Table 2). The analyses were conducted after each journal's website was evaluated by two researchers independently to prevent bias. The aim was to assess which transparency principles Turkish ORL-HNS journals complied with and which aspects needed to be improved.

In addition, the number of scientific articles published by the journals in 2020 and 2021 was collected by searching the journals' website archives, and the number of citations received by the relevant publications in 2022 was calculated using Google Scholar (5). First, the presence of a relationship between the calculated 2022 impact factor and the journal's compliance with transparency principles was calculated by dividing the number of citations a journal's 2020 and 2021 articles received in 2022 into the total number of citable articles published in that journal in the same two years. Journals for which a relationship was found were further evaluated through statistical analysis to identify with which transparency criteria/transparency criteria subheadings it was more closely related. As indicated in the COPE guidelines, ethics committee approval is not required for secondary research in which publicly available data is accessed (7).

Statistical Analysis

The possibility of a relationship between the impact factor in 2022 and compliance with the transparency principles was analyzed with Spearman non-parametric correlation tests due to the small number of samples using the IBM SPSS Statistics for Windows, Version 28.0. (Armonk, NY: IBM Corp) (6). The average, minimum, maximum, mode, median, standard deviation, and percentiles were calculated.

Table 1. Compatibility conditions for scientific journals with transparency criteria (Source: Principles of transparency and best practice in scholarly publishing, 2019) (1)

	Compliance with criteria
Name of journal	- Unique and not cause confusion with other journals
	- Not mislead about origin, scope, or association with other organizations
Website	- Take security precautions (e.g., use https and not http)
	- Compatibility with ethical standard and website standards
	- Unique design and logo
	- Declaration of source of the copied texts
	- Display of aim, scope, target reader, type of manuscripts, authorship criteria, ISSNs separately for print and electronic version on website
Publishing schedule	- Declaration of publishing frequency and exceptional circumstances
Archiving	- Declaration of electronic backup and long-term digital preservation plan (e.g., PubMed Central)
Copyright	- Statement of copyright terms of published content on the website and in the file of content
	- Declaration of copyright terms separate from the copyright terms of the website
	- Easily accessible copyright terms in a separate form which is available to everyone
Licensing	- Clear statement of licensing information on the website
	- Declaration of licensing terms on the full text of published articles (including HTML and PDF)
	- Clear statement of licensing policies about posting manuscripts and sharing with third party
	- Use of link to the correct license on the Creative Common Website if Creative Common licenses used
	- Use of open license in content with Open Access design
Publication ethics and related editorial policies	- Have policies on publication ethics (e.g., COPE's Core Practice Guidance) and clear statement on the website.
	- Authorship and contributorship
	- Handling complaints and appeals
	- Handling allegations of research misconduct
	- Conflicts of interest
	- Data sharing and reproducibility
	- Ethical oversight
	- Intellectual property
	- Post-publication discussion options
	- Corrections and retractions
Peer review	- Whether the content is peer reviewed
	- Who are conducting the peer review (e.g., external expert, editorial board member)
	- Type of peer review process
	- Use of reviewers recommended by author
	- Any masking of identities, explanation of who is masked and to whom
	- Whether supplementary material is peer reviewed
	- Whether review is posted with article
	- Whether review is anonymous
	- Declaration of decision process and involved people
	- Explanation of exceptions during peer review process
	- Statement of peer review schedule. In case of delay, inform the author and give the option to withdraw the manuscript
Access	- Description of gaining access for not freely accessible online content
	- Description of charges of offline versions (e.g., printed version)
Ownership and management	- Clear statement of ownership and management policies on the website of the journal
	- In the case of affiliation with institutions, sponsors, societies, providing links to their websites

Table 1. Continued

Advisory body	- Recognized expertise of editorial boards or advisory bodies in subject areas that are described in the aim and scope of the journal
	- Up-to-date declaration of the full names and affiliations of the members on the website
	- Periodic review of the board to avoid association with predatory journals
Editorial team/contact information	- Provide full names and affiliations of the editors
	- Declaration of editorial office contact information on the website (including full mailing address)
Author fees	- In case of author fees (e.g., page charge, editorial process charge, article process charge, language editing fee, submission fee, membership fee), clear statement on the website
	- In case of no fee, clear statement on the website
	- Easily accessible author fee information
	- Clear statement of possible future charges for the author
	- Clear statement of available waivers for author fees
	(who is eligible, when, and how to apply for a waiver)
	- Clear statement of irrelevance of author fees/waiver status and editorial decision making
Other revenue	- Declaration of business models or revenue sources on the website (e.g., author fees, subscriptions, sponsorships, subsides, advertising, reprints, supplements)
	- Irrelevance of business models or revenue sources and editorial decision-making
Advertising	- In case of accepting advertisements, statement of advertising and its policy on the website
	- Declaration of type of advertisements
	- Declaration of the responsible individuals for decision during advertisement accepting
	- Whether advertisements are linked to the content/reader behavior or displayed randomly
	- Irrelevance of advertisements and editorial decision making
Direct marketing	- Appropriate, well-targeted direct marketing activities on behalf of the journal
	- Truthful and not misleading information about the publisher/journal for readers/ authors

Results

During the study period between August and September 2023, we could access all the current websites of the eight Turkish ORL-HNS journals in the study. The evaluation of those journals according to the 16 transparency criteria is shown in Tables 2 and 3. The journals complied with an average of 11.25 criteria out of 16. It was seen that there was compatibility with a minimum of five and a maximum of 14 criteria (Table 3).

According to the calculated 2022 Impact factor, the first three journals out of eight were The Journal of International Advanced Otology, the Turkish Archives of Otorhinolaryngology, and the European Journal of Rhinology and Allergy. These journals complied with 13, 13 and 12 criteria, respectively, out of the 16 transparency criteria. The last three journals in the ranking are the Praxis of Otorhinolaryngology, the KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery, and The Turkish Journal of Ear, Nose and Throat. These journals were evaluated as complying with 8, 5 and 12 criteria, respectively. Due to insufficient sample size, the relationship between these two concepts could not be analyzed properly (Table 4).

Discussion

The principles of transparency and best practice in scholarly publishing, developed and published by COPE, DOAJ, OASPA and WAME, is an international publishing resource which defines a crucial standard-namely, the transparency principles-in scholarly journal publishing (1). It is critical for journals to organize their websites according to those 16 transparency principles for being indexed by major international indices such as DOAJ. Furthermore, the editors, their teams and journal managers are not only members of a journal, but also readers of their and many other journals. This study can enlighten them to improve their journals according to the up-to-date principles. Also, by learning these principles, readers who are also potential researchers can evaluate journals on their own and choose them wisely to publish their research which requires great effort.

In the presented study, we evaluated the adherence of Turkish ORL-HNS journals to the principles of transparency and best practice in scholarly publishing. The main objective of our study is to identify the aspects to be improved and to aid these journals in achieving better compliance with international standards.

