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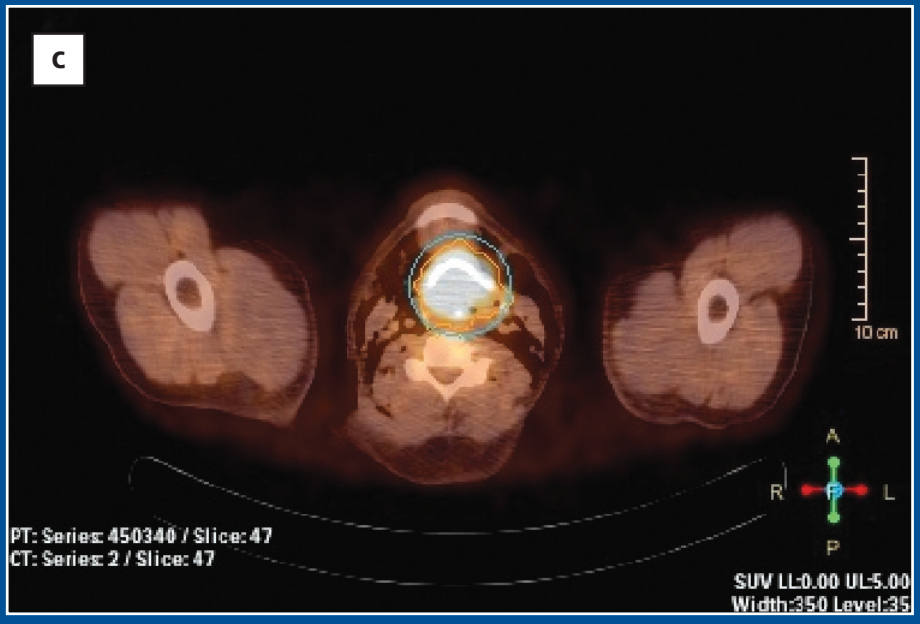

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Description

ENT Updates (formerly Journal of Medical Updates), is a periodical of the Continuing Education, and Scientific Research Association (CESRA), Turkey, which is published in both printed (p-ISSN 2149-7109) and electronic (e-ISSN 2149-6498) versions three times a year on April, August, and December. A peer-reviewed system is used to select manuscripts. The language of the journal is English. The journal is currently indexing and abstracting in Emerging Sources Citation Index (ESCI) by Thomson Reuters, TUBITAK ULAKBIM Turkish Medical Index, Proquest, EBSCO Host, Index Copernicus and Google Scholar.

Aims and Scope

The goal of the journal is to present and improve collective scientific knowledge and the scientific background dealing with otorhinolaryngological disorders and related subjects (allergy, pediatrics, neurology, psychiatry, neurosurgery, radiology, anesthesiology, pulmonology, etc.) via experimental and clinical studies, reviews, case reports, short communications and letters to the editor. The initial aim of this journal is to form a countrywide education platform and to share the recent information and learn about the treatment of various local or rare diseases in aware of the fact that a disease may be rare to a certain region while it is very common to another. The second aim of this journal and Continuous Education and Scientific Research Association (CESRA), a nonprofit organization serving for continuous education, is to represent our country in international arena of science and knowledge with the published papers. We aimed to undertake a novel effort in the international representation and attribution of published articles. That is why we have set an international editorial board from all over the world beside the national board spread to each corner of the country. The target readers of the ENT Updates include otorhinolaryngology specialists and residents as well as all other physicians working in the field of otorhinolaryngology or in related specialities.

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Gur Sokak, No: 7B

34720 Kadıkoy, İstanbul

Phone: +90 216 414 83 43 (Pbx)

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Predictive and prognostic values of pretreatment functional imaging-based biomarkers in advanced-stage laryngeal cancer

Görkem Eskiizmir[1], Gülgün Yılmaz Ovalı[2], Feray Aras[3], Beyhan Cengiz Özyurt[4], Serdar Tarhan[2]

[1]Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[2]Department of Radiology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[3]Department of Nuclear Medicine, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[4]Department of Public Health, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

Abstract

Objective: To determine the quantitative values of apparent diffusion coefficient (ADC), standardized uptake values (SUV_{max}, SUV_{mean}), metabolic tumor volume (MTV), metabolic tumor volume indexes (MTI_{max}, and MTI_{mean}) using diffusion weighted-MRI (DW-MRI) and positron emission tomography/computed tomography (PET/CT), and analyze the predictive and prognostic values of these biomarkers in a homogenous group of patients with advanced-stage laryngeal cancer.

Methods: Patients with newly diagnosed advanced-stage laryngeal cancer who had both DW-MRI and 18F-FDG PET/CT before treatment, and who had curative cancer treatment (surgery ± adjuvant therapy or radio ± chemotherapy) between 2011 and 2015 were included in this study. All patients were followed up clinically and radiologically, if necessary every 3 months for the first 2 years, every 4–6 months for year 3, and then annually thereafter.

Results: Thirty-eight patients were retrospectively analyzed. Our analysis demonstrated statistically significant differences when the pretreatment SUV and MTI_{mean} value were compared between patients with stages III and IV. Standardized uptake value was also a predictive factor for N-stage. Moreover, a statistically significant difference was determined when patients with and without perinodal involvement (PNI) were compared. Log rank analysis demonstrated that none of functional imaging-based biomarkers had a prognostic role for oncological outcomes.

Conclusion: Our results demonstrated that pretreatment SUV and MTI_{mean} values were predictive factors for staging, N-stage and PNI. Indeed, functional imaging-based biomarkers are promising, novel, non-invasive techniques that may provide additional information about tumor characteristics, treatment selection and prognosis in the near future.

Keywords: Predictive, prognostic, imaging-based biomarkers, laryngeal cancer.

Özet: İleri evre larenks kanserinde tedavi öncesi fonksiyonel görüntülemeye dayalı biyobelirteçlerin öngördürücü ve prognostik değeri

Amaç: Difüzyon ağırlıklı MR görüntüleme (DW-MRI) ve pozitron emisyon tomografi/bilgisayarlı tomografiyi (PET/BT) kullanarak görünür difüzyon katsayısının (ADC) nicel değerleri, standardize edilmiş tutulum değeri (SUV_{maks}, SUV_{ort}), metabolik tümör volümü (MTV), metabolik tümör volüm göstergelerini (MTI_{maks} ve MTI_{ort}) belirlemek ve ileri evre larenks kanserli homojen hasta grubunda bu biyobelirteçlerin öngördürücü ve prognostik değerlerini incelemektir.

Yöntem: Yeni tanı konmuş ileri evre larenks kanserli, tedavi öncesi hem DW-MRI hem de 18F-FDG PET/BT çektirmiş ve 2011–2015 yılları arasında küratif kanser tedavisi görmüş (cerrahi ± adjuvan tedavi veya radyoterapi ± kemoterapi) hastalar çalışmaya dahil edildi. Hastaların tümü gerektiğinde ilk 2 yıl 3 ayda bir, 3. yıl 4–6 ayda bir ve daha sonra yılda bir klinik ve radyolojik olarak izlendi.

Bulgular: Otuz sekiz hasta geriye dönük olarak incelendi. İncelememiz evre III ve IV hastalar arasında tedavi öncesi SUV ve MTI_{ort} değerleri açısından istatistiksel açıdan anlamlı farklılıklar olduğunu gösterdi. Standardize edilmiş tutulum değeri evresi de N-evresi için bir öngördürücü faktördü. Ayrıca perinodal tutulumu (PNT) olan ve olmayan hastalar arasında da istatistiksel açıdan anlamlı farklılık olduğu belirlendi. Logaritmik sıralama çözümlemesi, fonksiyonel görüntülemeye dayalı biyobelirteçlerin hiçbirisinin onkolojik sonuçlar açısından prognostik role sahip olmadığını gösterdi.

Sonuç: Bulgularımız tedavi öncesi SUV ve MTI_{ort} değerlerinin evreleme, N-evresi ve PNT açısından öngördürücü faktörler olduğunu göstermiştir. Gerçekten de fonksiyonel görüntülemeye dayalı biyobelirteçler tümörün özellikleri, tedavi seçimi ve yakın dönem prognozu hakkında ek bilgi sağlayan umut verici, yeni ve girişimsel olmayan tekniklerdir.

Anahtar sözcükler: Öngördürücü, prognostik, görüntülemeye dayalı biyobelirteçler, larenks kanseri.

Correspondence: Görkem Eskiizmir, MD., FTBORLHNS, sPh.D. Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey
e-mail: gorkemeskiizmir@yahoo.com

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Laryngeal cancer is one of the most common type of head and neck cancers with an incidence of 5.1–10/100,000 worldwide.[1] In laryngeal cancer, the survival rates are 63– 66% (5-year overall survival (OS) for glottic laryngeal cancer: 77% and 5-year OS for supraglottic laryngeal cancer: 51% for cancer).[2–4] However, the survival rates are suboptimal (≤50%) in patients with advanced-stage laryngeal cancer.[1,2,5–7]

Currently, cross-sectional imaging is of utmost important for accurate staging and treatment planning.[8] Therefore, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are frequently used for the imaging of patients with laryngeal cancer. In clinical practices, CT and/or MRI are generally recommended for the assessment of tumor extension and cervical lymph node involvement.[3,5,9] In addition, PET/CT is useful for the detection of lymph node metastasis, distant metastasis and second primary malignant neoplasms such as lung cancer.[10–13] Remarkably, recent advancements in the field of imaging technologies demonstrate that Diffusion weighted-MRI (DW-MRI) and PET/CT may provide significant additional information which are called as "*functional imaging-based biomarkers*". These biomarkers are promising candidates for the understanding of intrinsic tumor biology and features, and may be helpful for the depiction of tumor microenvironment, prediction of treatment response and prognosis in patients with cancer.[14–17] Briefly, DW-MRI, a form of functional MRI, evaluates the random motion of extracellular H_2O molecules which is quantitatively expressed as *apparent diffusion coefficient* (ADC). In literature, an inverse relationship between ADC values and cell proliferation and density has been reported in different neoplasms such as breast cancers, neuroepithelial tumors and nasopharyngeal cancers.[16,18,19] Moreover, several studies have demonstrated lower ADC values (showing high tumor cellularity) in malignant tumors of head and neck despite of different cut-off values (ranging $0.84–1.455\times10^{-3}$ mm^2/s).[20–26] In addition, PET/CT provides the measurement of different metabolic indexes such as standardized uptake values (SUV) and total lesion glycolysis (TLG), which is measured by metabolic tumor volume indexes (MTI), and volumetric parameters such as metabolic tumor volume (MTV) in several malignant neoplasms including cutaneous malignant melanoma, non-small cell lung cancer, bone and soft tissue sarcomas, brain tumors, breast cancers, renal cell carcinoma, T-cell leukemia, and head and neck cancers.[27–34] However, the predictive and prognostic roles of abovementioned functional imaging-based biomarkers are unknown in patients with advanced-stage laryngeal cancer. Therefore, the purpose of the current study is to determine the quantitative values of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} using DW-MRI and PET/CT, and analyze the predictive and prognostic values of these biomarkers in a homogenous group of patients with advanced-stage laryngeal cancer.

Materials and Methods

This retrospective study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Ethics Committee.[35]

Study population

The study population involved patients with advanced-stage laryngeal cancer who had curative cancer treatment (surgery ± adjuvant therapy or radio ± chemotherapy) between 2011 and 2015. The exclusion criteria were as follows: (i) patients who had a recurrent tumor, (ii) patients who had a palliative treatment or patients who rejected treatment, and (iii) patients who did not have pretreatment MRI and/or PET/CT. Therefore, all patients were newly diagnosed advanced-stage laryngeal cancer, and had both DW-MRI and 18F-FDG PET/CT before treatment. All patients were followed up clinically and radiologically, if necessary every 3 months for the first 2 years, every 4–6 months for year 3, and then annually thereafter. Any sign of recurrence at primary tumor burden and/or neck was defined as locoregional recurrence. In addition, any metastatic lesion at a solid organ (e.g. lung, liver, bone, etc.) was accepted as distant metastasis.

MRI acquisition

All MRI examinations were performed on a 1.5 Tesla scanner (Signa Excite HDX; General Electric Healthcare, Milwaukee, WI, USA). All patients also had conventional neck MRI before DW-MRI. Diffusion weighted-MRI was obtained with single-shot echo-planar imaging sequences in the axial plane with b=0 and 800 s/mm^2; TR/TE 2000/75 ms; 256×256 matrix; FOV: 230 mm; NEX: 16; 4 mm slice thickness; 0 mm interval. Images were processed in the workstation (Advantage Windows version 4.7; General Electric Healthcare, Milwaukee, WI, USA) with Functool software (General Electric Healthcare, Milwaukee, WI, USA). Apparent diffusion coefficient maps were processed and ADC values were calculated manually by an experienced radiologist (GYO, a European

Neuroradiology and Head and Neck certified specialist who has a 12 years' experience in head and neck imaging), who was blinded to clinical staging and PET-CT data. Contrast enhanced- and STIR images were compared and fusion images were performed with ADC maps to define the whole tumor volume (**Figs. 1a** and **1b**). The regions-of-interests (ROI) included all tumors' volume excluding necrotic parts. Apparent diffusion coefficient mean values and standard deviations were recorded for each patient individually.

18F FDG PET/CT acquisition

All patients acquired whole body and spot F-18 FDG PET/CT (Philips, Medical Systems, Cleveland, OH, USA). All patients were asked to fast for at least 6 hours before scanning. A peripheral blood glucose level of less than 180 mg/dl was confirmed initially, and patients received an intravenous injection of 145 µCi/kg (maximum 200 µCi) of FDG afterwards. All images were obtained from base of skull to mid thigh level (**Fig. 1b**). The SUV_{max} of primary tumor burdens and suspicious lymph node stations were detected automatically by the software after delineation of the ROI on attenuation-corrected PET/CT images. All F-18 FDG PET/CT scans were reevaluated by an author of the study (FA). Standardized uptake values (SUV_{max} and SUV_{mean}), MTV and MTI (MTI_{max} and MTI_{mean}) were calculated from primary tumor by automatic program.

Statistical analysis

All data were evaluated using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The descriptive results about study population and tumor characteristics were determined. Kolmogorov-Smirnov and Shapiro-Wilk tests demonstrated that study population was not normally distributed. Therefore, the predictive roles of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} were evaluated by Mann-Whitney U test. In addition, 2-year OS, locoregional control (LRC) and disease-free survival (DFS) were determined by Kaplan-Meier test. A "*receiver operating characteristic*" analysis was performed for a cut-off value of ADC value, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean}; however, we were unable to determine a value with a high sensitivity and specificity. Therefore, the median values of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} were measured. Thereby, study population was separated into two groups as "*low*" and "*high*" according to the median values of each variable. Thereafter, survival analysis was performed using log rank test. A p-value of <0.05 was accepted statistically significant.

Results

Descriptive statistics

Thirty-eight patients (33 males, 86.8%; 5 females, 13.2%) with advanced-stage laryngeal cancer were retrospectively analyzed. Of these patients, 18 presented with supraglottic carcinoma (47.4%), 5 with glottic carcinoma (13.2%) and 15 with transglottic carcinoma (39.5%). With regard to tumor stage, 19 (50%) patients presented with T3 tumors, 19 (50%) with T4 tumors. The distribution of tumor grades were as follows: 3 patients (7.9 %) with well differentiated tumors, 20 patients (52.6%) with moderately differentiated tumors, 9 patients (23.7%) with poorly differentiated tumors. The mean value of age was 64.4 (range: 47 to 87) years; and only 5 patients were female. The

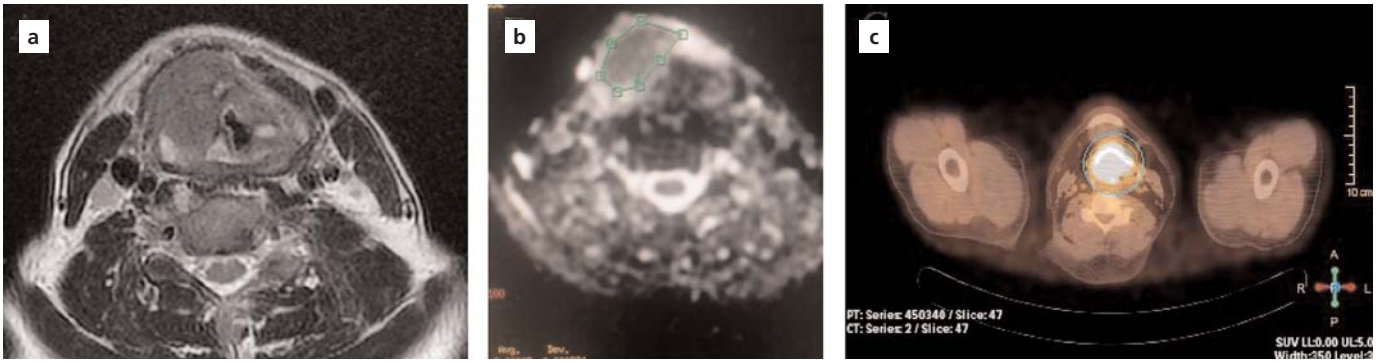


Fig. 1. Pretreatment MRI and PET/CT imaging of a case with advanced-stage laryngeal cancer. (**a**) Axial T2 weighted turbo spin echo imaging (TR/TE 4700/85), (**b**) ADC map showing laryngeal tumor with extralaryngeal extension, and (**c**) axial PET-CT demonstrated high SUV at the larynx. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

Table 1. Sociodemographic data and tumor characteristics.