Table 2. Evaluation of eight Turkish Otorhinolaryngology journals in terms of transparency criteria and calculated Google Scholar Impact Factor for 2022*

	Journal content						Journal practices		
	Name of journal	Website	Publishing schedule	Archiving	Copyright	Licensing	Publication ethics- related editorial policies	Peer review	Access
Turkish Archives of Otorhinolaryngology	+	+	+	+	+	+	+	+	+
European Journal of Rhinology and Allergy	-	+	+	+	+	+	+	+	+
The Turkish Journal of Ear. Nose and Throat	-	+	+	+	+	+	+	+	+
KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery	+	+	-	-	-	-	+	-	+
Journal of Ear Nose Throat and Head Neck Surgery	+	+	+	+	+	+	+	+	+
Praxis of Otorhinolaryngology	+	+	+	-	-	-	+	-	+
ENT Updates	+	+	+	+	+	+	+	+	+
The Journal of International Advanced Otology	+	+	+	+	+	+	+	+	+
Total compatibility with criteria	6/8	8/8	7/8	6/8	6/8	6/8	8/8	6/8	8/8

Table 2. continued

	Organization			Business practices					
	Ownership and management	Advisory body	Editorial team/contact information	Author fees	Other revenue	Advertising	Direct marketing	Transparency score of journals	Impact factor*
Turkish Archives of Otorhinolaryngology	+	-	+	+	-	+	-	13/16 (%81.25)	0.84
European Journal of Rhinology and Allergy	+	-	+	+	-	-	+	12/16 (%75)	0.40
The Turkish Journal of Ear. Nose and Throat	+	-	+	+	+	-	-	12/16 (%75)	0.16
KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery	+	-	-	-	-	-	-	5/16 (%31.25)	0.16
Journal of Ear Nose Throat and Head Neck Surgery	+	+	-	+	-	+	-	13/16 (%81.25)	0.19
Praxis of Otorhinolaryngology	+	-	+	+	-	-	-	8/16 (%50)	0.04
ENT Updates	+	+	+	+	+	-	-	14/16 (%87.5)	0.29
The Journal of International Advanced Otology	+	-	+	+	-	-	+	13/16 (%81.25)	1.53
Total compatibility with criteria	8/8	2/8	6/8	7/8	2/8	2/8	2/8		

*Calculated by extracting the data in Google Scholar and dividing the number of citations in 2022 to the articles published in 2020 and 2021 by the total number of articles published in 2020 and 2021

Table 3. Evaluation of the compatibility levels of Turkish otorhinolaryngology journals with 16 transparency principles

Analysis of total transparency scores of journals		
Average	11.2500	
Median	12.5000	
Mode	13.00	
Standard deviation	3.10530	
Minimum	5.00	
Maximum	14.00	
Percentile	25	9.0000
	50	12.5000
	75	13.0000

Table 4. Measurement of the relationship between the calculated impact factor of 2022 and the four main headings of the transparency criteria using Spearman non-parametric correlation analysis

	Correlation coefficient	**Significance (two-sided)**
Journal content	0.726*	0.42
Journal practices	0.697	0.055
Organization	0.274	0.511
Business practices	0.666	0.071
16 Criteria	0.648	0.082

*Correlation is statistically significant at 0.05 (two-sided) p<0.05

Significance: p

Our findings revealed that while all journals comply with the principles for website, publication ethics and related publication policies, access, ownership, and management, some fall short of the name, archive, copyright, license, peer review, editorial team, and contact information criteria. The reason for falling short of the principle of name could be because the name of the journal can be confused with those of other journals, potentially misleading authors and readers about the scope and origin of the journal.

In terms of archive criteria, the main reason for the incompatibility is that the lack of explanation of system that preserves the contents of the journal for a long time digitally on the website. Failure of a separate statement of the copyright conditions of the website and printed publications caused the journals to be found incompatible with the copyright principle. Absence of a statement about the license terms of the published articles (including HTML and PDF formats) and not sharing the license policies of the third parties where the publications are stored are among the reasons for incompatibility with this criterion. Some journals were not found to comply with this criterion of peer review because they did not clarify on their website the particular conditions of their peer review process, announcement of the result whether by wet signature or anonymously and whether referees recommended by the author were in charge during the evaluation.

Absence of up-to-date information about the editorial team and the deficiencies in the contact information of the editorial office are the main items that can be considered disqualifying for the editorial team and contact information criteria.

Most of evaluated journals (6/8) did not share the contact information of the advisory council, how the income-expense tally is kept, what the pricing and distribution policy is if the printed journal is published, what type of advertisements are accepted under what conditions and by whom, and this led to incompatibility with the advisory council, other income, direct marketing, and advertising principles (Table 2).

According to the 2022 Google Scholar Impact Factor calculated from the verified citations in Google Scholar, the first three among the eight journals are The Journal of International Advanced Otology, the Turkish Archives of Otorhinolaryngology and the European Journal of Rhinology and Allergy. The last three journals in the ranking are the Praxis of Otorhinolaryngology, the KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery, and the Turkish Journal of Ear, Nose and Throat, starting from the last (Table 4). While the first three journals comply with 12 to 13 principles, the last three journals comply with only 5 to 12 principles, suggesting that compliance with such international principles may be important for journals to be cited and included in important international indices such as Web of Science (WoS) and Scopus, which often seek citation analyses during the journal evaluation process. The first three journals with high compatibility rates to the transparency principles are indexed either in WoS or Scopus. However, only one of the last three journals is indexed in one of the indices; The Turkish Journal of Ear, Nose and Throat is indexed in Scopus and has the highest compliance rate among them. As a result of the analysis, the relationship of the calculated 2022 impact factor with the criteria covering the journal content was determined. This may suggest that qualitative publications can be effectively included in international indexes and get citations. However, the relationship between these two concepts could not be adequately analyzed due to insufficient sample size, which constitutes the main limitation of the presented study. Furthermore, the original impact factors are calculated from WoS citations in WoS journals and very few Turkish ORL-HNS journals are indexed in WoS, so a direct hypothesis on the relationship between the compliance and the impact factor could not be built.

Conclusion

Based on the findings of the presented study, in which we analyzed Turkish ORL-HNS journals in terms of compliance

with one of the most important international scholarly publishing standards, the principles of transparency and best practice in scholarly publishing, we suggest the Turkish ORL-HNS research community to study the missing and inapplicable criteria, and carry out the necessary studies, especially on journal websites, to improve compliance with the referred principles.

All ORL-HNS scientific journals in Türkiye will benefit from considering the fulfilment of the 16 transparency criteria to improve their publishing quality to gain presence on international platforms and receive citations. One of the issues that should be emphasized is the need to regulate primarily the sharing of details of the advisory bodies, other expenses, advertising, and other marketing content, with which fulfillment is complex. In addition, considering the criteria of the three journals with the highest impact factors among the evaluated journals, one of the important messages of this study is that the relationship between the impact factor and compliance with the transparency criteria should be investigated with a larger sample.

Main Points

- The evaluation of eight Turkish ORL-HNS journals according to 16 transparency criteria showed that the journals complied with an average of 11.25 criteria out of 16. Journals are found to be compatible with a minimum of 5 and a maximum of 14 criteria.
- According to the calculated 2022 Impact factor, the first three journals among eight are The Journal of International Advanced Otology, the Turkish Archives of Otorhinolaryngology and the European Journal of Rhinology and Allergy. The last three in the ranking are the Praxis of Otorhinolaryngology, the KBB Forum Electronic Journal of Otolaryngology-Head and Neck Surgery, and The Turkish Journal of Ear, Nose and Throat, starting from the last.
- Most of the evaluated journals do not comply with the criteria on advisory body, other revenue, advertising, and direct marketing.

Ethics

Ethics Committee Approval: As indicated in the COPE guidelines, ethics committee approval is not required for secondary research in which publicly available data is accessed (7).

Informed Consent: Since this study was not conducted on humans, patient consent was not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ç., Concept: E.Ç., C.U., Design: E.Ç., C.U., Data Collection and/or Processing: E.Ç., S.K., Analysis and/or Interpretation: E.Ç., S.K., C.U., Literature Search: E.Ç., Writing: E.Ç., C.U.