Characteristics		n (%)
Sex	Female	5 (13.2)
	Male	33 (86.8)
Age	<65	13 (34.2)
	>65	25 (65.8)
Tumor location	Supraglottic	18 (47.4)
	Glottic	5 (13.2)
	Transglottic	15 (39.5)
Stage	Stage III	19 (50.0)
	Stage IV	19 (50.0)
T-stage	T3	22 (57.9)
	T4	16 (42.1)
TCI	Absent	24 (63.2)
	Present	14 (36.8)
N-stage	N0	22 (57.9)
	N1	3 (7.9)
	N2	13 (13)
LNI	Absent	22 (57.9)
	Present	16 (42.1)
PNI	Absent	30 (78.9)
	Present	8 (21.1)
Tumor differentiation	Well differentiated	3 (7.9)
	Moderately differentiated	20 (52.6)
	Poor differentiated	9 (23.7)
	Unidentified	6 (15.8)
Treatment	Surgery±Adjuvant therapy	24 (63.2)
	Radiotherapy±Chemotherapy	14 (36.8)
LRR	Absent	32 (84.2)
	Present	6 (15.8)
DM	Absent	34 (89.5)
	Present	4 (10.5)
Status	Alive	24 (63.2)
	Dead	14 (36.8)

DM: distant metastasis; **LNI:** lymph node involvement; **LRR:** locoregional recurrence; **PNI:** perinodal involvement; **TCI:** thyroid cartilage involvement

sociodemographic results and tumor characteristics are shown in **Table 1**. The median and standard deviation of pretreatment ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} values were 0.61±0.42 (range: 0.09 to 1.77) mm^2/s, 11.3±8.54 (range: 5.10 to 45.90), 12.4±10.52 (range: 3.36 to 57.79), 4.8±1.94 (range: 2.77 to 12.70), 25.8±38.33 ml (range: 1.02 to 202.24), 369.1 (range: 3.44 to 4542.10) and 132.8±277.14 (range: 2.84 to 1038.19), respectively.

Predictive value of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer

The predictive roles of functional imaging-based biomarkers were presented in **Table 2**. Our analysis demonstrated statistically significant differences when the pretreatment SUV (stage III: 9.7±9.4 *vs.* stage IV: 11.9±7.5, p=0.02) and MTI_{mean} value (stage III: 94.4±221.0 *vs.* stage IV: 146.3±312.7, p=0.04) were compared between patients with stage III and IV. Standardized uptake value was also a predictive factor for N-stage (N0+N1: 10.4±8.5 *vs.* N2: 12.8±8.4, p=0.04). Moreover, a statistically significant difference was determined when patients with and without perinodal involvement (PNI) were compared (absent: 108.3±292.1 *vs.* present: 241.8±215.4, p=0.04).

Prognostic value of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer

The 2-year OS, DFS and LRC were 52.6%, 57.2% and 57.2%, respectively. Log rank analysis demonstrated that none of functional imaging-based biomarkers (ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean}) had a prognostic role for oncological outcomes (**Figs. 2** and **3**).

Discussion

To the best of our knowledge, this is the first study in which various functional imaging-based biomarkers were evaluated in patients with advanced-stage laryngeal cancer using both DW-MRI and 18F-FDG PET/CT. Our literature review demonstrated that few clinical studies reported the role of both imaging techniques in head and neck cancers[15,36–41] (**Table 3**). However, the major drawback of these studies was the clinical heterogeneity of study groups in which patients with different primary tumor burdens (e.g. oropharynx, hypopharynx, nasopharynx, larynx and oral cavity) and stages were included. As a matter of fact, the measured ADC, SUV, MTV and TLG and clinical outcomes might vary significantly between abovementioned study groups. In addition, as Zhang et al. emphasized, small head and neck neoplasms are generally difficult to detect using DW-MRI; hence, the ADC values are generally unreliable.[16] Therefore, patients with early-stage laryngeal cancer were not enrolled into this study, and a homogenous group of patients with advanced-stage laryngeal cancer was particularly selected in order to determine reliable relationships between all functional imaging-based biomarkers and tumor characteristics or clinical outcomes; thereby, study group related misconceptions were minimized.

Table 2. The predictive roles of ADC, SUV, SUV_{max}, SUV_{mean}, MTV, MTI_{max}, and MTI_{mean} in advanced-stage laryngeal cancer.

		ADC		SUV		SUV_{max}		SUV_{mean}		MTV		MTI_{max}		MTI_{mean}	
		Median±SD	p	Median±SD	p	Median±SD	p	Median±SD	p	Median±SD	p	Median	p	Median±SD	p
Sex	Female	0.2±0.2	0.14	10.0±6.3	0.32	11.2±6.27	0.32	5.3±0.9	0.32	16.5±14.4	0.26	287.6	0.31	94.4±90.3	0.31
	Male	0.6±0.4		11.5±8.8		12.5±11.0		4.8±2.0		27.0±40.4		396.8		134.5±292.6	
Age	<65	0.8±0.4	0.08	10.6±7.9	0.07	11.6±10.0	0.07	4.9±1.9	0.15	27.0±27.7	0.35	229.6	0.18	94.1±208.8	0.21
	>65	0.3±0.3		11.9±8.7		12.5±10.7		4.8±1.9		25.5±43.1		371.8		134.5±308.9	
Grade	Well and moderately differentiated	0.6±0.4	0.14	12.8±9.0	0.53	13.6±11.0	0.14	5.4±1.9	0.05	32.0±45.7	0.19	453.7	0.12	148.8±319.0	0.18
	Poor	0.1±0.3		11.8±8.9		10.6±11.1		4.5±2.0		16.9±20.9		207.3		75.8±201.0	
Tumor location	Supraglottic/ Glottic	0.6±0.3	0.44	11.8±9.7	0.45	13.2±11.8	0.11	5.0±2.1	0.09	31.8±41.1	0.22	453.7	0.13	161.3±285.2	0.13
	Transglottic	0.3±0.4		11.1±6.6		10.8±8.0		4.4±1.4		24.2±34.5		247.1		94.4±269.4	
Stage	Stage III	0.3±0.3	0.14	9.7±9.4	0.02*	12.1±11.8	0.16	4.5±2.1	0.09	21.6±19.6	0.06	366.3	0.08	94.4±221.0	0.04*
	Stage IV	0.6±0.4		11.9±7.5		13.2±9.2		5.1±1.7		34.3±48.4		396.8		146.3±312.7	
T-stage	T3	0.4±0.3	0.22	10.3±10.1	0.08	12.5±12.4	0.34	4.7±2.2	0.50	22.9±20.4	0.08	369.1	0.18	106.4±232.3	0.11
	T4	0.6±0.4		11.7±5.9		11.4±7.5		5.0±1.5		35.3±51.7		373.5		141.6±322.5	
TCI	Absent	0.5±0.3	0.23	11.2±9.8	0.22	12.8±11.9	0.41	4.8±2.2	0.31	22.9±20.4	0.98	369.1	0.14	106.4±229.4	0.09
	Present	0.7±0.5		11.3±6.0		11.1±7.5		4.8±1.3		35.3±54.5		373.5		141.6±338.0	
N-stage	N0±N1	0.5±0.4	0.32	10.4±8.5	0.04*	11.6±10.7	0.15	4.5±1.9	0.11	24.2±40.6	0.31	366.3	0.24	118.4±271.0	0.21
	N2	0.6±0.3		12.8±8.4		13.6±10.4		5.3±1.9		34.3±34.8		396.8		146.3±294.6	
LNI	Absent	0.6±0.4	0.20	10.5±9.0	0.17	11.5±11.2	0.21	4.6±2.0	0.27	24.2±43.1	0.23	358.2	0.25	113.4±287.5	0.18
	Present	0.4±0.3		11.8±8.0		12.8±9.7		4.9±1.8		36.5±31.8		425.3		170.8±270.1	
PNI	Absent	0.4±0.4	0.12	10.8±8.4	0.12	11.9±10.5	0.16	4.6±1.9	0.06	23.9±41.6	0.06	300.3	0.06	108.3±292.1	0.04*
	Present	0.8±0.3		12.3±9.0		13.4±10.7		5.6±1.9		43.7±22.1		559.0		241.8±215.4	
LRR	Absent	0.5±0.4	0.09	11.3±9.1	0.47	11.9±11.3	0.46	4.8±2.0	0.47	23.9±41.3	0.16	318.9	0.24	113.3±298.9	0.21
	Present	0.9±0.4		11.2±3.3		12.8±2.8		4.9±0.9		33.1±16.9		427.0		147.5±102.8	
DM	Absent	0.6±0.4	0.33	11.1±8.0	0.25	12.3±10.0	0.43	4.8±1.8	0.34	24.8±39.7	0.11	358.2	0.19	124.7±280.7	0.14
	Present	0.5±0.4		12.6±12.7		12.0±15.3		5.0±2.7		52.6±25.3		684.5		267.0±266.1	

*Statistically significant ($p<0.05$)

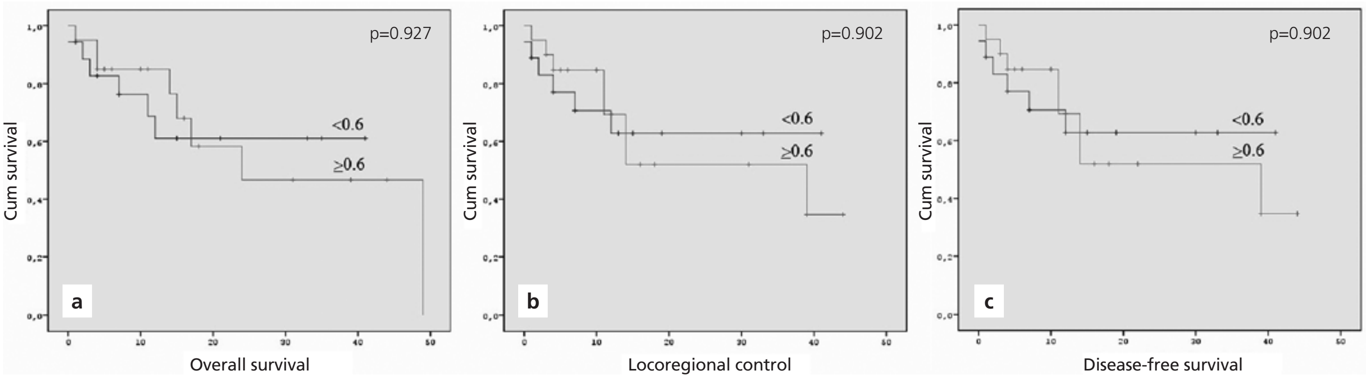


Fig. 2. The comparison of 2-year (**a**) OS, (**b**) LRC and (**c**) DFS according to pretreatment ADC values in patients with advanced-stage laryngeal cancer.

In laryngeal cancer, the association between pretreatment functional imaging-based biomarkers and tumor characteristics such as grade, neoplastic invasion or stage are inconclusive. In general, poorly differentiated tumors have more aggressive behavior and tendency to metastasize and recur. In addition, tumor cellularity is frequently high in poorly differentiated tumors. A recent meta-analysis demonstrated a moderate inverse correlation between ADC value and tumor cellularity in head and neck cancers, even though the number of included cases was less than 50 patients.[42] However, the authors emphasized that the association between ADC value and tumor cellularity var-

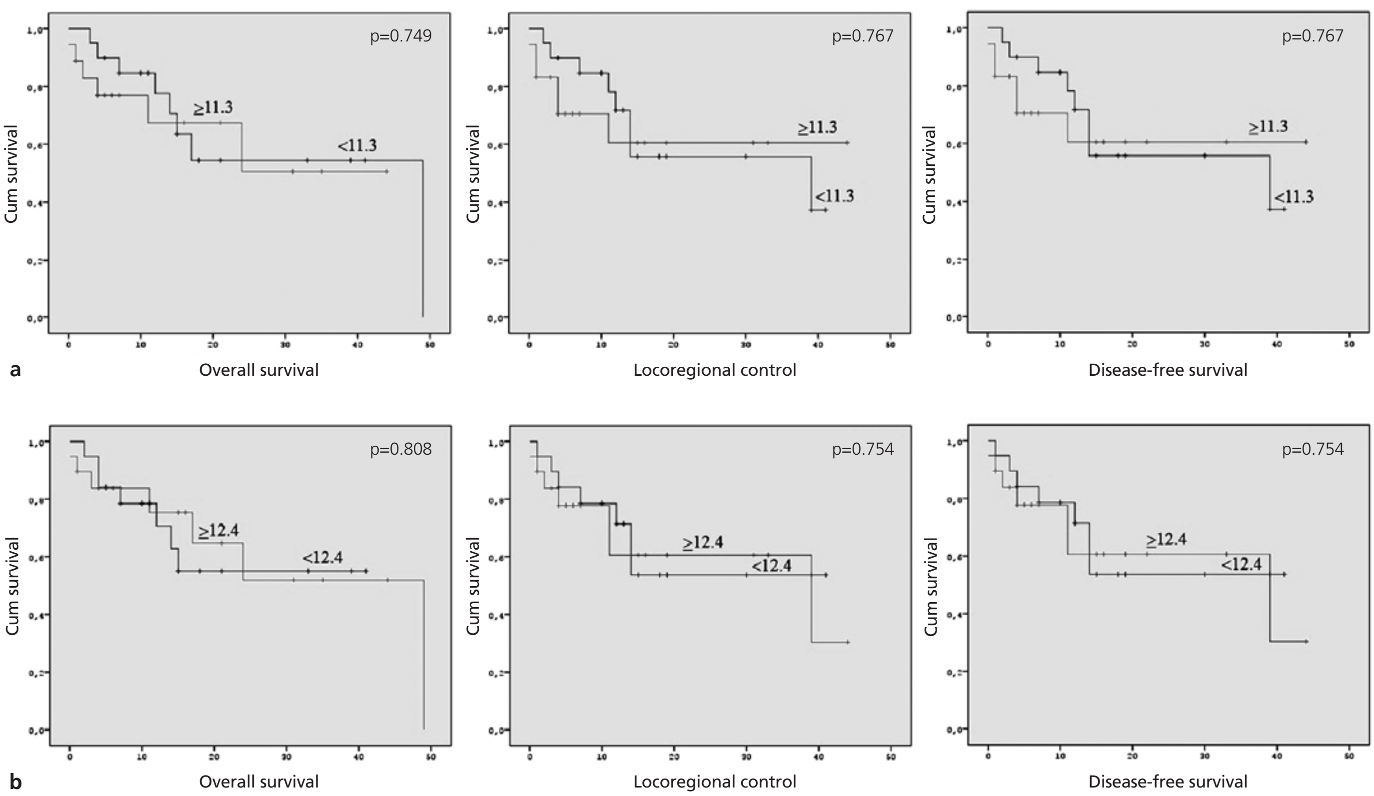
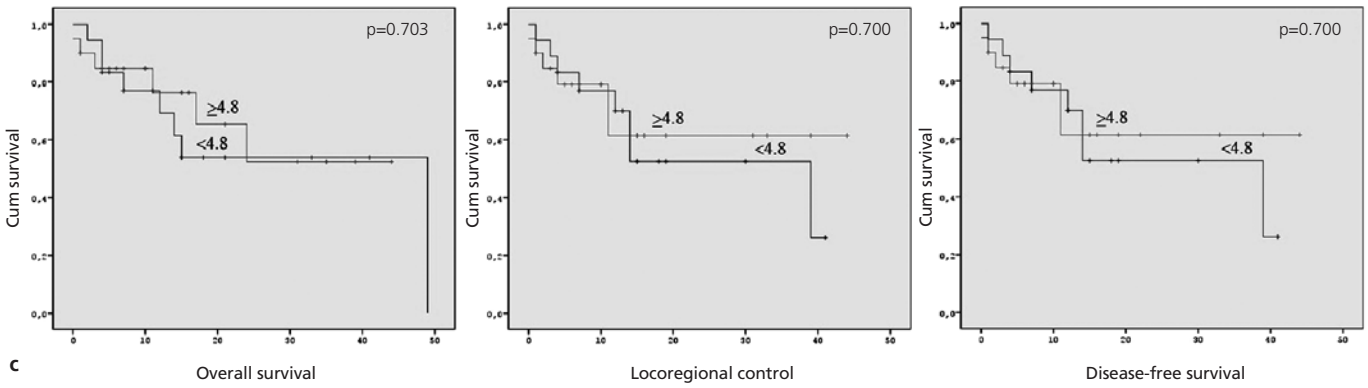
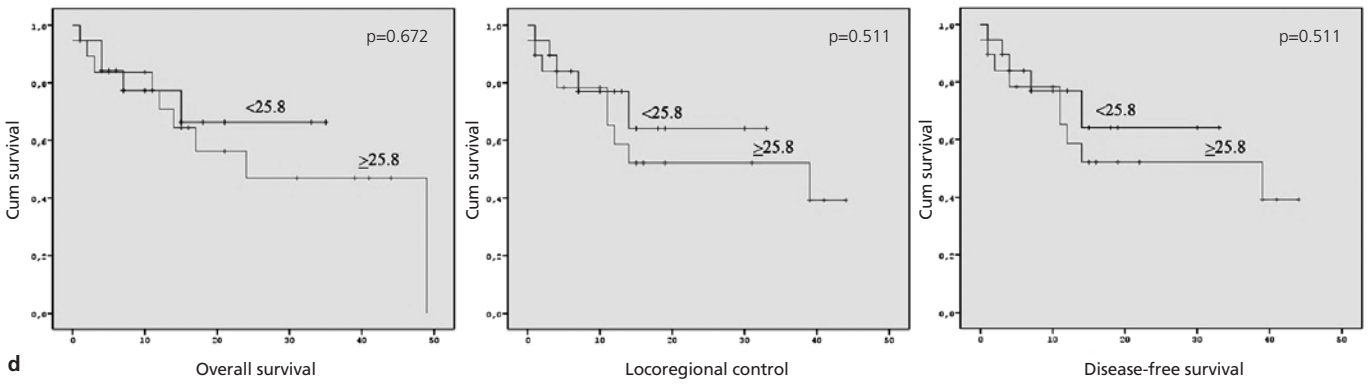