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An Unusual Ectopic Parathyroid Adenoma Location: Pyriform Sinus

Case Report

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Abstract

Primary hyperparathyroidism (pHPT) is caused by a single or multiple parathyroid adenomas in 85% of cases, by parathyroid hyperplasia in 15%, and by parathyroid carcinomas in less than 1%. Due to the embryological development characteristics of parathyroid tissues, ectopic parathyroid adenomas can be found in various locations. Although the incidence of pHPT varies, it is not considered a rare disease. Some unusual locations of ectopic parathyroid adenomas can make it difficult for clinicians and surgeons to detect them. For this reason, it is important to understand embryology thoroughly and to use complementary preoperative imaging methods. The detection and accurate localization of adenomas are important to avoid recurrent surgeries and to increase surgical success. We aimed to contribute to the literature by presenting a case of an adenoma located in the right pyriform sinus.

Keywords: Head and neck surgery, hyperparathyroidism, parathormone, parathyroid adenomas, pyriform sinus, case report

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Introduction

The incidence of primary hyperparathyroidism (pHPT) is relatively common, with estimates ranging widely between 0.4 and 82 per 100,000 population. The incidence of pHPT has increased significantly in countries where routine biochemical screening for parathyroid hormone (PTH) levels has been implemented (1). It can cause a wide range of clinical symptoms. Although most patients are clinically asymptomatic, some may present with non-specific complaints such as fatigue, cognitive impairment, and mild depression. These symptoms result from prolonged elevated levels of PTH and the associated hypercalcemia.

In affected individuals, complications may include renal disorders such as nephrolithiasis and renal failure; gastrointestinal issues such as nausea, vomiting, peptic ulcers, and even pancreatitis; musculoskeletal symptoms such as bone pain, muscle weakness, pathological fractures, and osteitis fibrosa cystica; and neuropsychiatric manifestations such as lethargy, psychosis, and coma (2).

There are various underlying pathologies that can cause pHPT. Approximately 85% of cases are due to single or multiple parathyroid adenomas, 15% are attributed to parathyroid hyperplasia, and less than 1% are caused by parathyroid carcinoma.

Although parathyroid adenomas can occur at any age, they are most commonly diagnosed in the fifth and sixth decades of life. While some studies suggest that adenomas of the inferior parathyroid glands are more frequent than those of the superior glands, contradictory evidence also exists in the literature (3).

We aimed to contribute to the literature by presenting a case of an ectopic parathyroid adenoma located in the pyriform sinus, an extremely rare location.

Case Presentation

A 53-year-old female patient presented with complaints of excessive water intake for the past two years, bone pain in her right ankle, stiffness in her arms and hands, and generalized weakness. The patient had no history of pathological bone fractures, nephrolithiasis, gastrointestinal problems, or a family history of hyperparathyroidism. Flexible endoscopy revealed a raised lesion on the medial wall of the right pyriform sinus. Other ear nose and throat and systemic examinations were unremarkable.

Serum total calcium level was 11.37 mg/dL (normal: 8.8-10.6 mg/dL), albumin level was 4.25 g/dL (reference range: 3.5-5.2 g/dL), and phosphorus level was 2.38 mg/dL (reference: 2.7-4.5 mg/dL). The serum parathormone (PTH) level for differential diagnosis was markedly elevated at 516.9 pg/mL (reference: 14-72 pg/mL). Neck ultrasonography (USG) did not reveal any lesions compatible with parathyroid adenoma in either eutopic or ectopic locations.

In Technetium 99m sestamibi (99mTc-sestamibi) single-photon emission computed tomography (SPECT/CT) imaging, focal tracer uptake was observed at the level of the superior right thyroid lobe, showing retention suggestive of an ectopic parathyroid adenoma, consistent with the lesion seen on CT (Figure 1). Four-dimensional CT (4D-CT) revealed a lesion measuring approximately 10×10×14 mm in the right pyriform sinus, consistent with a parathyroid adenoma (Figure 2a, b, c).

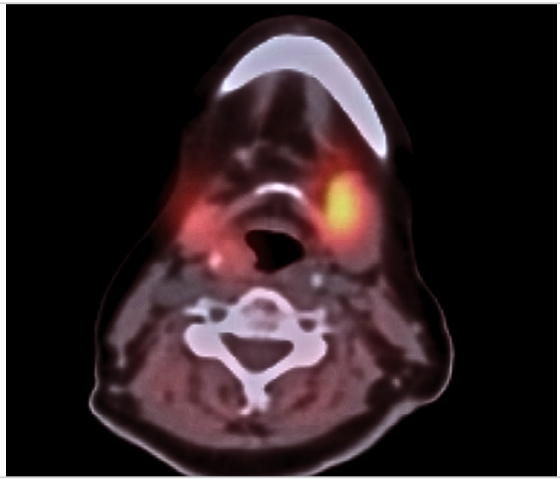

Figure 1. SPECT/CT imaging demonstrates focal radiotracer uptake in the right pyriform sinus, consistent with an ectopic parathyroid adenoma
SPECT/CT: Single-photon emission computed tomography

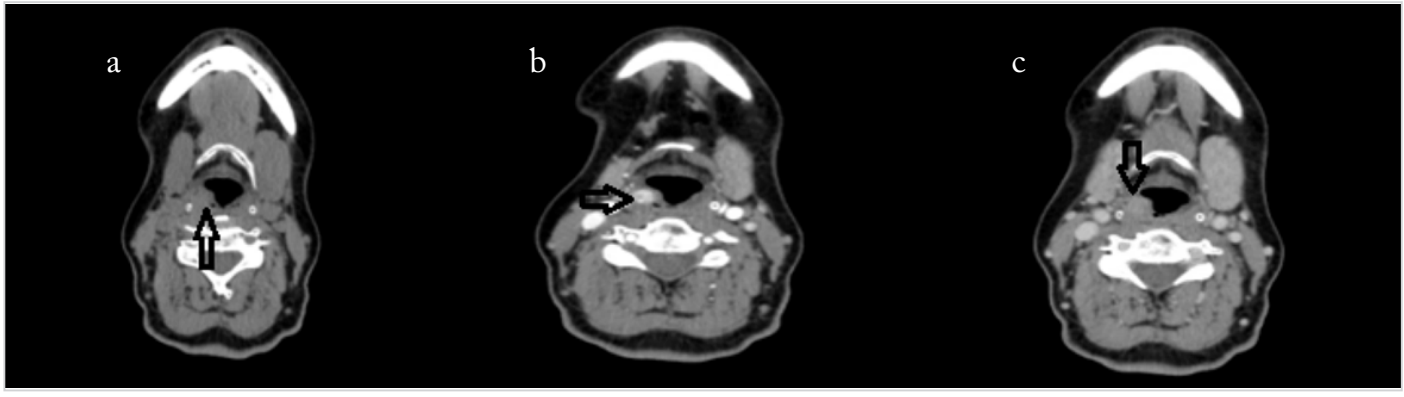

Figure 2. Axial sections of neck computed tomography showing a lesion consistent with parathyroid adenoma in the right pyriform sinus: pre-contrast, early post-contrast, and delayed post-contrast phases

The patient underwent direct laryngoscopy under general anesthesia. During the procedure, a capsulated mass measuring approximately 2 cm was observed on the medial wall of the right pyriform sinus (Figure 3). The mass was excised using microscissors and laryngeal cautery. The intraoperative rapid PTH test showed that the PTH value, 406.5 pg/mL before excision, had decreased to 31.3 pg/mL approximately 15 minutes after excision. Postoperatively, both PTH and serum calcium levels returned to within normal limits. The histopathological examination of the surgical specimen confirmed the diagnosis of parathyroid adenoma (Figure 4). The patient was discharged uneventfully. At the last follow-up, conducted 18 months postoperatively, no recurrence or pathology was observed. Informed consent was obtained from the patient for publication.

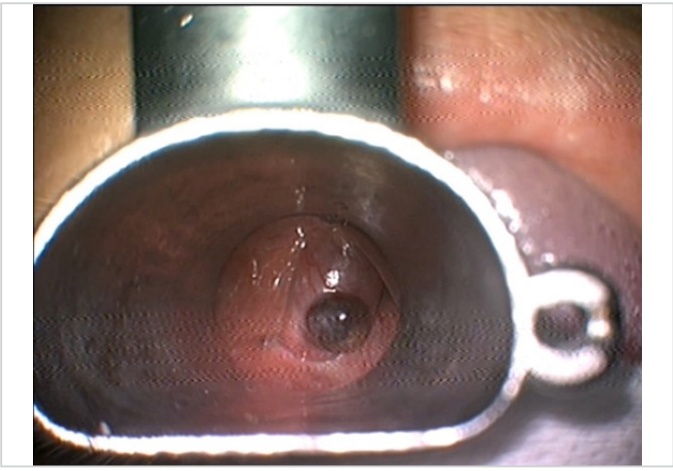

Figure 3. Intraoperative direct laryngoscopy image showing a well-defined lesion on the medial wall of the right pyriform sinus, suggestive of an ectopic parathyroid adenoma

Figure 4. Image of the mass excised during surgery

Discussion

The ectopic location of parathyroid adenomas has been attributed to their abnormal migration during embryogenesis. Five pairs of pharyngeal pouches are formed when the embryo is approximately 26 days old. Parathyroid glands begin to develop during the fifth week of intrauterine life. The inferior glands originate from the third pharyngeal pouch, while the superior glands arise from the fourth pharyngeal pouch, becoming histologically visible by the 14th week. The fact that the fourth pharyngeal pouch also contributes to the development of the pyriform sinus explains the ectopic location observed in this case (4). Several previous case reports have described parathyroid adenomas located in this rare anatomical region (5-9).

Currently, imaging methods such as preoperative USG, 99mTc-sestamibi scintigraphy (MIBI), and 4D-CT are available to determine the location of parathyroid adenomas.

The typical ultrasonographic appearance of a parathyroid adenoma is an oval-shaped, hypoechoic nodule closely associated with the thyroid gland. However, ectopic parathyroid adenomas may be missed on USG due to factors such as operator experience, interpretive error, or technical limitations like the absence of an acoustic window. The sensitivity and positive predictive value (PPV) of USG have been reported as 76.1% and 93.2%, respectively (10). In our case, USG was used as the initial imaging modality; however, no suspicious lesion was detected. This highlights the importance of considering alternative imaging modalities in cases of suspected parathyroid adenoma when USG findings are negative.

99mTc-sestamibi SPECT has pooled sensitivity and PPV rates of 78.9% and 90.7%, respectively (10). As demonstrated in our case, we consider this imaging technique to be both complementary and reliable.

The 4D-CT is another widely used imaging tool. With this technique, abnormal parathyroid glands as small as 1×6 mm can be identified. It is particularly useful in detecting adenomas that are missed by other imaging methods or in cases of unsuccessful prior neck explorations. However, the radiation exposure associated with 4D-CT is a notable disadvantage compared to standard CT. The overall sensitivity and PPV of contrast-enhanced neck CT, including the 4D variant, have been reported as 89.4% and 93.5%, respectively (10).

In our clinical practice, if the findings of USG and SPECT/PET are consistent, we consider the localization to be adequately established and typically do not proceed with 4D-CT. However, when discrepancies exist between USG and SPECT/PET findings, we believe that 4D-CT is useful both for precise localization and for planning an accurate surgical approach.

Conclusion

Some uncommon locations of ectopic parathyroid adenomas may pose significant challenges for clinicians and surgeons in detecting the adenoma. For this reason, a thorough understanding of parathyroid embryology and the use of complementary preoperative imaging modalities are essential. The detection and precise localization of adenomas play a critical role in preventing recurrent surgeries and in improving surgical outcomes.

Ethics

Informed Consent: Informed consent was obtained from the patient for publication.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.C.Ö., E.D., Concept: E.C.Ö., E.D., Design: E.C.Ö., E.D., Data Collection and/or Processing: E.C.Ö., G.G.S., E.D., E.D., Analysis and/or Interpretation: E.C.Ö., G.G.S., E.D., E.D., Literature Search: E.C.Ö., E.D., Writing: E.C.Ö., E.D.

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Main Points

- Parathyroid adenomas are an important pathology that can lead to various gastrointestinal, musculoskeletal, renal, and neuropsychiatric complications.
- Due to their embryological development, parathyroid adenomas may be located in unusual anatomical sites.
- Preoperative imaging particularly ultrasound, four-dimensional computed tomography, and Technetium 99m sestamibi single-photon emission computed tomography plays a crucial role in determining the exact location of the adenoma.

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First Report of the Coexistence of Langerhans Cell Histiocytosis and Epithelioid Hemangioma of the Larynx

Case Report

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Abstract

Langerhans cell histiocytosis (LCH) is a complex disorder of the mononuclear phagocyte system. Laryngeal epithelioid hemangiomas are rare, benign vascular tumors in adults. Here, we report the first known case of the coexistence of LCH and epithelioid hemangioma in the larynx. A 42-year-old man presented with progressive swelling on the left side of the neck and hoarseness. Endoscopic examination revealed a mass obliterating the left pyriform sinus, false vocal cord, and aryepiglottic fold. Computed tomography (CT) showed a mass destroying the thyroid cartilage, extending to the left false and true vocal cords, and obstructing the airway. Fine-needle aspiration biopsy suggested hemangioendothelioma. However, histopathological examination after total laryngectomy revealed both LCH and epithelioid hemangioma. Positron emission tomography/CT indicated suspected LCH involvement of the pituitary gland and cervical lymph nodes. The patient was treated with chemotherapy. No recurrence was observed at the six-month follow-up. This case highlights the potential association between the mitogen-activated protein kinase pathway, LCH, and epithelioid hemangioma. It also emphasizes the importance of repeating a biopsy in cases of rare laryngeal tumors when initial results are inconclusive.

Keywords: Langerhans cell histiocytosis, epithelioid hemangioma, laryngeal neoplasms, total laryngectomy, case report

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Introduction

Langerhans cell histiocytosis (LCH) is a complex disorder involving the proliferation, differentiation, and aberrant functioning of the mononuclear phagocyte system, and it may present with a wide range of clinical manifestations (1). LCH is observed in individuals under the age of 15 at an annual incidence of 2.6 to 8.9 per million and occurs less frequently in adults, at an incidence of 0.07 per million. Approximately half of the patients present with single-organ involvement, while the rest show multisystem involvement. The most commonly affected sites are the skeletal system, skin, lymph nodes, and visceral organs such as the lungs, liver,

and spleen (2). Lytic bone lesions are the most common finding; however, other features include skin rashes, soft tissue or lymph node swelling, and gingival hypertrophy (3). Laryngeal involvement in LCH is exceedingly rare, with only six previously reported cases (4-9). Epithelioid hemangioma (EH) presents as angioma-like nodular lesions, frequently occurring in the skin, muscle, or bone tissue, and more rarely in the salivary glands, oral mucosa, and various visceral organs (10,11). Here, we report a unique case of a patient who underwent total laryngectomy due to the coexistence of LCH and EH in the larynx.