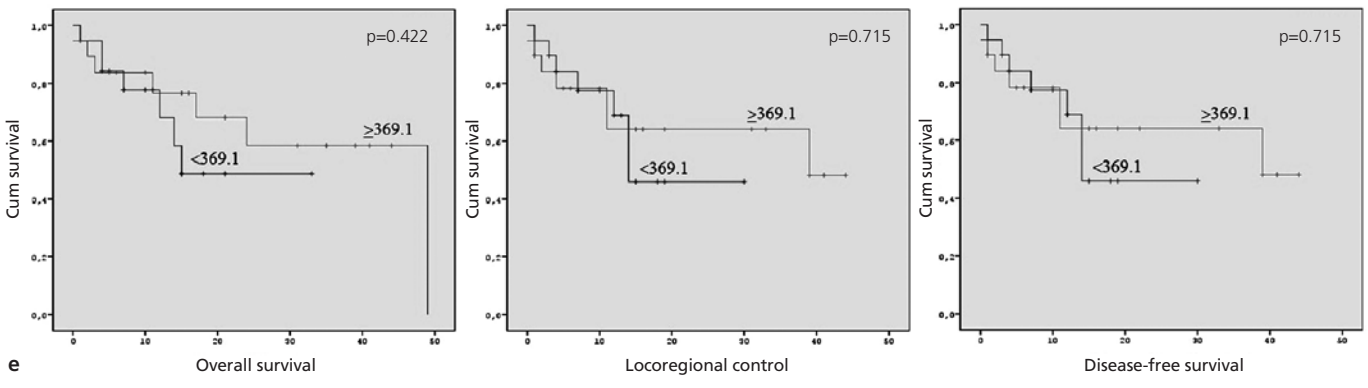
Fig. 3. The comparison of 2-year OS, LRC and DFS according to pretreatment (**a**) SUV, (**b**) SUV_{max}, (**c**) SUV_{mean}, (**d**) MTV, (**e**) MTI_{max}, and (**f**) MTI_{mean} values in patients with advanced-stage laryngeal cancer. *[Continued on next page]*


p=0.703
≥4.8
<4.8
Cum survival
Overall survival
p=0.700
≥4.8
<4.8
Cum survival
Locoregional control
p=0.700
≥4.8
<4.8
Cum survival
Disease-free survival

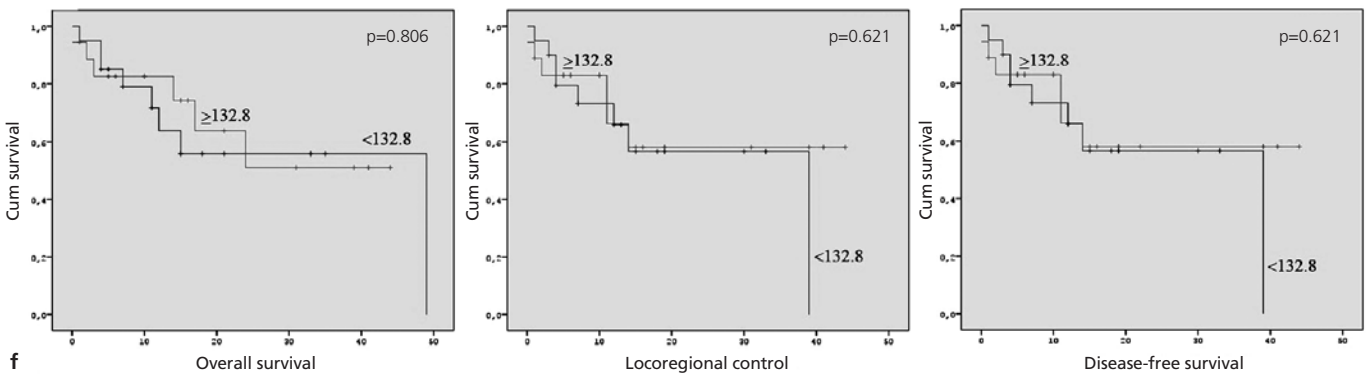
c


p=0.672
<25.8
≥25.8
Cum survival
Overall survival
p=0.511
<25.8
≥25.8
Cum survival
Locoregional control
p=0.511
<25.8
≥25.8
Cum survival
Disease-free survival

d


p=0.422
≥369.1
<369.1
Cum survival
Overall survival
p=0.715
≥369.1
<369.1
Cum survival
Locoregional control
p=0.715
≥369.1
<369.1
Cum survival
Disease-free survival

e


p=0.806
≥132.8
<132.8
Cum survival
Overall survival
p=0.621
≥132.8
<132.8
Cum survival
Locoregional control
p=0.621
≥132.8
<132.8
Cum survival
Disease-free survival

f

Table 3. Systemic review of clinical studies in which the predictive and/or prognostic roles of both DW-MRI and PET/CT were assessed in patients with head and neck cancers.

Author	Study population	Tumor location	T-Stage	N-Stage	Stage	SUV (cut-off value)	ADC (cut-off value $\times 10^{-3}$)	Treatment	Highlights
Choi et al., 2011	47	Oral cavity Pharynx Sinonasal cavity	NS	NS	NS	NA	NA	Surgery Radiotherapy Chemotherapy	Both ADC and SUV values were low in poorly differentiated tumor
Nakajo et al., 2012	26	Larynx Hypopharynx Oropharynx Oral cavity Maxillary sinus	T1–T4	N0–N3	I–IV	12.1	0.88	Radiotherapy Surgery	Lower ADC and higher SUV values were related with a significant decrease in 2-year DFS
Houweling et al., 2013	18	Oral cavity Oropharynx Nasopharynx	T1–T4	NS	NS	NS	NS	Radiotherapy	Both SUV and ADC values were helpful for dose painting in HNC
Varoquaux et al., 2013	34 (24 primary, 10 suspected recurrence)	Larynx Hypopharynx Oropharynx Oral cavity Parotid gland Paranasal sinus	T1–T4	NS	NS	NS	NS	Surgery Radiochemotherapy	There was no statistically significant relationship between tumor grade and SUV or ADC values ADCmean, ADCmin, and SUVmean values were not different between primary and recurrent HNC
Preda et al., 2016	57	Oral cavity Oropharynx	T1, T2 and T4	N0–N2	NS	5.75	ADC_{max}=1.18 ADC_{mean}=0.98 ADC_{min}=0.58	Surgery Radiochemotherapy Multimodal treatment	Patients with high SUV_{max} and ADC_{min} values had the worst prognosis

ied significantly in different types of cancers with an inconsistent data between clinical studies. They also speculated that the variability in results might be related with tumor features (cellular proliferation, nucleic areas, etc.) and microenvironment (stroma-parenchyma ratio, microvessel density, necrotic areas, etc.). In fact, Driessen et al. were unable to detect an association between ADC value and tumor grade.[43] Similarly, our results demonstrated that none of the functional based-imaging biomarkers was associated with tumor differentiation (**Table 2**). In clinical practices, the detection of neoplastic invasion of thyroid cartilage is of utmost important for treatment selection and strategy, and prognosis. Currently, CT and/or MRI are frequently used despite of inadequate sensitivity, specificity, and positive and negative predictive values.[44,45] Therefore, novel techniques are required for the improvement of these imaging modalities. Hence, Taha et al. reported that DW-MRI had high sensitivity and specificity for the prediction of TCI in patients with laryngeal cancer; however, the authors did not give any information about ADC values.[46] In addition, Kendi et al. evaluated several PET/CT-based imaging biomarkers including SUV_{max}, SUV_{mean}, SUV_{peak}, MTV, TLG, standardized added metabolic activity and normalized standardized added metabolic activity in patients with larynx cancer, and reported that none of the forementioned parameters was either sensitive or specific enough for the prediction of TCI.[47] In this study, we were also unable to detect an association between pretreatment functional imaging-based biomarkers and TCI (**Table 2**).

In fact, patients with advanced-stage head and neck cancers have a tendency to have high PET/CT-based

imaging biomarkers.[37,48] Our results also demonstrated statistically significant association between stage and pretreatment SUV (stage III: 9.7±9.4 *vs.* stage IV: 11.9±7.5, p=0.02) and MTI_{mean} (stage III: 94.4±221.0 *vs.* stage IV: 146.3±312.7, p=0.04) values. Moreover, pretreatment SUV of primary tumor were remarkably high in patients with N2-stage (N0+N1-stage=10.4±8.5 *vs.* N2=12.8±8.4, p=0.04). On the other hand, none of the functional imaging-based biomarkers demonstrated a statistically significant difference when patients with and without LNI were compared. However, pretreatment ADC value was relatively low in patients with LNI (patients without LNI: 0.6+0.4 *vs.* patients with LNI: 0.4+0.3, p=0.20). It is noteworthy that lower pretreatment ADC values were reported in metastatic cervical lymph nodes.[49–52] On the other hand, Sumi et al. detected lower pretreatment ADC values in benign lymph nodes when compared with metastatic lymph nodes.[53] Presumably, the reason for this discrepancy might be related with tumor heterogeneity and presence/absence of necrotic portions in lymph nodes.[54] Moreover, Kwee et al. emphasized the limitations in intra- and interobserver reproducibility of ADC measurements of lymph nodes.[55]

In laryngeal cancers, the prognostic role of pretreatment functional based-imaging biomarkers remains controversial. In this study, no correlation between pretreatment ADC values and oncological outcomes including 2-year OS, LRC and DFS was determined (**Fig. 2**). It is noteworthy that our literature review was unable to determine a clinical study which was particularly focused on the prognostic role of pretreatment ADC value in patients with laryngeal cancer. However, Hatakenaka et al. examined the prognostic role of pretreatment ADC values in patients treated with radiotherapy for head and neck cancers and determined high risk of local failure in patients with high pretreatment ADC value.[56] Similarly, Preda et al. emphasized that high pretreatment ADC_{min} value (cut-off value: 0.58×10^{-3} mm^2/s) was a poor prognostic factor for patients with head and neck cancer.[40] In contrast, Nakajo et al. reported a significant decrease in 2-year DFS in patients with low pretreatment ADC value (cut-off value: 0.88×10 mm^2/s).[37] Nevertheless, both Preda et al. (cut-off value: 5.75) and Nakajo et al. (cut-off value: 12.1) demonstrated an inverse correlation between pretreatment SUV of primary tumor and survival in patients with head and neck cancers. However, Park et al. were unable to determine a statistically significant correlation between pretreatment SUV_{max} (cut-off value: 10) and oncological outcomes including 3-year LRC and OS in patients with laryngeal and hypopharyngeal cancer.[57] On the other hand, Kitajima et al. particularly evaluated the prognostic value of pretreatment SUV in patients with laryngeal cancer and reported that pretreatment SUV of primary tumor (cut-off value: 2.85) was a prognostic imaging biomarker for patients who were treated by radio±chemotherapy.[58] Interestingly, they did not find a correlation between pretreatment SUV of primary tumor (cut-off value: 8.6) and survival in patients who were treated by surgery with/without adjuvant treatment. In contrast, Joo et al. reported that patients who were treated by supracricoid laryngectomy had unfavorable outcome and poor prognosis when the pretreatment SUV_{max} of primary tumor was higher than 7.0.[59] In our study, we were unable to determine a correlation between pretreatment SUV (cut-off value: 11.3), SUV_{max} (cut-off value: 12.4), and SUV_{mean} (cut-off value: 4.8) of primary tumor and oncological outcomes (**Fig. 3**). It is known that patient related- (e.g. plasma glucose level, body mass index, etc.), tumor related- (e.g. tumor size, shape and microenvironment) and technique related-factors (e.g. post-injection PET scan time, acquisition protocol, imaging procedure, software, etc.) may affect the measured SUV values. Therefore, a variety of novel quantification techniques such as MTV and TLG were presented recently. A systematic review and meta-analysis demonstrated that MTV and TLG were prognostic imaging biomarkers for patients with head and neck cancers, and high MTV and TLG values caused more than 3-fold increase in mortality risk.[60] However, the authors also noted that their study had several limitations including different cut-off values for MTV and TLG, protocol related measurement changes, and clinical heterogeneity (e.g. primary tumor burden, tumor differentiation and stage) in head and neck cancers. Nonetheless, Yabuki et al. determined an inverse correlation between pretreatment MTV values (cut-off value: 4.9 ml) and survival in patients who were treated by radio+chemotherapy for laryngeal cancer.[61] Furthermore, same group also reported that patients with high pretreatment MTV values (cut-off value: 4.9 ml) had better survival outcomes when surgery-based treatment strategy was performed.[62] Hence, they suggested that MTV might be used for treatment selection in laryngeal cancer. As abovementioned, our study population was composed of patients with advanced-stage laryngeal cancer; therefore, the median value for MTV (cut-off value: 25.8 ml) was remarkably higher than forementioned studies. However, our results did not show a survival difference between patients with high and low MTV values (**Fig. 3**).

Conclusions

This is the first study that particularly focused on evaluating the predictive and prognostic roles of pretreatment functional imaging-based biomarkers in patients with advanced-stage laryngeal cancer. Our results obviously demonstrated that pretreatment SUV and MTI_{mean} values were predictive factors for staging, N-stage and PNI. Indeed, functional imaging-based biomarkers are promising, novel, non-invasive techniques that may provide additional information about tumor characteristics, treatment selection and prognosis in the near future. However, tumor- and protocol related differences are the major drawbacks. Therefore, well-stratified, multicenter, prospective clinical studies with tumor-specific standardized cut-off values and protocols are required.

Conflict of Interest: No conflicts declared.

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Detection of human papilloma virus in normal and tumoral oropharyngeal tissue using HPV DNA in situ hybridization and p16 expression and its clinicopathologic importance

Özlem Önerci Çelebi[1], Ebru Şener[2,3], Makbule Çisel Aydın[2], Gaye Güler Tezel[2]

[1]*Department of Otolarygology - Head and Neck Surgery, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[2]*Department of Pathology, Faculty of Medicine, Hacettepe University, Ankara, Turkey*
[3]*Department of Pathology, Faculty of Medicine, Atatürk University, Erzurum, Turkey*

Abstract

Objective: The rise in the number of cancer cases with human papilloma virus (HPV)-positive squamous carcinoma of the oropharynx makes the detection of HPV clinically important. We aimed to investigate the HPV positivity in our patients who have oropharyngeal cancer and compare the two different HPV detection methods, which are HPV in situ hybridization (ISH) and p16 immunohistochemistry (IHC), and show the staining patterns.

Methods: Twenty-three specimens of oropharyngeal cancer patients and ten tonsillectomy specimens that revealed no cancerous tissue (control group) were collected from retrospective file analysis. All specimens were evaluated by both p16 IHC and HPV ISH on paraffin blocks.

Results: Seven of 23 cases showed p16 expression. Of all these 7 cases that showed p16 expression, six showed high p16 expression and one showed low p16 expression. All six cases that showed high p16 expression were HPV ISH (+). One case that showed low expression of p16 was HPV ISH (-). All cases that were p16 (+) showed diffuse p16 expression and none of the cases showed focal p16 expression.

Conclusion: High p16 expression (>70%) is a reliable marker of HPV positivity. Combining p16 IHC with HPV ISH will further improve its specificity. All p16 positive cases showed diffuse p16 expression, thus did not show tumor heterogeneity, suggesting that even a biopsy specimen showing diffuse p16 expression shows p16 positivity of the whole tumoral tissue.

Keywords: Human papilloma virus, oropharyngeal cancer, p16 immunohistochemistry, in situ hybridization.

Özet: Normal ve tümöral orofaringeal dokuda in situ hibridizasyon ve p16 ekspresyonu ile human papilloma virüsü varlığının değerlendirilmesi ve klinikopatolojik önemi

Amaç: Human papilloma virüs (HPV) pozitif orofaringeal hücreli kanser olgularında son yıllarda görülen artış, bu virüsün tespitinin klinik önemini artırmaktadır. Bu çalışmada amacımız orofaringeal kanser hastalarımızın HPV pozitiflik oranlarını bulmak, farklı HPV tespit yöntemleri olan p16 immünohistokimya (IHC) ve in situ hibridizasyonunun (ISH) etkinliğini karşılaştırarak boyanma paternlerini göstermektir.

Yöntem: Retrospektif dosya taraması ile bulunan 23 hasta ve 10 kontrol çalışmaya dahil edilerek hastaların patoloji arşivinden bulunan parafin bloklarında p16 IHC ve HPV ISH çalışıldı.

Bulgular: Yirmi üç olgunun 7'si p16 pozitif idi. Bunların altısı yüksek p16 ekspresyonu gösterirken biri düşük p16 ekspresyonu göstermekteydi. 23 olgunun altısı ISH pozitif idi. Yüksek p16 ekspresyonu gösteren tüm olgular HPV ISH pozitif iken düşük ekspresyon gösteren bir olgu HPV ISH negatif idi. Tüm p16 pozitif olgular diffüz p16 ekspresyonu göstermekteydi, dolayısıyla tümör heterojenitesi göstermemekteydi.

Sonuç: Yüksek p16 ekspresyonu (>%70) HPV pozitifliğinin güvenilir bir göstergesidir ve p16 IHC ile kombine etmek spesifitesini artırmaktadır. Olgular tümör heterojenitesi göstermemekte, dolayısıyla alınan az miktarda biyopsi parçasında bile p16 ekspresyonunun gözlenmesi bize tüm tümöral dokuda p16 ekspresyonu olduğunu göstermektedir.

Anahtar sözcükler: Human papilloma virüs, orofaringeal kanser, p16 immunohistokimya, in situ hibridizasyon.

Correspondence: Özlem Önerci Çelebi, MD. Department of Otolarygology - Head and Neck Surgery, Faculty of Medicine, Hacettepe University, Ankara, Turkey.
e-mail: oonerci@yahoo.com

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Cancer of the head and neck is the sixth most common cancer diagnosed worldwide, with tobacco and alcohol abuse being the most established risk factors.[1,2] However, human papilloma virus (HPV) has also been shown to have a role in development of cancer of head and neck, especially in the oropharynx.[1,3–5] The number of head and neck cancers has shown a steady decrease over the recent years, whereas the number of oropharyngeal squamous cell carcinoma has shown an increase, which may be attributed to increased rates of HPV infection.[6,7] The HPV-positive squamous cell carcinoma (SCC) is different from HPV-negative SCC in that it commonly occurs in younger patients with multiple sex partners and higher exposure to oral sex, and is less related to alcohol and tobacco consumption when compared to HPV-negative SCC.[5,8] There is also data suggesting that patients who have HPV-positive oropharyngeal cancer differ from the HPV patients regarding the prognosis and survival.[9,10] Therefore, it has become even more important to detect HPV infection.

There are a couple of methods used for detection of HPV. However, the best method for detection of HPV is still controversial. HPV-positive oropharyngeal cancers have been increasing, making it increasingly important to identify the HPV status in oropharyngeal SCC. The current study aimed to examine the HPV positivity in tissues of oropharyngeal cancer and normal oropharyngeal mucosa, compare two different methods of HPV detection that were HPV in situ hybridization (ISH) and p16 immunohistochemistry (IHC), and study the relationship between the existence of HPV DNA and p16 expression in normal and cancerous oropharyngeal tissues.

Materials and Methods

Twenty-three specimens of oropharyngeal cancer patients and ten tonsillectomy specimens that revealed no cancerous tissue were retrieved from the paraffin block archives in the Department of Pathology, Hacettepe University from 1990 to 2014. The formalin-fixed paraffin-embedded tissue specimens and Hematoxylin and Eosin stained slides of tumors for each case were retrieved. The patients who had their pathologic specimens obtained in another hospital and were referred to our hospital for further treatment, patients with inconsistent or missing data, patients with any previous treatments, patients whose paraffin block was not available in the pathology archives or whose specimen was limited to do additional research were excluded. All slides of cases were re-examined for confirmation the diagnosis, and the paraffin block which included adequate tumor tissue was selected for DNA isolation. Demographics of the patients, clinical findings and the pathological characteristics of the tumor including histopathological differentiation, tumor extension, and nodal status were recorded. Ten cases in the control group were selected from the patients who had tonsillectomy for reasons other than malignancy (i.e. chronic tonsillitis, obstructive sleep apnea syndrome). The study protocol was approved by the Ethics Committee of the University and was conducted in accordance with the Declaration of Helsinki.

p16 immunohistochemistry

All specimens were examined for expression of p16 by IHC. p16 IHC was performed using a proprietary kit (Roche mtm laboratories AG, Basel, Switzerland). The positive control was determined as a squamous cell carcinoma of the tonsil with high p16 expression. Normal tonsil was used as a negative control. Staining was graded as: 0=negative; 1+=1% to 25% of cells positive; 2+=26% to 50%; 3+=51% to 75%; 4+=76% to 100%.[11]

High-risk (HR) HPV in situ hybridization

HR HPV ISH was performed using proprietary reagents (Inform HPVIII Family 16 Probe (B); Ventana Medical Systems Inc, Oro Valley, AZ, USA), which can detect high-risk HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66). Positive control was determined as a head and neck squamous cell carcinoma case that was HPV-positive, and negative control was determined as normal tonsil sections. The HR HPV ISH test was reported to be positive when there was any blue reaction product with the nuclei of malignant cells.[12]

Interpretation of HPV tests

Two head and neck pathologists independently evaluated the p16 IHC and HR HPV IHS tests. Consensus was established between pathologists in cases where results were inconsistent.

Statistical analysis

Statistical tests were performed using SPSS 22.0 statistical software (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to define the characteristics of each group. The association of p16 expression with clinicopathological features was carried out by the chi-square test and Fisher's exact test, where appropriate. The statistical significance of all tests was set to a $p<0.05$.

Results

Our study included 23 patients, 21 of which were men (91%) and 2 were women (9%). All the patients were diagnosed with squamous cell cancer of the oropharynx. The mean age of the patients was 59.4 years, ranging from 41 to 74. Patient ages showed normal distribution (Kolmogorov-Smirnov test, Shapiro-Wilk test; p>0.05) Demographics of the patients, clinical findings and pathological characteristics of the tumor can be seen in **Table 1**. There was no statistically significant difference between HPV positivity and gender (Fischer's exact test, p=0.462), primary tumor site (chi-square test, p=0.519), smoking (chi-square test, p=0.283), alcohol use (chi-square test, p=0.665), T stage (chi-square test, p=0.093) and N stage (chi-square test, p=0.177).

Of all our patients with oropharyngeal SCC, 6 (26%) were HPV ISH (+). Seven of these 23 cases showed p16 expression. Of these 7 cases, six showed high p16 expression (++++) and one showed low p16 expression (++). All 6 cases that showed high p16 expression were HPV ISH (+) (**Fig. 1**). One case that showed low expression of p16 was HPV ISH (-) (**Fig. 2**). The recurrent biopsies of the HPV ISH and p16 (+) patients were also HPV ISH and p16 (+).

Six patients showed high p16 expression and were HPV ISH (+). In 4 of these patients, the tumor was localized in the tonsil and the tumor was localized in the base of tongue in two patients. All cases that were p16 (+) showed diffuse p16 expression and none of the cases showed focal p16 expression.

The mean ages of the HPV (+) and HPV (-) groups were 59.5 and 59.4, respectively, thus the ages of the two groups were similar. The data regarding smoking and alcohol use was available for 21 of the 23 cases. Of the 6 HPV (+) cases, data regarding smoking and alcohol use was available for 5 cases. Of these 5 patients that were HPV (+), 3 reported they did not smoke or use alcohol. Only one of these 5 HPV (+) cases had history of smoking

Table 1. Demographic, clinical and pathological characteristics of the patients.

No	Age (Range)	Primary	T stage	N stage	HPV ISH	p16	Smoking (PPY)	Alcohol use
1	60–70	BOT	4	2c	-	-	60	+
2	60–70	BOT	2	0	+	++++	0	+
3	50–60	BOT	3	1	-	-	60	+
4	40–50	Tonsil	2	2b	-	-	15	-
5	60–70	BOT	2	2b	+	++++	25	+
6	60–70	BOT	3	1	-	++	50	+
7	>70	Tonsil	2	0	-	-	0	-
8	>70	Tonsil	2	1	+	++++	0	-
9	40–50	Tonsil	3	2c	-	-	25	+
10	40–50	BOT	3	0	-	-	ND	ND
11	>70	BOT	3	0	-	-	0	-
12	40–50	Tonsil	4a	2c	+	++++	ND	ND
13	50–60	Tonsil	3	0	-	-	80	+
14	60–70	Tonsil	1	2a	+	++++	0	-
15	60–70	Tonsil	2	1	-	-	40	SD
16	60–70	BOT	4a	2c	-	-	20	SD
17	50–60	Tonsil	3	2b	-	-	30	-
18	60–70	Tonsil	3	2b	-	-	40	+
19	50–60	Tonsil	2	2a	+	++++	0	-
20	50–60	BOT	2	0	-	-	20	+
21	60–70	BOT	3	2c	-	-	30	-
22	>70	BOT	2	2c	-	-	80	+
23	60–70	Tonsil	2	2b	-	-	80	+

BOT: base of tongue; **No:** patient number; **ND:** no data; **PPY:** pack per year; **SD:** social drinker

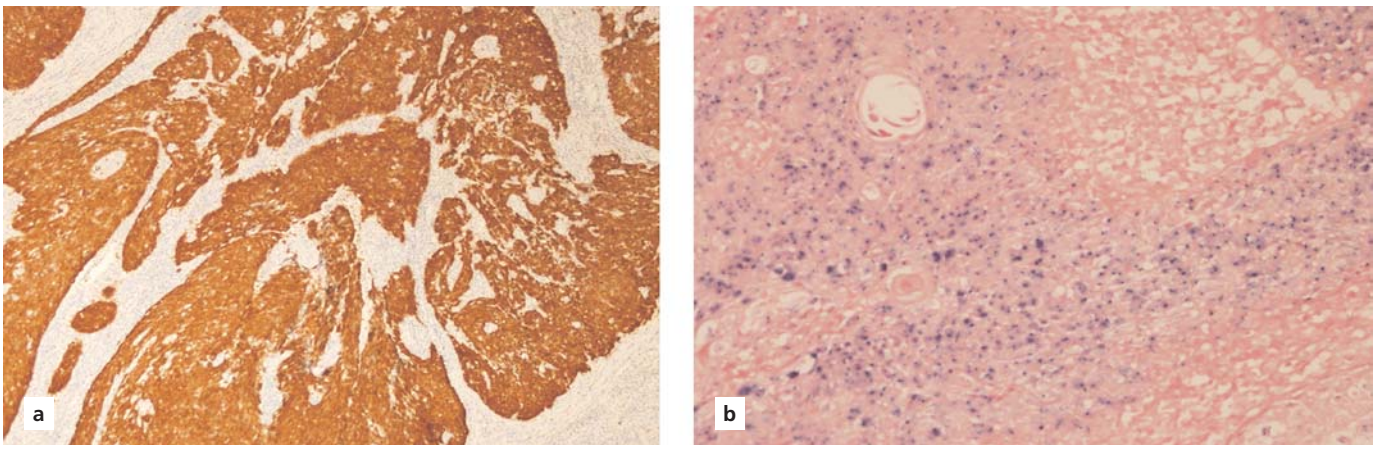

Fig. 1. Specimen of a case with oropharyngeal squamous cell cancer. (**a**) Tumor cells showing diffuse and strong nuclear and cytoplasmic p16 expression (×100 magnification). (**b**) The specimen was positive for high-risk HPV by in situ hybridization (×400 magnification). [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

and this case smoked 25 PPY (pack per year). The nonsmokers were more common in the HPV (+) group.

Six cases reported that they did not smoke, and 4 of these cases were HPV (+). Fifteen cases reported that they smoked 43.6 PPY on average.

The age of the HPV16-positive group was similar to that of the HPV16-negative group (mean 59.5 vs. 59.4 years).

The control group comprised of 10 cases with normal oropharyngeal tissue without evidence of any malignancy. The mean age of the control group was 37.5 years, ranging from 25 to 55. Five cases (50%) in the control group were female and 5 (50%) cases were male.