Case Presentation

A 42-year-old man presented to University of Health Sciencess Türkiye, Gülhane Training and Research Hospital, with a two-month history of progressive swelling on the left side of his neck and hoarseness. His medical history included hypertension and obesity, and he had a 25-pack-year smoking history. On physical examination, a 5 cm firm, immobile mass was palpated in the left lateral neck. Flexible endoscopic examination revealed a mass obliterating the left pyriform sinus, false vocal cord, and aryepiglottic fold, with significantly limited movement of the left vocal cord.

Computed tomography (CT) revealed a cystic-necrotic mass with calcifications in the left neck, which had completely destroyed the thyroid cartilage and extended to the left false and true vocal cords, causing airway obstruction (Figures 1a, 1b). Magnetic resonance imaging (MRI) showed a 50×53×36 mm heterogeneous mass with diffusion restriction, hypointense on T1-weighted and hyperintense on T2-weighted sequences (Figures 1c, 1d). As there was no apparent involvement of the laryngeal mucosa, fine-needle aspiration biopsy (FNAB) was recommended. Cytological evaluation revealed polygonal cells with distinct intracytoplasmic vacuoles, suggestive of hemangioendothelioma. Core and excisional biopsies were discussed with the patient, who opted for an excisional biopsy.

During surgery, a limited left neck dissection was performed to expose the mass and larynx. Intraoperatively, invasion of the left pyriform sinus and thyroid cartilage precluded a partial laryngectomy, necessitating a total laryngectomy (Figure 2). The pharynx was closed using a primary T-closure technique with continuous sutures. Oral intake was initiated one week postoperatively, and a voice prosthesis was placed on postoperative day 10. The patient was discharged without complications.

Histopathological evaluation of the laryngectomy specimen revealed two distinct lesions (Figure 3a). The first consisted of capillary-sized vessels lined with epithelioid endothelial cells, positive for immunohistochemical stains CD34 (Figure 3b) and ETS-related gene. The second lesion was composed of histiocytoid cells with convoluted nuclei and slightly eosinophilic cytoplasm, accompanied by eosinophils, eosinophilic microabscesses, and multinucleated giant cells. These cells tested positive for Langerin (Figure 3c), CD1a

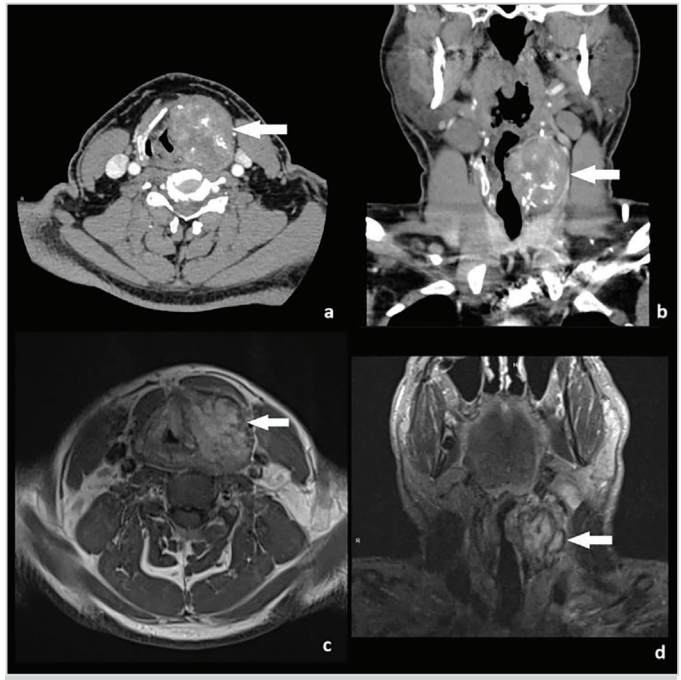

Figure 1. a, b) Axial and coronal computed tomography sections of the neck demonstrate a mass in the left side with cystic-necrotic components and calcifications, completely destroying the thyroid cartilage and extending to the left false and true vocal cords, resulting in airway obstruction.
c, d) Axial T1-weighted and coronal T2-weighted magnetic resonance imaging show a heterogeneous mass in the same region (Arrows indicate the mass.)

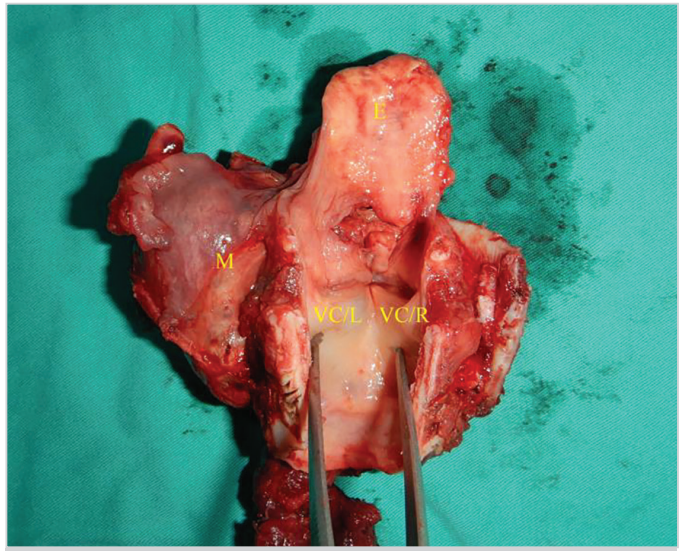

Figure 2. Total laryngectomy specimen, posterior view. The tumor invades the left laryngeal ventricle, false vocal cord, aryepiglottic fold, and cricoarytenoid unit

E: Epiglottis; M: Mass, CV/L: Left vocal cord, CV/R: Right vocal cord

(Figure 3d), and S100, supporting a diagnosis of LCH. LCH involvement was also identified in cervical lymph nodes (Figures 4b-4d).

To assess for systemic involvement, positron emission tomography/CT (PET/CT) was performed, revealing suspected LCH involvement in the pituitary gland and some cervical lymph nodes. Bone scintigraphy was normal. Laboratory investigations showed elevated thyroid-stimulating hormone (144 mLU/mL) and normal prolactin (15.24 ng/mL) and other hormone levels. The patient was referred to hematology and endocrinology. Chemotherapy with cytarabine (100 mg/m^2/day for five days per cycle, over six monthly cycles) was administered. At the six-month follow-up, no recurrence was noted.

Written informed consent was obtained from the patient for publication of this case report.

Discussion

Involvement of the ear, nose, and neck in LCH most commonly affects the mastoid, middle ear, and external auditory canal (12). Temporal bone involvement can mimic otitis media or mastoiditis, especially in pediatric patients. Other noninfectious conditions that may resemble acute mastoiditis include acute myeloid leukemia, rhabdomyosarcoma, and lymphoma (13). Awareness of these differential diagnoses is critical to avoid delays in treatment.

Laryngeal involvement in LCH is extremely rare. Of the six prior reported cases, four occurred in adults (4). Symptoms depend on the site of involvement and may include dyspnea, hoarseness, cough, cervical mass, sore throat, and stridor. A broad differential diagnosis, including benign and malignant laryngeal tumors, should be considered. CT and MRI are essential for evaluating the extent of disease before biopsy or surgery. CT is useful for identifying bony destruction, while MRI can reveal soft tissue involvement and contrast enhancement. Although Guo et al. (12) recommend CT as the initial imaging modality, we believe MRI should also be performed in all cases to fully assess potential laryngeal involvement.