Discussion

Squamous cell cancer of the oropharynx has increased significantly over recent years.[6,7] Tural et al. demonstrated a continuous increase in the proportion of HPV positive oropharyngeal squamous cancer from 33% between 1996 and 1999 to 70% between 2008 and 2011 in Turkey.[13] This increase makes detection of HPV status clinically important in our country, like the other countries. HPV status also has been shown to be important in oropharyngeal positive SCC (OPSCC) regarding prognosis and survival.[9,10]

There are a couple of methods to detect HPV, each with different sensitivity and specificity.[14,15] Strong association

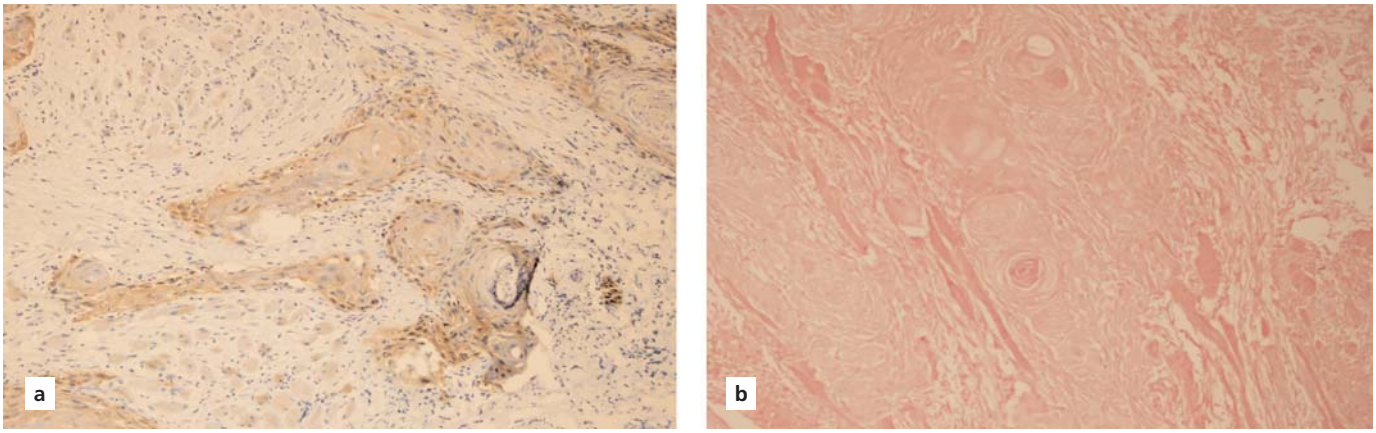

Fig. 2. Specimen of a case with oropharyngeal squamous cell cancer. (**a**) Tumor cells showing low p16 expression (×200 magnification). (**b**) The specimen was negative for high-risk HPV by in situ hybridization (×400 magnification). [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

has been reported between detection of the integrated HPV and over-expression of p16 protein, thus it was suggested that p16 immunohistochemistry could be an alternative procedure for detection of HPV in clinical practice for patients with oropharyngeal carcinoma; as it was simple, inexpensive and highly sensitive.[16–18] It was reported that p16 IHC is a better alternative for detection of HPV mRNA.[19] OPSCC cases were suggested to be screened using p16 IHC, and if the case was p16 positive, then ISH can be used.[20] However, some studies suggest that no procedure like p16 IHC should be used as an alternative to the more reliable diagnostic procedures, based on HPV nucleic acid detection.[21]

The purpose of this study was therefore to compare different HPV detection methods, particularly p16 immunohistochemistry and in situ hybridization, and show the staining patterns.

The proportion of HPV (+) cases in our study was 26% (6/23). This is lower than the current literature, which demonstrates that HPV may account for 70–80% of oropharyngeal squamous cell carcinoma.[22,23] One reason suggested by several studies could be that oropharyngeal HPV infection may be acquired sexually.[24,25] Our community is conservative, therefore this could be attributed to rarity of high-risk sexual behavior. Besides, our study sample is small which could have an impact on the results.

History of tobacco use was another factor related to with HPV status. Our cases with HPV infection tended not to have a history of smoking. Six cases were HPV ISH (+) and 5 of these cases had data regarding smoking and alcohol history. Of these 5 HPV (+) cases, 4 were non-smokers. Only one of these 5 HPV (+) cases had history of smoking and these cases smoked 25 PPY. Compared to the average tobacco consumption of the smoking cases (43.6 PPY), this number is well below the average PPY. Besides, in total, 6 cases had no history of smoking and 4 of these cases (67%) were HPV (+). All these findings are consistent with the literature, as HPV (+) squamous cell carcinoma is less strongly associated with alcohol and tobacco use compared with HPV-negative SCC.[5,8]

The age of the HPV16-positive group was similar to that of the HPV16-negative group (mean 59.5 vs. 59.4 years). However, it is stated in the literature that HPV (+) tumors are more likely to be seen in younger population.[4,12,22] This difference might result from the small number of our study population.

In the literature, oropharyngeal cancers that are HPV positive were reported to be more likely to present with an early T stage, but relatively advanced involvement of the lymph nodes.[4,12,22] In our study, the HPV (+) patients were more likely to be present with early T stage but relatively advanced stage, consistent with the literature, although this was not statistically significant.

Our study showed that almost all of the specimens (6/7) that were p16 (+) on IHC were HPV ISH (+). The amount of HPV (+) / p16 (-) specimens was 0%, like in similar studies.[17] Only one specimen (1/7), which was p16 (+), was HPV ISH (-) (14%). This specimen was weak p16 (+). The amount of HPV (-) / P16 (+) tumors differ in the literature, changing from 5% to 20.45%.[6,14,17] The result of our study (14%) is in this range. However, we would like to point out that the p16 (+) specimen that was HPV ISH (+) was noted to show low p16 expression on IHC. There are also studies that classify >70% staining as high p16 (+). According to this classification, again, 6 of the 7 p16 (+) specimens were classified as high p16 (+), thus our results did not change according to different classifications among different studies.[21] Therefore, it can be concluded that high p16 expression is a reliable marker of HPV positivity. Additional tests are needed only if the specimen shows low p16 expression, as this would be much more cost-effective. IHC is a simple test, with low cost and high sensitivity.[16,18] p16 IHC can be combined with PCR or ISH to improve its specificity as a test.

A cancerous tissue might exhibit distinct molecular features, known as tumor heterogeneity, resulting in resistance to treatment.[26] However, in our study, all our cases that were p16 positive showed diffuse p16 expression, thus did not show tumor heterogeneity. This is particularly important. This would suggest that even a biopsy specimen showing diffuse p16 expression shows p16 positivity of the whole tumoral tissue.

Our study has a few limitations, one of which is the retrospective design of the study. All clinical and pathological data were collected from patient charts, which may decrease the reliability of the data. In addition, the number of our study population is small and the number of female cases is much lower than the male cases (2 female and 21 male patients). Lastly, it is reported that paraffin-embedded specimens are poorer in detection of HPV compared to fresh specimens.[16]

Conclusions

High p16 expression is a reliable marker of HPV positivity. IHC is a simple test, with low cost and high sensitivity. Combining p16 IHC with HPV ISH will further improve

its specificity as a test. The specimens did not show tumor heterogeneity, suggesting that even a biopsy specimen showing diffuse p16 expression shows p16 positivity of the whole tumoral tissue. Studies with larger number of patients would be beneficial to show the value of p16 expression and IHC for detection of HPV.

Conflict of Interest: No conflicts declared.

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An evaluation of peripheral arterial tonometry for the diagnosis of obstructive sleep apnea

Zerrin Özergin Coşkun[1], Engin Dursun[1], Ünal Şahin[2], Özlem Çelebi Erdivanlı[1], Suat Terzi[1], Metin Çeliker[1], Münir Demirci[1]

[1]*Department of Otorhinolaryngology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey*
[2]*Department of Chest Diseases, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey*

Abstract

Objective: Peripheral arterial tonometry (PAT) as a portable method of monitoring sleep quality is a relatively recent innovation. The aim was to compare the results of PAT and polysomnography (PSG) and to evaluate the role of PAT in diagnosing obstructive sleep apnea syndrome (OSAS).

Methods: This study included adult patients who admitted to ENT clinic with OSAS complaints (excessive daytime sleepiness, snoring, and witnessed apnea), undergone sleep monitorization using PAT system (WatchPAT 200™; Itamar Medical Ltd., Caesarea, Israel) and had single-blind, level 1 polysomnography at sleep laboratory of Chest Diseases Department.

Results: For the two sleep monitoring sessions as conducted at different times: the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI) values were strongly correlated between sessions (r=0.749, r=0.753; p<0.001). The oxygen desaturation index (ODI) values were very strongly correlated (r=0.861; p<0.001). When the AHI scores calculated using PAT for the patients enrolled in the trial were taken into consideration; 89.7% of the patients were correctly diagnosed with OSAS (AHI≥5); for RDI calculated (RDI≥5) using PAT, 100% of OSAS diagnoses were correct; for AHI values calculated with the PAT method, taking 15 as cut-off point, the sensitivity was found to be at an extremely high level of 96.1%.

Conclusion: PAT and PSG values were highly correlated. This finding demonstrated that the reproducibility of the results obtained with PAT was also high. This study shows that PAT can be used as a screening test for OSAS and in a group of patients who are highly suspected for OSAS.

Keywords: Obstructive sleep apnea, peripheral artery tonometry, polysomnography, apnea-hypopnea index, oxygen desaturation index.

Özet: Obstrüktif uyku apnesi tanısında periferik arteriyel tonometrinin değerlendirilmesi

Amaç: Periferik arteriyel tonometrinin (PAT), uyku monitörizasyonunda taşınabilir bir yöntem olarak kullanımı kısmen yeni bir yöntemdir. Bu çalışmada, PAT sonuçları ile polisomnografi (PSG) sonuçlarının karşılaştırılması ve obstrüktif uyku apnesi sendromu tanısında PAT'ın rolününün değerlendirilmesi amaçlandı.

Yöntem: Bu çalışmaya KBB kliniğine OSAS şikayetleri (gündüz uykululuk hali, horlama ve tanıklı apne) ile başvurmuş ve uyku monitörizasyonu PAT sistemi (WatchPAT 200™; Itamar Medical Ltd., Caesarea, İsrail) ile yapılmış, daha sonra Göğüs Hastalıkları Uyku Laboratuvarında kör olarak level 1 polisomnografi uygulanmış erişkin hastalar dahil edildi.

Bulgular: İki farklı zamanda yapılmış uyku monitörizasyonunda apne hipopne indeksi (AHI) ve solunum bozukluğu indeksi (RDI) değerleri yüksek oranda korele idi (r=0.749, r=0.753; p<0.001). Oksijen desatürasyon indeksi (ODI) değeri ise çok yüksek oranda korele saptandı (r=0.861; p<0.001). Çalışmaya dahil edilen hastaların AHI skorları PAT yöntemiyle ölçüldüğünde; hastaların %89.7'si OSAS için (AHI≥5) doğru tanı aldı; PAT testinde, RDI'ye göre yapılan değerlendirmede (RDI≥5) OSAS tanılarının %100'ü doğru idi; PAT yöntemiyle yapılan ölçümde AHI değeri için eşik değeri 15 olarak kabul edildiğinde, duyarlılık %96.1 olarak oldukça yüksek bulundu.

Sonuç: PAT ve PSG değerleri yüksek oranda korele idi. Bu durum PAT ile elde edilen sonuçların tekrarlanabilirliğinin de yüksek olduğunu göstermiştir. Çalışmamız PAT'ın OSAS'da tarama testi olarak ve yüksek oranda OSAS şüphesi olan hasta grubunda kullanılabileceğini göstermektedir.

Anahtar sözcükler: Obstrüktif uyku apnesi, periferik arteriyel tonimetri, polisomnografi, apne hipopne indeksi, desatürasyon indeksi.

Correspondence: Zerrin Özergin Coşkun, MD. Department of Otorhinolaryngology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey.
e-mail: zerrin.coskun@erdogan.edu.tr

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Obstructive sleep apnoea (OSA) is a disorder of moderate prevalence in which there are alternating intervals of obstructive apnoea and hypopnoea. Sleeps becomes fragmented as a result of the patient's upper airway being closed repeatedly as he or she sleeps. OSA is the most frequently encountered of the sleep disorders within the International Classification of Sleep Disorders (ICSD) scheme, with a prevalence of between 3 and 17% of male adults, and 2 to 9% of females.[1–4]

Uncontrolled OSA produces a large number of health-related issues, such as excessive diurnal tiredness, reduced ability to think, mood disturbance, reduced well-being, metabolic disturbance, greater risk of circulatory disease and extreme diurnal drowsiness, which may lead to road traffic accidents or occupational injury.[5] OSA, combining with disproportionate diurnal drowsiness for which no other cause can be found, is labeled obstructive sleep apnea syndrome (OSAS).[6] Despite the level of seriousness of these complications, and whilst it is agreed that to establish the diagnosis of OSA at the gold standard level requires both a sleep laboratory and technical staff in attendance to perform a level 1 polysomnogram, in reality many patients are not diagnosed until late as a result of inadequate sleep laboratory facilities as well as long waiting times. There is a need for a technique that is diagnostic for OSA which is inexpensive, easily accessible, easy to use and measures accurately.

Peripheral arterial tonometry (PAT) is classified as a portable sleep monitoring device. In the PAT system, there is a fingertip sensor that continuously measures arterial volume changes by subtracting peripheral venous oscillations. Arterial volume changes are regulated by α-adrenergic innervation and reflect sympathetic activity. The resulting apnea, hypopnea episodes and arousals cause the sympathetic nervous system to be activated and thus peripheral vasoconstriction occurs and peripheral arterial volume reduces. These also cause the PAT signal to weaken and apnea is detected.[7]

In this study, we compared the results of PAT and polysomnography (PSG) and evaluated the role of PAT in diagnosing OSAS. In this study, the relationship between non-simultaneous level 1 polysomnography and PAT-based sleep monitoring was investigated in adult OSAS patients.

Materials and Methods

This study was undertaken at the ENT Department of the Faculty of Medicine at Recep Tayyip Erdoğan University, Rize, Turkey. Ethical Committee approval (No: 49/2016) was obtained from the University's Research Ethics Committee.

Subjects

For this study, adult patients who presented to the ENT clinic with symptoms of OSAS (daytime sleepiness, snoring and apnea witnessed by another person) were included. In the initial stage, sleep monitoring using a peripheral arterial tonometric system (WatchPAT 200™; Itamar Medical Ltd., Caesarea, Israel) was performed, then a blinded Level 1 polysomnogram was recorded in the sleep laboratory of Chest Diseases Department.

Exclusion criteria were as follows: moderate or severe degree of chest, neuromuscular or peripheral vascular disease, congestive heart failure, non-sinus cardiac arrhythmia, implantation of a permanent pacemaker, having undergone bilateral cervical or thoracic sympathectomy, a finger deformity which precludes fitting of the PAT probe, dependence on hypnotic or narcotic substances, having taken an alpha blocker within the past 24 hours, more than one month interval between the two sleep monitoring sessions or a change in body mass index (BMI) between administration of the two tests.

Peripheral arterial tonometry

Tonometry was undertaken using the WatchPAT 200™ device on patients who were suspected to be suffering from OSAS. They had symptoms such as snoring, disproportionate daytime drowsiness and episodes of apnea during sleep which had been observed by their spouses. WatchPAT can be worn when moving around, does not need to be under the control of a technician whilst in use, and records four channels, in particular, PAT signal, cardiac rate and oxygenation ratio for hemoglobin. An actigraphy allowed to estimate the length of time the patient spent asleep whilst the stages of sleep could be correlated with the spectral components of the PAT and the actigraphy measurements.

Device placement was on the patient's non-dominant side, around the wrist, with the PAT probe positioned on the same side, on the index finger, together with an oximeter, also on the same side, but on the ring finger. The device records the test, using special proprietary software (zzzPat™) which employs an algorithm capable of extracting 14 features from 2 stretches of time in which PAT amplitude and Interpulse periods (IPP) have been recorded.

Polysomnography

The patients entered in the trial all had Polysomnography performed in the sleep laboratory using the Comet computerised device (Grass-Telefactor, Astro-Med, West Warwick, RI, USA), set up to record 24 channels as fol-

lows: 8 channels for electroencephalography, 2 channels for electro-oculography, 2 channels for submental plus 4 channels leg electromyography, ECG, nasal and oral airflow (using a thermistor), thoracic and abdominal respiratory movement sensors, pulse oximetry (detecting SpO_2), microphone to detect snoring and a sensor detecting what position the patient is in.

Procedures for scoring test

The polysomnogram was interpreted following the 2012 Guidelines of the American Academy of Sleep Medicine (AASM). To meet the definition of apnea, airflow had to be decreased by at least 90% compared to just before the episode occurred, in a stretch of sleep lasting at least ten seconds. Hypopnea needed to satisfy the following criteria: (1) The amplitude of the highest signal strength had to be 30% less than before the episode, (2) Such decrease had to last at least ten seconds, and (3) either there was 3% lower oxygen saturation or the patient was aroused during the episode.

Apnea-hypopnea index (AHI) consisted of the total episodes of apnea and hypopnea over a period made up of sleep lasting in total for one hour (sleep-hour). Respiratory disturbance index (RDI) consisted of episodes of apnea, hypopnea and respiratory event related arousals (RERAs) per sleep-hour and oxygen desaturation index (ODI) was defined as total events featuring at least 3% reduction in oxygenation per sleep-hour.

The AASM Guidelines describes the stages of OSA as follows: RDI between 5 and 15 is "mild", above 15 and up to 30 is "moderate", whilst an RDI greater than 30 indicates a "severe" level of OSA.[8]

Interpretation of the test results was carried with blinding method for the WatchPAT results' conditions by a physician and sleep technician, both of whom had experience in sleep medicine.

In the report provided by our hospital, since arousals linked to respiratory events were included with the episodes of hypopnea, the reported AHI and RDI values were same; however, in the scores calculated by the PAT device and its dedicated software, the RDI and AHI results were indicated separately.

Statistical analysis

For this study, the following statistics were generated from the WP and PSG results: AHI, RDI, ODI, time spent in N3 stage sleep as a percentage of total time asleep (N3%), time spent in REM stage sleep as a percentage of total time asleep (REM%), mean oxygen saturation (MEAN $Sp0_2$), minimum oxygen saturation (MIN SpO_2) and the apnea-hypopnea index with the patient in a supine position (SUPINE AHI).

For the analysis of the data, the IBM SPSS Statistics 20 software (SPSS Inc., Chicago, IL, USA) was employed, using the following statistical tests: Spearman's rho test, Bland-Altman plot test, paired-samples t-test and McNemar's test. A p value of less than 0.05 was accepted significant in Spearman's rho test. Correlations were accepted significant at 0.05 level and above in paired-samples t-test and Mc Nemar's test.

Results

In total, 41 patients were enrolled in the study. Two patients were later excluded from the study. One patient's recording device developed a battery problem whilst the sleep data were being gathered, the other patient's data were partially lost whilst attempting to upload the device data onto the computer.

Of the 39 patients whose results were taken into account in the analysis, 31 were male (79.5%), 8 were female (20.5%). Their average age was 45.7±11.6 (range: 26 to 73) years, and BMI was 32.6±4.7 (range: 26 to 45).

The cases were categorized according to polysomnography as: normal (1 case, 2.5%), mild (11 cases, 28.2%), moderate (2 cases, 5.1%) and severe (25 cases, 64.1%). Mean AHI calculated from PSG results was 33.09±20.64 (range: 4.70 to 75), and was 32.88±21.96 (range: 1.30 to 81.10) according to WatchPAT results. **Table 1** shows the comparison of the mean values of the sleep variables between PSG and WatchPAT.

When the results of the two sleep-monitoring sessions were compared, AHI, RDI and ODI were found to be highly correlated between sessions (r=0.749, r=0.753, r=0.861; p<0.001). See **Table 2** and **Figs. 1–3**.

There was no significant difference (p>0.05) between the two sleep-monitoring sessions in terms of AHI, RDI, and ODI values (**Table 3**).

There was no significant difference between the mean values obtained for supine AHI (p>0.05) and moderate correlation was found (r=0.568).

Mean SpO_2 values were highly correlated (r=0.779) between WP and PSG, and no significant difference was found between their mean values (p>0.05). Although Min SpO_2 values were highly correlated on paired samples test-

Table 1. Measurements obtained by PAT and polysomnography*.

		PAT		PSG	
	N	Mean±SD	Min-max	Mean±SD	Min-max
AHI	39	32.88±21.6	1.30–81.10	33.09±20.4	4.70–75
RDI	39	35.73±20.8	4.90–81.30	33.09±20.4	4.70–75
Mean SpO_2	39	92.69±2.94	83.00–97.00	92.23±2.77	84.20–96.30
Min SpO_2	39	79.90±8.97	57.00–93.00	75.90±10.0	50.00–90.00
ODI	39	25.09±21.7	0.30–72.90	25.51±22.3	0.70–78.60
N3%	39	15.51±7.52	2.3–30.75	11.04±7.52	1.7–25.8
REM%	39	20.52±8.49	3.32–38.32	13.84±7.23	3.10–25.70
Supine AHI	39	42.98±27.4	2.1–101.3	44.74±26.6	2.9–87.50
Pulse MIN	39	66.21±10.9	66.9±10.2	66.62±10.1	41.00–88.00

*The data presented are for the total period of sleep. **Mean SpO_2:** mean oxygen saturation, **Min SpO_2:** minimum oxygen saturation; **N3%:** time spent in N3 stage sleep as a percentage of total time asleep; **ODI:** oxygen desaturation index; **Pulse MIN:** minimum pulse rate; **REM%:** time spent in REM stage sleep as a percentage of total time asleep; **Supine AHI:** apnea-hypopnea index with the patient in a supine position.

ing, there was a statistically significant difference between their mean values ($p<0.05$) (**Tables 2** and **3**).

The values for time spent in N3 stage sleep as a percentage of total time asleep (N3%) and time spent in REM stage sleep as a percentage of total time asleep (REM%) were significantly different ($p<0.05$).

Agreement in outcome between these two methods is illustrated by Bland-Altman plot in **Figs. 4** and **5**. In a single case, the only (2.5% of total observations) difference was between AHI and RDI beyond the acceptable deviation (1.96 standard deviation from the mean).

Table 2. Spearman's rho test results.

	r	p-value
BMI *vs* AHI 1	0.252	0.121
BMI *vs* AHI 2	0.262	0.107
AHI 1 *vs* AHI 2	0.749*	0.000
RDI 1 *vs* RDI 2	0.753*	0.000
ODI 1 *vs* ODI 2	0.861*	0.000
Min SpO_2 1 vs Min SpO_2 2	0.783*	0.000
Mean SpO_2 1 vs Mean SpO_2 2	0.779*	0.000
N3% 1 *vs* N3% 2	0.457	0.003
REM% 1 *vs* REM% 2	0.054	0.746
Supine AHI 1 *vs* Supine AHI 2	0.568*	0.000
Pulse Min 1 *vs* Pulse Min 2	0.745*	0.000

*Correlation is significant at the level where r equals to 0.05 and above. **1:** the data derived from sleep apnea testing with PAT; **2:** the data derived from PSG; **BDI:** body mass index; **Mean SpO_2:** mean oxygen saturation; **Min SpO_2:** minimum oxygen saturation; **N3%:** time spent in N3 stage sleep as a percentage of total time asleep; **ODI:** oxygen desaturation index; **Pulse Min:** minimum pulse rate; REM **%:** time spent in REM stage sleep as a percentage of total time asleep; **Supine AHI:** apnea-hypopnea index with the patient in a supine position; **vs:** versus.

Table 3. Paired samples t-test results.

	n	Mean	SD	p-value
AHI 1	39	32.88	21.965	0.922*
AHI 2	39	33.09	20.641	
RDI 1	39	35.73	20.689	0.223*
RDI 2	39	33.09	20.641	
Mean SpO_2 1	39	92.69	2.948	0.066*
Mean SpO_2 2	39	92.23	2.773	
Min SpO_2 1	39	79.90	8.979	0.000
Min SpO_2 2	39	75.90	10.303	
ODI 1	39	25.09	21.272	0.838*
ODI 2	39	25.51	22.633	
N3% 1	39	15.51	7.528	0.001
N3% 2	39	11.04	7.237	
REM% 1	39	20.52	8.498	0.000
REM% 2	39	13.84	5.232	
Supine AHI 1	39	42.98	27.046	0.641*
Supine AHI 2	39	44.74	26.468	
Pulse Min 1	39	66.21	10.494	0.698*
Pulse Min 2	39	66.62	10.210	

*Correlation is significant at the level where p equals to 0.05 and above. **1:** the data derived from sleep apnea testing with PAT; **2:** the data derived from PSG; **Mean SpO_2:** mean oxygen saturation; **Min SpO_2:** minimum oxygen saturation; **N3%:** time spent in N3 stage sleep as a percentage of total time asleep; **ODI:** oxygen desaturation index; **Pulse Min:** minimum pulse rate; **REM %:** time spent in REM stage sleep as a percentage of total time asleep; **SD:** standard deviation; **Supine AHI:** apnea-hypopnea index with the patient in a supine position.

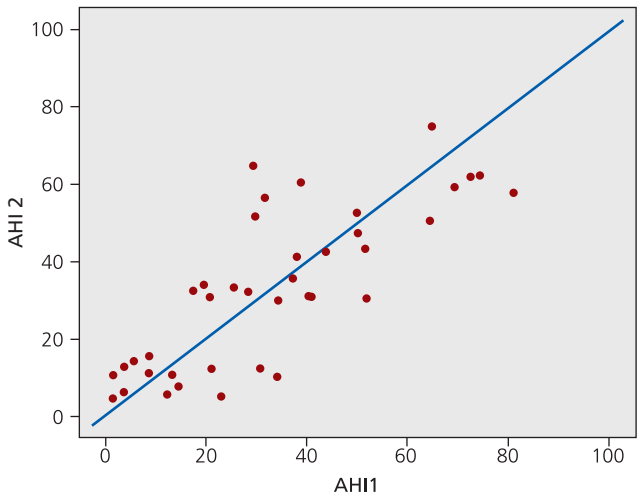

Fig. 1. Scatter plot of AHI 1 versus AHI 2. There was a high correlation between AHI 1 versus AHI 2 (r=0.749, p<0.001). ***Hint:*** **AHI 1:** AHI values calculated with the PAT method; **AHI 2:** AHI values calculated with the PSG.

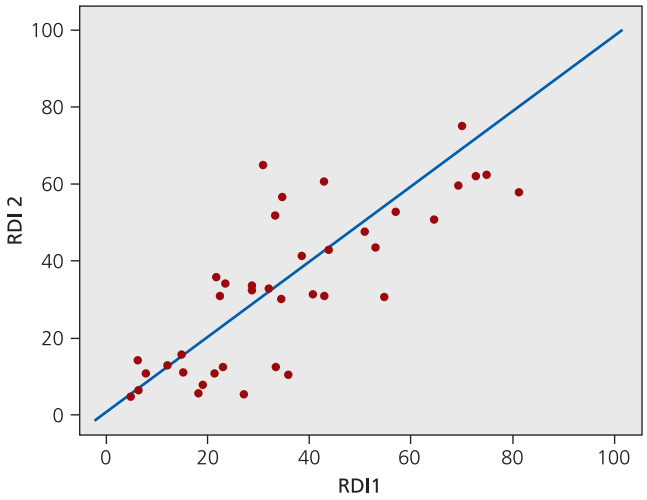

Fig. 2. Scatter plot of RDI 1 versus RDI 2. There was a high correlation between RDI 1 versus RDI 2 (r=0.753, p<0.001). ***Hint:*** **RDI 1:** RDI values calculated with the PAT method; **RDI 2:** RDI values calculated with the PSG.

When the PAT and AHI scores for the patients enrolled in the trial were taken into consideration; 89.7% of the patients were correctly diagnosed with OSAS (AHI≥5) (**Table 4**); for RDI measured by PAT, 100% of OSAS diagnoses (AHI≥5) were correct (**Table 5**); for AHI values calculated using the PAT method, taking 15 as the cut-off point, the sensitivity was found to be at an extremely high level of 96.1% (**Table 4**).

Discussion

Early diagnosis of all patients with OSAS is a public health priority from the point of view of preventing the severe morbidities that develop alongside the illness.[9] Once diagnosed, it is a chronic illness that may require long-term follow-up. Therefore, there is a need for a technique

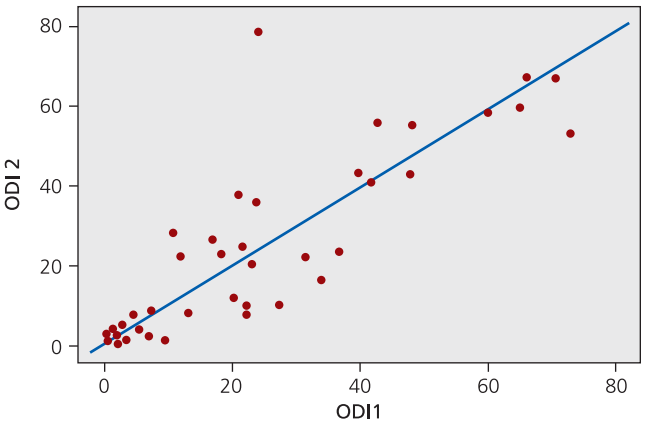

Fig. 3. Scatter plot of ODI 1 versus ODI 2. There was a high correlation between ODI 1 versus ODI 2 (r=0.861, p<0.001). ***Hint:*** **ODI 1:** ODI values calculated with the PAT method; **ODI 2:** ODI values calculated with the PSG.

Table 4. McNemar's test results for AHI measurements (PAT *versus* PSG).

Cut-off	McNemar's p-value	Sensitivity	Specificity	Positive predictive	Negative predictive	Accuracy
AHI≥5	0.250*	89.7%	100%	100%	25%	92.3%
AHI≥15	0.375*	96.1%	69.2%	86.2%	90%	89.1%
AHI≥30	0.023*	70.8%	92.8%	94.4%	65%	83.3%

*Correlation is significant at the level where p equals 0.05 and above. **AHI≥5:** McNemar's test results using a cut off of AHI≥5. **AHI≥15:** McNemar's test results using a cut off of AHI≥15. **AHI≥30:** McNemar's test results using a cut off of AHI≥30.

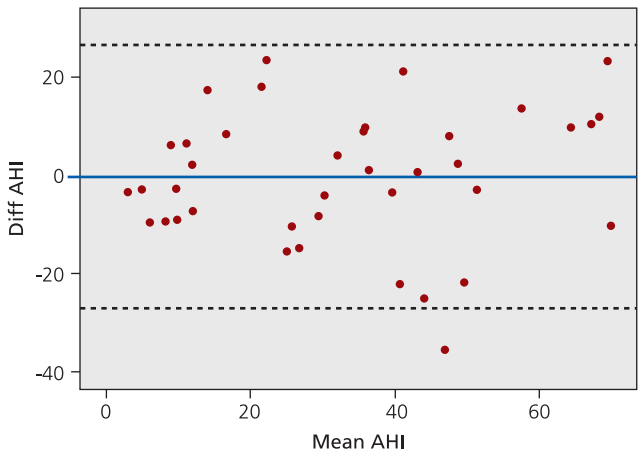

Fig. 4. Bland-Altman plot of PSG AHI vs PAT AHI. *Hint:* **PSG AHI:** AHI values calculated with the PSG; **PAT AHI:** AHI values calculated with the PAT method; Mean AHI=(PAT_AHI+PSG_AHI)/2; Diff AHI= PAT_AHI - PSG_AHI.

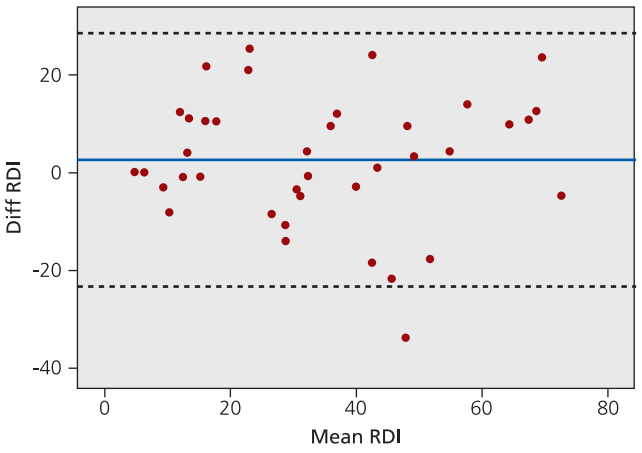

Fig. 5. Bland-Altman plot of PSG RDI versus PAT RDI. *Hint:* **PSG RDI:** AHI values calculated with the PSG; **PAT RDI:** AHI values calculated with the PAT method; Mean RDI=(PAT_RDI+PSG_RDI)/2; Diff RDI=PAT_RDI - PSG_RDI.

that is diagnostic for OSA and can be used for follow-up, which is inexpensive, easily accessible, easy to use, measures accurately and does not cause any side effects.

Schnall et al. identified and published their findings in 1999 that the sympathetic nervous system causes upper airway constriction and arousal from sleep, vasoconstriction peripherally and changes in arterial tone.[10] From 2003 onwards, the first studies involving sleep monitoring that make use of this discovery have begun to appear in the literature.[11] There are research articles confirming the value of WatchPAT for the diagnosis of OSA already available.[7,12] In a meta-analysis conducted using 14 studies comparing PAT and PSG, there was a high correlation (r=0.889, p<.001) in terms of RDI and AHI values. The correlation for the ODI value was also very high (r=0.942; p<0.001).[13] Undiagnosed and untreated OSA is a significant burden on the healthcare system, with increased healthcare utilization seen in those with untreated OSA.[14]

The devices for sleep monitoring can be put into 4 separate categories (types 1, 2, 3 and 4).[15] In Level 1, full polysomnography requires an attendant and goes on over the course of a night. Level II is a complete PSG over the entire night, but minus an attendant. Level III PSG has limitations of generally only recording airflow through the mouth and nose and breathing movements of the chest and abdomen (although it may also encompass lying position and snoring volume), and again does not require an attendant. Level IV is very restricted, confined to airflow through the nose and mouth and oxygenation level.[12] The WatchPAT device detects three principal effects. Roughly, this is the awareness of the patient via the actigraph component, sympathetic activation level via the tonometry apparatus (a type of opticopneumatic sensor), and oxygenation via the digital pulse oximeter. After integrating all these data streams, the device issues a detailed and thorough report listing AHI and RDI as well as RERAs.