FNAB may lead to misdiagnosis, as in our case. If a laryngeal mass is clearly visualized, direct laryngoscopy with biopsy is preferable. Previous reports also indicate that multiple biopsies may be necessary for a definitive diagnosis of LCH (4). In our case, the coexistence of EH and LCH may have contributed to the initial diagnostic difficulty. This case emphasizes the importance of considering repeat biopsy and maintaining close communication with pathologists when evaluating rare laryngeal tumors.

LCH lesions have been reported in the subglottic area, epiglottis, and false vocal cords (4). In our patient, the

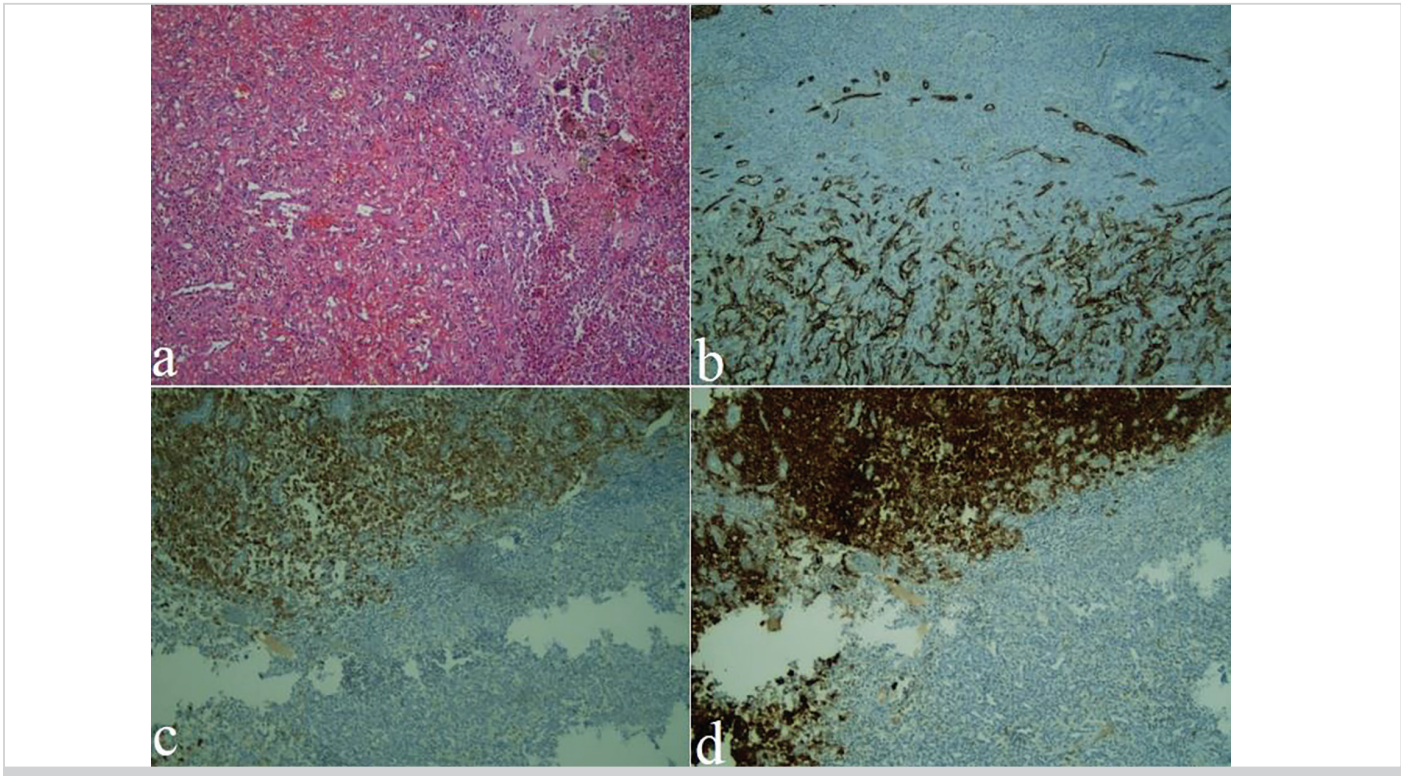

Figure 3. a) Epithelioid hemangioma (left) and Langerhans cell histiocytosis (right) in the larynx (Hematoxylin-Eosin, ×100). **b)** CD34-positive immunohistochemical staining of epithelioid endothelial cells in the larynx (×100). **c)** Langerin-positive immunohistochemical staining of Langerhans cells in the larynx (×100). **d)** CD1a-positive immunohistochemical staining of Langerhans cells in the larynx (×100)

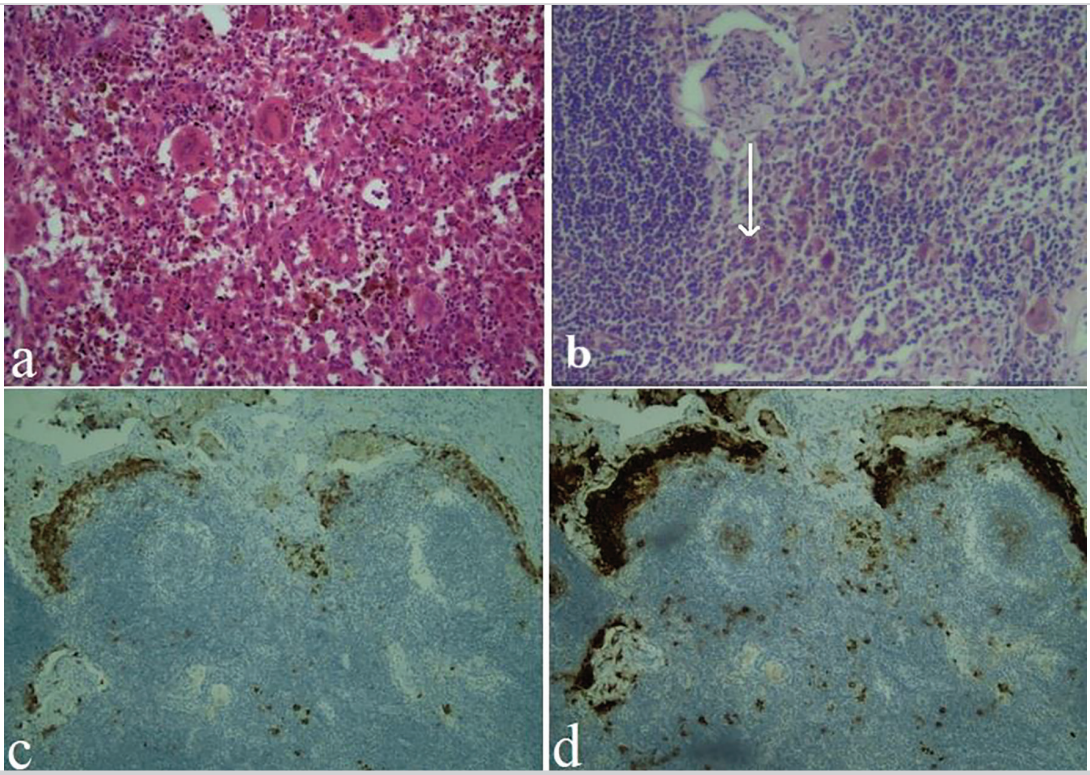

Figure 4. a. Langerhans cells, eosinophils, and multinucleated giant cells in the larynx (Hematoxylin-Eosin, ×200). **b.** Langerhans cells in a cervical lymph node (white arrow) (Hematoxylin-Eosin, ×100). **c.** Langerin-positive immunohistochemical staining of Langerhans cells in the lymph node (×100). **d.** CD1a-positive immunohistochemical staining of Langerhans cells in the lymph node (×100).

mass invaded the thyroid cartilage and obstructed the left pyriform sinus and airway, necessitating total laryngectomy. The preliminary diagnosis was hemangioendothelioma, a borderline tumor.