The portable monitor implementing a PAT system that was used in our research gave results that correlate

Table 5. McNemar's test results for RDI measurements (PAT *versus* PSG).

Cut-off	McNemar's p-value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
RDI≥5	1.000*	100%	100%	100%	100%	100%
RDI≥15	0.375*	96.1%	38%	75%	83%	76.9%
AHI≥30	0.227*	79.1%	92.8%	95%	72.2%	84.2%

*Correlation is significant at the level where p equals 0.05 and above. **RDI≥5:** McNemar's test results using a cut off of RDI≥5. **RDI≥15:** McNemar's test results using a cut off of RDI≥15. **RDI≥30:** McNemar's test results using a cut off of RDI≥30.

strongly with those obtained by a type 1 polysomnogram. Despite being obtained at different times, values for AHI, RDI and ODI, calculated by the two different methods, were well correlated and similar to each other.

To diagnose OSA, the plan should encompass taking a history focused on sleep, physical examination and diagnostic investigations. The results here confirm what other studies have claimed regarding the validity and reliability of WatchPAT in diagnosing OSA.[7,12,13,16,17]

Type III sleep monitoring (unattended) is endorsed by AASM as a component of a full OSA diagnostic work-up, provided that initial clinical suspicion is high and the patient does not have other co-occurring illnesses. In the group with comorbidities, PSG should be standard for those with systolic or diastolic cardiac insufficiency, treated as a guideline recommendation for those with coronary artery disease, and as optional for patients with a history of stroke or transient ischaemic attacks.[18]

Diagnosed cases of OSA are only the visible part of a far larger latent epidemic of patients whose breathing problems remain unseen and untreated. 17% of drivers in a European survey report having become drowsy at some point in the previous two years whilst in control of a vehicle, indicates the fact that such drowsiness is frequent .[19] Factors linked with drowsiness whilst driving included inadequate sleep, being young, being male, driving a lot, experiencing drowsiness in general during the day and tending to develop OSA. Having OSA puts you in great hazard of a traffic accident.[20,21]

One warning about applying the results described here is that hypopnea and apnea cannot reliably be differentiated by the WatchPAT apparatus, since it cannot quantify airflow. However, in general, the high level of correlation and correspondence of key respiratory indicators between PSG and WatchPAT, e.g. AHI, RDI and ODI, is a notable finding.

In sleep monitoring using PAT, RDI sensitivity was higher than AHI sensitivity when the cut-off point was set to 5. When the AHI value was found to be 5 or below, especially in the PAT test, RDI value needs to be carefully considered. When the reference values were taken as 15 and 30 in PAT measurements, no significant difference was found between the sensitivities of AHI and RDI. Patients with a score of 15 or more on PAT can have OSA detected 96.1% of the time correctly.

There are some limitations to this study. One of the limitation is a possibility of night-to-night variation because the PSG and sleep monitoring with PAT were not conducted simultaneously on the same night. However, both this study and the study of Pittman et al.[7] showed that there was a good concordance between values calculated with PSG and PAT. The other limitation is the small number of subjects.

In conclusion, this research indicates that, for the screening of potential OSAS cases, and likewise, where a high clinical index of suspicion exists at first diagnosis, as well as for the follow-up of certain particular patient groups, just as the American Academy of Sleep Medicine underlined in their 2017 report,[22] PAT can be used confidently by clinicians.

Conflict of Interest: No conflicts declared.

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Comparison of CE-Chirp ABR and Click ABR methods in patients with bilateral sensorineural hearing loss

Seval Ceylan[1], Atilla Gümüşgün[2], Ferhan Feratlar[1]

[1]*Division of Audiology, Department of Otorhinolaryngology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey*
[2]*Department of Otorhinolaryngology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey*

Abstract

Objective: In this study, we aimed to compare ABR threshold values, V. wave latency times, amplitudes obtained using Click ABR and CE-Chirp ABR methods and procedural times of these tests in patients with bilateral hearing loss.

Methods: A total of 19 adult male patients were included in the study. ABR latency times with 10 dB decreases starting from 100 dB, V. wave latencies, V. wave amplitudes obtained using Click ABR and CE-Chirp ABR methods and procedural times were compared for both ears.

Results: Procedural time for CE-Chirp ABR test was found to be shorter than that of Click ABR test (p=0.001). For both ears, mean CE-Chirp ABR threshold values were more favorable than those of Click ABR test [(60.15±10.34 vs. 62.27±9.93) dB nHL, p<0.006]. For both ears, the threshold values of mean pure tone audiometry were estimated as following: 1 KHz (55.00±14.36 dB), 2 KHz (60.00±13.40 dB) and 4 KHz (63.48±10.57 dB). The corresponding values were calculated 62.27±9.93 dB nHL and 60.15±10.34 dB nHL using Click ABR and CE-Chirp ABR methods, respectively. Procedural time for CE-Chirp ABR test was shorter than that of Click ABR test [(24.89±4.74 vs. 28.63±4.98) min., p=0.001].

Conclusion: It has been determined that the use of CE-Chirp stimulus shortened ABR procedural time and provided responses closer to behavioral threshold values. In conclusion, we observed that CE-Chirp method was more advantageous than Click ABR method for the evaluation of the patients with bilateral sensorineural hearing loss.

Keywords: CE-Chirp ABR, Click ABR, bilateral sensorineural hearing loss.

Özet: Bilateral sensorinöral işitme kayıplı hastalarda CE-Chirp ABR ve Click ABR yöntemlerinin karşılaştırılması

Amaç: Bu çalışmada bilateral sensorinöral işitme kaybı olan hastalarda Click ABR ve CE-Chirp ABR yöntemleri ile elde edilen ABR eşikleri, V. dalga latans bulguları, amplitüd bulguları ve test sürelerinin karşılaştırılması amaçlanmıştır.

Yöntem: Bilateral sensorinöral işitme kaybı bulunan 19 yetişkin erkek hasta çalışmaya dahil edildi. Click ABR ve CE-Chirp ABR yöntemleri ile her iki kulakta 100 dB'den başlanarak 10 dB'lik düşüşlerle elde edilen ABR eşikleri, V. dalga latansları, V. dalga amplitüdleri ve test süreleri karşılaştırıldı.

Bulgular: CE-Chirp ABR test süresi Click ABR test süresinden daha kısa bulundu (p=0.001). Her iki kulak için ortalama CE-Chirp ABR eşikleri Click ABR eşiklerinden daha iyi saptandı [(60.15±10.34 vs. 62.27±9.93) dB nHL, p<0.006]. Her iki kulakta ortalama *pure tone* audiometry 1 KHz eşikleri 55.00±14.36 dB, 2 KHz eşikleri 60.00±13.40 dB, ve 4 KHz eşikleri 63.48±10.57 dB olarak tespit edildi. Bu değerler, Click ABR ile 62.27±9.93 dB nHL, CE-Chirp ABR ile 60.15±10.34 dB nHL olarak ölçüldü. CE-Chirp ABR test süresi Click ABR test süresinden daha kısa bulundu [(24.89±4.74 vs. 28.63±4.98) dakika, p=0.001].

Sonuç: CE-Chirp uyaran kullanımının ABR test süresini kısalttığı ve davranışsal eşiklere daha yakın cevaplar sağladığı belirlenmiştir. Sonuç olarak bilateral sensorinöral işitme kayıplı hastaların değerlendirilmesinde CE-Chirp ABR yönteminin Click ABR yönteminden daha avantajlı olduğu gözlenmiştir.

Anahtar sözcükler: CE-Chirp ABR, Click ABR, bilateral sensorinöral işitme kaybı.

Evoked auditory brainstem responses (ABRs) are auditory evoked potentials emerging between 2–12 milliseconds after delivery of auditory stimuli.[1,2] Click ABR method is the most frequently preferred and used method for ABR recordings.[2] In Click ABR measurements, the time interval for a sound wave to reach cochlear apex is prolonged. In an area of lower frequency, the peak point of the response becomes manifest milliseconds after the region of high fre-

Correspondence: Seval Ceylan, MD. Division of Audiology, Department of Otorhinolaryngology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey.
e-mail: sevalkilercioglu@gmail.com

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quency. Therefore, cells of the basal membrane are not stimulated at the same time and as a result, depolarization of the nerve cells cannot be achieved at the same time.[3,4] This condition may be described as the travelling time of the sound wave inside the cochlea or cochlear travel delay.

CE-Chirp stimulus has been developed to evaluate auditory brainstem responses and ensure synchronized stimulation of cochlea.[5] Click-stimulus and CE-Chirp-stimulus have the same range of frequency spectrum ranging between 350 and 11,300 Hz.[6] The difference between CE-Chirp and Click stimuli arises from delivery times of components with low, moderate and high frequencies so as to stimulate all areas of frequencies simultaneously.[7] All components of high frequencies are sent later than the components with lower frequencies. Due to especially adjusted temporal distribution of its components, CE-Chirp stimulus simultaneously accesses into characteristic regions of the basal membrane. Since all cochlear regions are simultaneously depolarized by CE-Chirp stimulus, ABR waves with higher amplitude are obtained. CE-Chirp stimulus seems to be the most optimal model for an average human cochlea.[8]

In this study, we compared ABR threshold values, V. wave latencies, V. wave amplitudes achieved and procedural times of Click ABR and CE-Chirp ABR methods in patients with bilateral sensorineural hearing loss.

Materials and Methods

Study design

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (08.03.2016-119). Written informed consent was obtained from all subjects. This research study was realized between March and July 2016 in the Audiology Laboratory of Clinics of Ear-Nose-Throat of Izmir Military Hospital. As a result of pure-tone audiometry and tympanometry tests, 19 young men with bilateral sensorineural hearing loss were included in the study. Patients with lower IQs, psychiatric problems, patients who woke up before completion of the test which requires a state of sleep were not included in the study.

Outcome parameters

The patients with bilateral sensorineural hearing loss detected as an outcome of pure-tone audiometry and tympanometry applied were subjected to Click ABR and CE-Chirp ABR tests.

ABR test: Test electrodes were placed as follows: positive line was placed on the upper part of the forehead, ground line on the lower part of the forehead, one of the negative electrodes on the left mastoid and the other one on the right mastoid processes. ABR recordings were done using Interacoustics Eclipse Ep 15 ABR system (Interacoustics, Middelfart, Denmark). Test parameters were as follows: Rate: 20.1, Polarity: Alternating, HPF: 100 Hz, LPF: 3KHz and the type of signal delivered to the patient was selected (Click or CE-Chirp). Tests were started before using 100 dB click stimulus. Then with 10 dB decreases, ABR threshold values of both ears of each patient were determined. When required, 5 dB changes were made in sound intensities to identify V. Wave. Then, the same test method was repeated with CE-Chirp stimulus.

Statistical analyses

The data were analyzed using the IBM Statistical Package for Social Sciences v17 (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Data were expressed as mean±SD or median (interquartile range), as appropriate. All differences associated with a chance probability of .05 or less were considered statistically significant. ABR V. wave latencies and V. wave amplitudes achieved using each type of stimulus were compared using Wilcoxon Signed-Rank analysis. The lowest level of sound intensities (ABR thresholds) observed was statistically compared. Paired t-test method was used to compare procedural times of Click ABR and CE-Chirp ABR tests. The type of ABR method which yielded results closer to behavioral thresholds (pure tone audiometry 1, 2, 4 KHz regions) was investigated.

Results

Procedural time of CE-Chirp ABR test was longer than that of the Click ABR test (24.89±4.74 vs. 28.63±4.98 minutes, p=0.001). Mean CE-Chirp ABR threshold values of both ears were lower than those of Click ABR test (60.15±10.34 vs. 62.27±9.93 dB nHL, p<0.006) (**Table 1**). For both ears, the threshold values of mean pure tone audiometry were determined as following: 1 KHz (55.00±14.36 dB HL) 2 KHz (60.00±13.40 dBHL) and 4 KHz (63.48±10.57 dBHL). The threshold values were measured 62.27±9.93 dB nHL and 60.15±10.34 dB nHL using Click ABR and CE-Chirp ABR methods respectively (**Table 2**).

For both ears, lower threshold values were obtained using CE-Chirp ABR method when compared with Click ABR method (60.15±10.34 vs 62.27±9.93 dBHL). For right ears, CE-Chirp ABR threshold values (59.71±9.6) were lower than threshold values measured using Click ABR test (62.65±9.54) (p=0.008). For left ears, no statistically significant difference was found between threshold values obtained using Click ABR and CE-Chirp ABR tests (p>0.05) (**Table 1** and **Fig. 1**).

Mean procedural time of CE-Chirp ABR test (24.89±4.74 min.) was shorter than that of the Click ABR test (28.63±4.98 min.) (p=0.001).

For right ears, CE-Chirp ABR threshold values were closer to pure tone average (PTA) 1 KHz and 2 KHz threshold values when compared with Click ABR threshold values. Click ABR threshold values were found to be closer to PTA 4 KHz threshold values relative to CE-Chirp threshold values (**Table 2**).

For both ears, CE-Chirp ABR threshold values were found to be closer to PTA 1 KHz and 2 KHz threshold values when compared with Click ABR threshold values. Click ABR threshold values were closer to PTA 4 KHz threshold values relative to CE-Chirp threshold values (**Table 2**).

Based on Wilcoxon signed-rank analysis, no statistically significant difference was found between the latencies of Click ABR and CE-Chirp ABR (p>0.05). However, at sound intensity levels of 70, 80, 90 and 100 dB, Click ABR latencies were longer than those of CE-Chirp ABR (p<0.05) (**Fig. 2**).

Table 1. Click ABR and CE-Chirp ABR threshold values.

Paired samples t-test	mean±SD	min-max	p-value
Click ABR threshold (right)	62.65±9.54	45–80	0.008
CE-Chirp ABR threshold (right)	59.71±9.6	40–75	
Click ABR threshold (left)	61.88±10.63	50–85	0.261
CE-Chirp ABR threshold (left)	60.63±11.38	45–80	
Click ABR threshold (right-left)	62.27±9.93	45–85	0.006
CE-Chirp ABR threshold (right-left)	60.15±10.34	40–80	

SD: Standard deviation

Wilcoxon Signed- Rank analysis was performed for the comparison between CE-Chirp ABR and Click ABR amplitudes and at sound intensity levels of 90 and 100 dB, Click ABR V. wave amplitudes were higher than CE-Chirp ABR V. wave amplitudes (p=0.001, p=0.001). At other sound intensity levels, no statistically significant difference was found between Click ABR and CE-Chirp ABR V. wave amplitudes (p>0.05) (**Fig. 3**).

Discussion

In our study, procedural time of CE-Chirp ABR test was longer than that of Click ABR test. Stuart et al. compared CE-Chirp ABR and Click ABR methods in 23 newborns, and similarly they reported shorter procedural times for Chirp ABR.[9] New Zealand Ministry of Health National Screening Programme demonstrated that CE-Chirp ABR method yielded results nearly 3–5 minutes faster than Click ABR method.[10] Cebulla et al. compared Click ABR and

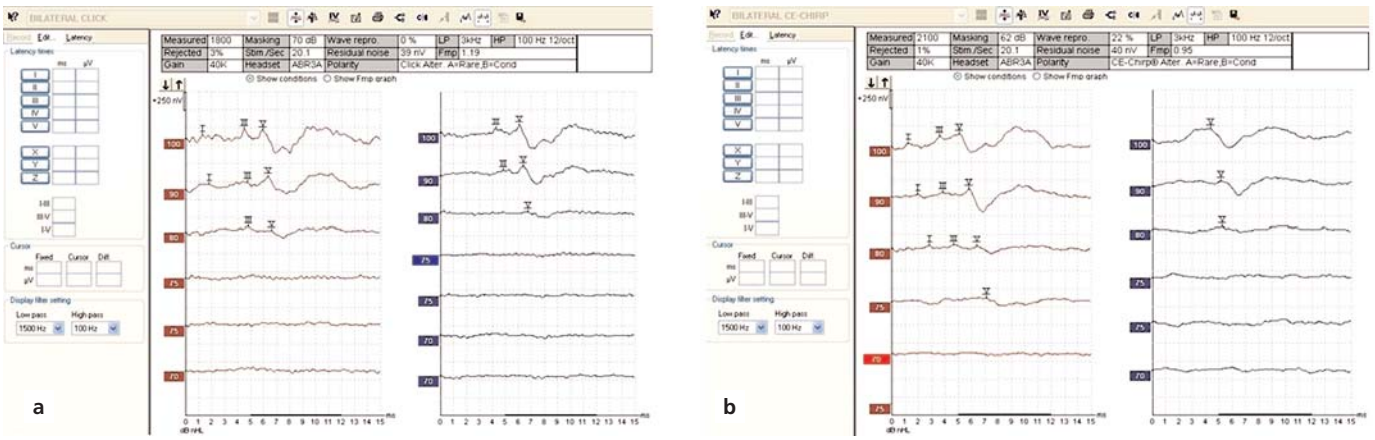

Fig. 1. The exemplary case where Click ABR (**a**) and CE-Chirp ABR (**b**) threshold values in patients with bilateral sensorineural hearing loss were compared. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

Table 2. The correlation between CE-Chirp ABR and Click ABR threshold and behavioral threshold values.