The coexistence of EH and LCH is highly unusual. We hypothesize that mutations in the mitogen-activated protein kinase (MAPK) pathway, including B-Raf proto-oncogene, serine/threonine kinase (BRAF), may underlie both lesions (1,14). However, the prognostic impact of EH on LCH remains unclear.

Management and prognosis of LCH depend on the location and extent of disease. A multidisciplinary approach is crucial. Comprehensive evaluation, including PET/CT, bone scintigraphy, and endocrine testing, is essential to determine disease dissemination. Surgical resection, radiotherapy, and corticosteroids may be used for isolated lesions, while systemic involvement often requires chemotherapy (1,4). The *BRAFV600E* mutation is found in 25-64% of LCH cases and is associated with increased recurrence risk (14). Targeted therapy such as vemurafenib may be considered in mutation-positive patients.

Conclusion

We present the first reported case of the coexistence of LCH and EH in the larynx. This case highlights the potential link between the MAPK pathway and both pathologies and underscores the need for careful histopathological evaluation and communication with the pathology team in rare laryngeal tumors.

Ethics

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

Footnotes

Authorship Contributions

Concept: S.C.M., L.Y., Design: S.C.M., L.Y., Data Collection and/or Processing: S.C.M., L.Y., E.A., Analysis and/or Interpretation: S.C.M., L.Y., E.A., Literature Search: S.C.M., L.Y., E.A., Ö.G., Y.F.Y., Writing: S.C.M., L.Y.

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

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Main Points

- Langerhans cell histiocytosis (LCH) of the larynx is a very rare disease of which only six prior cases have been reported.
- We report a unique case of a patient who underwent a total laryngectomy due to the coexistence of LCH and epithelioid hemangioma (EH) of the larynx.
- The mutations in the mitogen-activated protein kinase pathway, including B-Raf proto-oncogene, serine/threonine kinasemay have a role in the coexistence of EH and LCH.
- Whether EH influences the prognosis of LCH is not known.

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A Rare Case of Mammary Analogue Secretory Carcinoma Localized in the Submandibular Gland

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Case Report

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Abstract

Mammary analogue secretory carcinoma (MASC) is a recently described rare salivary gland malignant tumor. A limited number of cases localized in the submandibular gland have been reported. A 56-year-old male patient presented with a slow growing mass in the left neck region. On physical examination, there was a mobile mass measuring approximately 5x4 cm in the left submandibular area. Radiologic imaging revealed a septated cystic mass with peripheral contrast enhancement, containing both solid and fluid components. Fine needle aspiration biopsy (FNAB) result was reported as atypia of uncertain significance. Submandibular gland excision was performed in the first stage. Since the pathology result was MASC and the tumor stage was T3, ipsilateral neck dissection was performed. On histopathological examination, neoplastic cells were seen to be rich in eosinophilic cytoplasm and vacuolization. Immunohistochemical examination revealed cytokeratin 7, mammaglobin and gross cystic disease fluid protein-15 positivity. By presenting this case report, we aimed to add a new case to the already limited number of submandibular gland localized MASC cases in the literature and contribute to the pool of knowledge on this subject. MASC should be considered especially in cases with submandibular gland localization in which the FNAB result is reported as atypia of uncertain significance.

Keywords: Mammary analogue secretory carcinoma, salivary gland neoplasms, submandibular gland, case report

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Introduction

Mammary analogue secretory carcinoma (MASC) was first described as a different type of salivary gland carcinoma by Skálová et al. (1) in 2010. Before this date, it was classified as a zymogen-poor variant of acinic cell carcinoma (AciCC). It mostly originates from the parotid gland. Its localization in the submandibular gland and minor salivary glands is very rare (2,3). Patients usually present with a painless mass that gradually grows for months or even years (1,2). It is a low-grade malignant tumor with good clinical prognosis and good response to surgical treatment (4).

In this report, we aimed to contribute to the pool of knowledge on this subject by presenting a case of MASC localized in the submandibular gland.

Case Presentation

Written informed consent was obtained from the patient for publication of this case report. A 56-year-old male patient

presented with a mass on the left side of the neck that had been present for 10 years and was gradually growing. There was no history of malignant disease in the patient or his family. There was no history of smoking and alcohol use. The patient was receiving treatment for hypertension and benign prostatic hypertrophy. Physical examination revealed a mobile, painless mass approximately 5x4 cm in size in the left submandibular region. No palpable lymphadenopathy was detected in the neck. Examination of all cranial nerves, especially the facial nerve, was normal.

Neck ultrasonography revealed a smoothly circumscribed and septated cystic mass with solid components and calcifications in the left submandibular region. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a septated cystic mass in the submandibular region, with indistinct borders from the gland, demonstrating peripheral contrast enhancement, containing both dense solid and fluid components, and including calcification foci. On radiologic imaging, the mass was located posterior to the submandibular gland, appeared adherent to it, and its borders could not be clearly distinguished from the gland. There was no lymph nodes of pathological size or characteristics (Figures 1, 2).

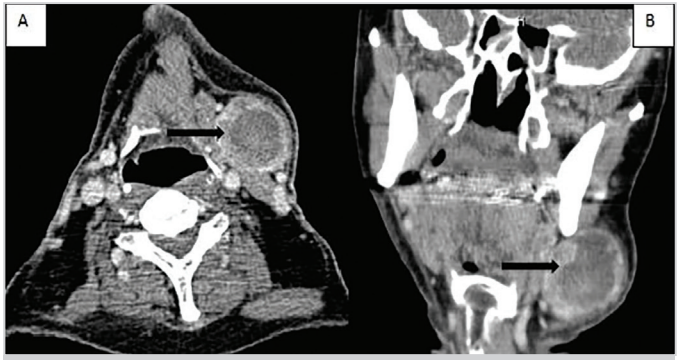

Figure 1. Contrast-enhanced CT images of the mass in the left submandibular area (A: axial, B: coronal)
CT: Computed tomography

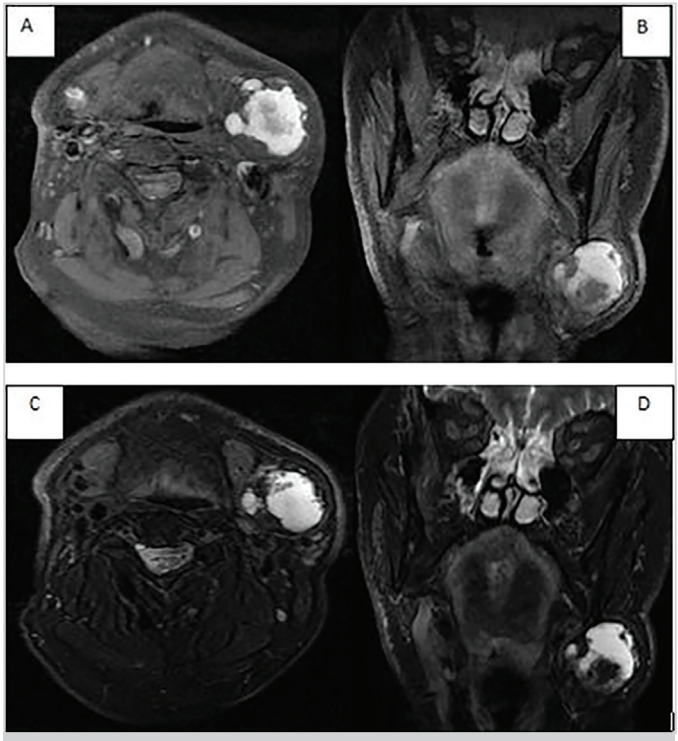

Figure 2. Contrast-enhanced MRI images of the mass in the left submandibular area (A: T1 axial, B: T1 coronal; C: T2 axial, D: T2 coronal)
MRI: Magnetic resonance imaging

Histopathologic examination revealed that the neoplastic cells had a tubular architecture and were rich in eosinophilic cytoplasm with prominent vacuolization (Figure 3). Immunohistochemical analysis demonstrated positive staining for cytokeratin 7 (CK7), mammaglobin, and gross cystic disease fluid protein-15 (Figure 4). There was no evidence of lymphovascular or perineural invasion, and the surgical margins were free of tumor. The tumor was classified as low grade based on its histological features.

Given the diagnosis of MASC originating from the submandibular gland and staged as T3, the patient underwent ipsilateral neck dissection involving levels 1A, 1B, 2, and 3 during a second surgical session. No metastatic lymph nodes

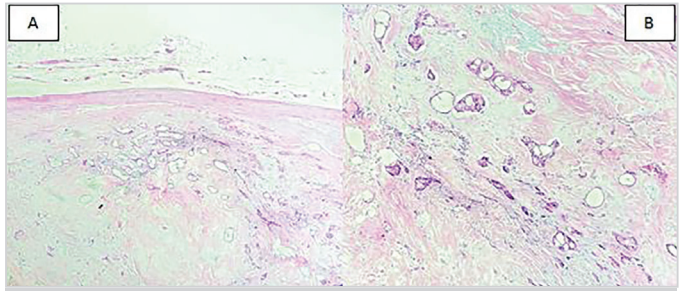

Figure 3. Histopathological appearance of the case (A: well-circumscribed tumor with prominent fibrosclerotic stroma and glandular structures with microcystic, follicular and tubular morphology, B: tumor cells have low grade atypia, characterized by cytoplasmic vesicular features, finely granular nuclear)

Figure 4. Immunohistochemical staining characteristics of the case (A: Tumor cells exhibit diffuse Mammaglobin positivity, B: GCDFP-15 immunohistochemistry is diffusely positive)
GCDFP-15: Gross cystic disease fluid protein-15

were identified. Consequently, no adjuvant therapy such as chemotherapy or radiotherapy was deemed necessary.

At the 20-month postoperative follow-up, which included physical examination, neck CT and MRI, no signs of recurrence were observed. Positron emission tomography-CT was not performed, as the tumor was low grade, surgical margins were negative, and there was no lymph node metastasis.

Discussion

Skálová et al. (1) re-evaluated the pathological features of 16 cases which were previously classified as AciCC or adenocarcinoma not otherwise classified. They classified cases with histopathologic features such as absence of zymogen granules, mammaglobin positive staining and presence of intracellular colloid-like material as MASC.

A limited number of cases of MASC localized in the submandibular gland have been reported in the literature. In a multicenter study, a total of 40 cases of MASC were presented and only two (5%) of them were reported to be localized in the submandibular gland (4). Chiosea et al. (2) reported that only three of 36 cases (8.3%) were localized in the submandibular gland. We believe that our case is also valuable in terms of its rare localization in the submandibular gland.

It is usually impossible to diagnose MASC with FNAB. In almost all cases, definitive diagnosis is made by histopathological examination of the postoperative specimen. In the cases of MASC presented by Wiles et al. (4), 50% of the FNAB results were reported as malignant (19/38). Of the FNAB results, 26% (10/38) were reported as suspicious for malignancy, 18% (7/38) as salivary gland neoplasm with uncertain malignancy potential, and 6% (2/38) as atypia of undetermined significance. In our case, the FNAB result was reported as atypia of undetermined significance and the definitive diagnosis was made by histopathological examination of the postoperative specimen.

Cystic, tubular and/or papillary appearance, presence of eosinophilic vacuolated cytoplasm and intraluminal and/or intracellular colloid-like secretions are histopathologic features of MASC (1,2). In AciCC, which is often confused with MASC, the presence of cytologically zymogen granules, lymphocyte infiltration rather than eosinophilia or absence of intracellular colloidal material is important in differential diagnosis (1).

Mammaglobin, S-100, and vimentin positive staining are typical and allow differentiation from other salivary gland tumors (1). CK7, CK8, GCDFP, MUC-1, MUC-4, BRST-2 and STAT5a positivity have also been shown (1). Our case had a cystic and tubular structure with eosinophilic vacuolated cytoplasm and intracellular colloidal appearance, and only mammaglobin, CK7 and GCDFP15 positivity was present.

Kurokawa et al. (5) defined the characteristic radiological features of MASC cases as a mass lesion with cystic and/or papillary, but not solid, appearance characterized by the presence of high-density cystic content in MRI images. In our case, the mass was radiologically cystic, as described by Kurokawa et al. (5), with peripheral contrast enhancement and containing both dense solid and fluid components, defined as a well-circumscribed cystic mass.

Although MASC has a good prognosis, the risk of lymph node metastasis is higher than AciCC. Chiosea et al. (2) found cervical lymph node metastases in four (22%) of 18 MASC patients who underwent neck dissection, compared to only three (7.9%) of 38 AciCC patients. Wiles et al. (4) reported that 22.5% of their patients had cervical lymph node metastasis and two of them also had brain and lung metastases. In our case, there was no cervical lymph node or distant organ metastasis.

Neck dissection is typically guided by the presence or risk of lymph node metastasis (2). The likelihood of nodal involvement is influenced by the tumor's T stage, histopathological type, and anatomical localization-being particularly higher in MASC cases arising from the submandibular gland (6,7). Postoperative radiotherapy is generally recommended in the presence of cervical lymph node metastasis, close (<5 mm) or positive surgical margins, perineural invasion, and in tumors classified as T3 or T4. In the present case, ipsilateral neck dissection was performed due to the tumor's submandibular origin and T3 staging. Radiotherapy was not required, as no metastatic lymph nodes were detected and surgical margins were negative.

Conclusion

Reported cases of MASC localized in the submandibular gland remain extremely rare. This diagnosis should be considered in salivary gland tumors, particularly when FNAB results indicate atypia of uncertain significance. A definitive diagnosis is established through histopathological and immunohistochemical evaluation of the postoperative specimen.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.K., S.Ö., Concept: Z.K., S.Ö., Design: Z.K., S.Ö., H.Ü., Data Collection and/or Processing: Z.K., S.Ö., H.Ü., Analysis and/or Interpretation: H.Ü., Literature Search: Z.K., S.Ö., Writing: Z.K., S.Ö.

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

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

Main Points

- Mammary analogue secretory carcinoma (MASC) should be considered in submandibular gland masses when suspected malignancy is reported by fine needle aspiration biopsy.
- The presence of eosinophilic vacuolated cytoplasm and intraluminal and/or intracellular colloid-like secretions on histopathology and the presence of markers such as mammaglobin, vimentin, S-100 in immunohistochemical staining is important in differentiating MASC from other salivary gland tumors, especially acinic cell carcinoma.
- A neck dissection should be performed in addition to gland excision in cases of MASC localized to the submandibular gland or minor salivary glands and/or at an advanced stage (T3-T4).

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