			Click ABR threshold (right)	p-value	CE-Chirp ABR Threshold (right)	p-value
Right	Pure Tone 1 KHz threshold	52.06±14.04	62.65±9.54	**0.004**	59.71±9.6	**0.031**
	Pure Tone 2 KHz threshold	59.41±13.10		0.207		0.891
	Pure Tone 4 KHz threshold	62.94±10.62		0.884		0.119
			Click ABR threshold (left)	**p-value**	**CE-Chirp ABR Threshold (left)**	**p-value**
Left	Pure Tone 1 KHz threshold	58.13±14.48	61.88±10.63	0.323	60.63±11.38	0.526
	Pure Tone 2 KHz threshold	60.63±14.13		0.728		1.000
	Pure Tone 4 KHz threshold	64.06±10.83		0.430		0.194
			Click ABR threshold (right-left)	**p-value**	**CE-Chirp ABR threshold (right-left)**	**p-value**
Right-Left	Pure Tone 1 KHz threshold	55.00±14.36	62.27±9.93	**0.006**	60.15±10.34	0.048
	Pure Tone 2 KHz threshold	60.00±13.40		0.287		0.937
	Pure Tone 4 KHz threshold	63.48±10.57		0.466		**0.041**

CE-Chirp ABR methods in 96 newborns, and indicated that duration of Click ABR test was more prolonged relative to CE-Chirp ABR test.[11]

Cho et al. compared the results of CE-Chirp ABR and Click ABR tests in 22 individuals with normal hearing acuity and 22 patients with sensorineural hearing loss.[12] A correlation was found between PTA 0.5, 1, 2 and 3 KHz threshold values and threshold values of CE-Chirp ABR tests and also between Click ABR threshold values and PTA 1, 2, 3, 4 KHz threshold values. A correlation especially between CE-Chirp ABR threshold values and 0.5 KHz PTA threshold values were observed.[12] In our investigation, we found CE-Chirp ABR threshold values closer to PTA 1, 2 KHz threshold values when compared with Click ABR threshold values, while Click ABR threshold values were closer to 4 KHz behavioral threshold values. As literature reviews have indicated, CE-Chirp ABR and Click ABR methods were more frequently compared in patients with normal hearing acuity. In a study performed by Khorsand et al. in individuals with normal hearing acuity, CE-Chirp ABR threshold values were found to be 5 dB better than those of Click ABR.[13] Our study has supported the assertion that CE-Chirp stimulus achieved more improved threshold values both in individuals with normal hearing acuity and also in patients with bilateral sensorineural hearing loss. In studies performed by Rodrigues et al. among individuals with normal hearing acuity, Ce-Chirp ABR wave amplitudes were found to be higher than those achieved by Click ABR at all levels other than 80 dB NHL (60, 40, 30, 20, 10 dB nHL).

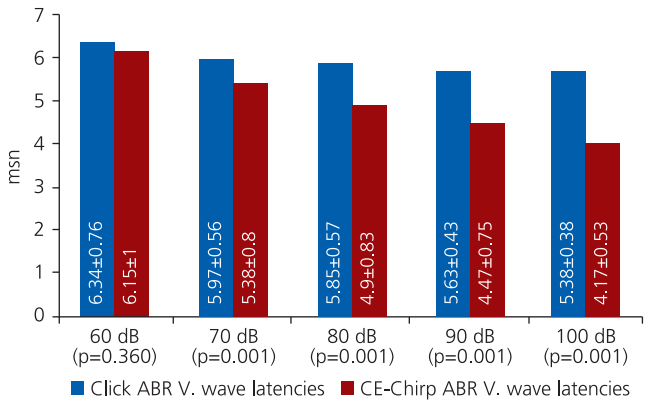

Fig. 2. Comparison of Click ABR and CE-Chirp ABR V. of the cases.

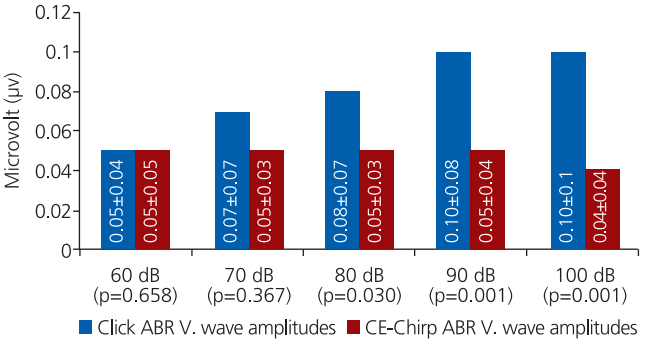

Fig. 3. Comparison of Click ABR and CE-Chirp ABR V. wave amplitudes of the cases.

Maloff et al. compared ABR results achieved using chirp or click stimuli, and they found greater AR V. wave amplitudes relative to Click ABR V. amplitudes especially at lower sound intensities.[14] However, in our study, Click ABR V. amplitudes at 90 dB and 100 dB sound intensity levels were greater than CE-Chirp ABR V. wave amplitudes. In studies performed in individuals with normal hearing acuities, at higher sound intensity levels as 80 dB, Click ABR V. amplitudes were indicated to be greater than CE-Chirp ABR V. wave amplitudes.[15,16] In our investigation at sound intensity levels below 90 dB, we found no statistically significant difference between Click ABR and CE-Chirp ABR V. wave amplitudes. As a result, CE-Chirp stimulus did not provide sound waves with higher amplitude in patients with sensorineural hearing loss, while they demonstrated characteristics of a V. wave at lower sound intensity levels. Soha et al. indicated that they had achieved more improved wave morphologies using chirp stimuli, rather than Click stimuli in 30 individuals with normal hearing acuity and 30 patients with moderate hearing loss.[15]

Di Scipio and Mastronardi performed a study on the use of chirp stimuli for intraoperative monitorization.[17] They indicated that intraoperative use of chirp ensured faster response with greater wave amplitudes, and as a result, they provided quicker feedback for the surgeon who performed the operation.

When we reviewed the literature, we have observed that the use of chirp stimulus has not been restricted only to ABR test, but it has been also used in compound action potentials and auditory steady state response (ASSR) tests. Chertoff et al. performed compound action potential tests in 16 adults with normal hearing acuities using click stimulus and chirp stimulus and reported that higher N1 wave amplitudes were obtained using chirp stimuli.[18]

It has been indicated that inadequacies of CE-Chirp stimulus might be compensated with level-specific chirp stimulus. Kristensen and Elberling compared ABRs achieved with LS Chirp, CE-Chirp and Click stimuli.[19] As a conclusion, they indicated that LS Chirp stimulus provided higher wave amplitudes relative to CE-Chirp ABR even at the level of 80 dB nHL.

Conclusions

As an outcome of this investigation, we found that duration of CE-Chirp ABR test was shorter than that of Click ABR test. For both ears, CE-Chirp ABR threshold values were better than those of Click ABR test. In conclusion, in the evaluation of the patients with bilateral sensorineural hearing loss, we determined that CE-Chirp ABR method was more advantageous than Click ABR method. We believe that various types of chirp stimuli in ABR and other audiological electrophysiologic test methods may be used prevalently.

Conflict of Interest: No conflicts declared.

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Retrospective evaluation of the relationship between seasonal factors and idiopathic sudden sensorineural hearing loss

Kasım Durmuş[1], Adem Bora[1], Selim Çam[2,3], Emine Elif Altuntaş[1]

[1]*Department of Otolaryngology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
[2]*Department of Production Management, Faculty of Business, Gaziosmanpaşa University, Tokat*
[3]*Statistician, Cumhuriyet University Hospital, Sivas, Turkey*

Abstract

Objective: We aimed to investigate whether climatic conditions of the region where we live and meteorological parameters had any effect on pathogenesis and prognosis of idiopathic sudden sensorineural hearing loss (ISSNHL) or not.

Methods: Sixty-eight ISSHL patients, who were treated in our department, were evaluated retrospectively. Meteorological data, including monthly ambient, maximum and minimum temperatures, relative humidity, atmospheric pressure and rainfall, were obtained from the observation station of the Central Weather Bureau of Sivas. The meteorological data for 10 days before the onset of the disorder and in a period of 21 days after the beginning of the treatment were used to investigate the relationship between climatic data and ISSNHL. Siegel's criteria were used to evaluate the treatment success.

Results: The relationship between ISSNHL and seasons was observed to be statistically significant when the seasonal distributions of the cases were evaluated statistically ($p<0.05$; $p=0.008$). The change between Siegel's criteria and season was also statistically significant ($p<0.001$). As recovery in hearing of cases with ISSNHL in accordance with Seigel's criteria and meteorological parameters were evaluated, a statistically significant difference was determined in terms of weather temperature; minimum pressure, and rainfall in the period of 10 days before the treatment. However, when patients were evaluated based on meteorological variables in the period of 21 days after the treatment, there was a statistical correlation with the hearing recovery of the patients according to Siegel's criteria only in terms of rainfall ($p<0.005$).

Conclusion: Our study is the first one indicating that there might be a relationship between rainfall and both pathogenesis and prognosis of ISSNHL. Even though the results of the related studies in the literature varied, we concluded that the relationship between ISSNHL and temperature, pressure, rainfall, and season should not be ignored.

Keywords: Sudden sensorineural hearing loss, season, weather conditions, etiology, recovery.

Özet: İklim şartları ile idiyopatik ani sensörinöral işitme kaybı arasındaki ilişkinin retrospektif değerlendirmesi

Amaç: Kendi yaşadığımız bölgenin iklim şartları ve meteorolojik parametrelerin idiyopatik ani sensörinöral işitme kaybının (ISSNHL) patogenezi ve prognozu üzerinde bir etkisinin olup olmadığını araştırmayı amaçladık.

Yöntem: Bölümümüzde tedavileri yapılmış olan 68 ISSNHL tanısı olan hasta retrospektif olarak incelendi. Aylık ortam sıcaklığı, maksimum ve minimum sıcaklık, bağıl nem, atmosfer basıncı ve yağış miktarını içeren meteorolojik veriler, Sivas Meteoroloji Müdürlüğü gözlem istasyonundan elde edildi. İklimsel veriler ile ISSNHL arasındaki ilişkileri araştırmak için hastalığın başlamasından 10 gün önceki ve tedaviye başlanmasından itibaren 21 günlük bir periyottaki meteorolojik veri değerleri kullanıldı. Tedavi başarısının değerlendirilmesinde ise Siegel kriterleri kullanıldı.

Bulgular: Olguların mevsimlere göre dağılımları istatistiksel açıdan değerlendirildiğinde ISSNHL ile mevsimler arasındaki ilişkinin istatistiksel açıdan anlamlı olduğu izlendi ($p<0.05$; $p=0.008$). Siegel kriterleri ile mevsim arasındaki değişim de istatistiksel açıdan anlamlı idi ($p<0.001$). ISSNHL'li olguların Siegel kriterlerine göre işitmelerindeki düzelme ile meteorolojik parametreler değerlendirildiğinde, tedavi öncesi 10 günlük dönemde minimum, maksimum, ortalama hava sıcaklığı; minimum basınç ve yağışla istatistiksel olarak anlamlı bir farklılık olduğu tespit edildi. Bununla birlikte, tedavi sonrası 21 günlük periyottaki meteorolojik değişkenlerden sadece yağış miktarı ile Siegel kriterlerine göre hastaların işitmelerindeki düzelme arasında istatistiksel açıdan bir korelasyon söz konusu idi ($p<0.005$).

Sonuç: Çalışmamız yağış miktarı ile ISSNHL'nin hem patogenezi hem de prognozu arasında bir ilişki olabileceğini işaret eden ilk çalışmadır. Literatürde yer alan bu konuda yapılmış çalışmaların sonuçları farklılıklar göstermekle birlikte ISSNHL ile sıcaklık, basınç, yağış ve mevsim arasındaki ilişkinin de göz ardı edilmemesi gerektiği kanısındayız.

Anahtar sözcükler: Ani sensörinöral işitme kaybı, mevsim, hava koşulları, etyoloji, iyileşme.

Correspondence: Kasım Durmuş, MD. Department of Otolaryngology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey.
e-mail: kasimdurmus5@gmail.com

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The most common definition of sudden sensorineural hearing loss (SSNHL) that was defined by De Kleyn et al., in 1944 for the first time is made according to audiological and temporal parameters.[1,2] A hearing loss of more than 30 dB at 3 consecutive frequencies within 3 days is defined as idiopathic SSNHL (ISSNHL), which is a common medical emergency.[3] Even though this type of hearing loss influences especially elders, it is seen at every age. Its incidence is estimated to be 10–20/100,000/year, but in fact it is probably much higher because it is increasingly seen in industrialized countries and most of cases are frequently misdiagnosed or considered as age-related unavoidable disorder.[4,5]

SSNHL has a sophisticated course with possible multiple etiologies and treatment modalities. The etiology of SSNHL is usually unknown and is therefore frequently considered as ISSNHL. Despite the lack of well-clarified etiology of ISSNHL, some theories concerning the reason of injury in such situations indicate vascular injury, rupture of membranes, viral or bacterial infection, and immune mediated injury.[6]

Being known to influence human health for many years,[7] seasonal climatic changes are effective on both the development of sudden deafness and its healing. Because of only few reports on ISSNHL associated with weather conditions, the relationship between them has not been completely clarified. In this regard, general characteristics of the weather such as atmospheric pressure and temperature as well as their variation and covariation have been commonly investigated.[8–14]

The results of studies assessing the relationship between ISSNHL and parameters of weather condition in the literature are different from the results of the studies we could reach. Our clinical observations revealed that the number of cases with ISSNHL increased in certain periods. Because the number of studies investigating the effects of weather and seasonal changes on incidence of ISSNHL in the literature is limited and the results vary, we aimed to investigate whether or climatic conditions of the region where we live and meteorological parameters had any effect on pathogenesis and prognosis of ISSNHL or not.

Materials and Methods

Study population

Sixty-eight consecutive ISSHL patients, who were treated at our department, were examined retrospectively. Definition of ISSNHL is a hearing loss of at least 30 dB in 3 consecutive frequencies in 72 hours.[3]

Exclusion and inclusion criteria, which were based on the study of Durmuş et al.[15] on ISSNHL cases, were used in our clinic in the present study and both situations were described below. Inclusion criteria were as follows: applying to hospital within one week from the onset of the disease, no history of steroid treatment, and undergoing pure tone hearing test during the first visit. Exclusion criteria were as follows: having an acute inflammation, infection, a history of otologic surgery, trauma or barotrauma during the previous 4 weeks, cerebellopontine angle pathology or congenital cochlear malformations, neurologic disorders predisposing to hearing loss, the recent use of ototoxic medications, neoplasm within the previous 2 years, or other major diseases (such as heart failure, hypertension, coronary artery disease, cor pulmonale, liver or renal dysfunction, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea, connective tissue diseases, and inflammatory bowel diseases), any otologic disease such as otitis media during the last 4 weeks, chronic otitis media, otosclerosis, and Meniere's disease.

All of the cases included in the study were applied with standard treatment protocol which is applied to patients diagnosed with ISSNHL in our clinic. The protocol is as follows: All of the patients were administered methylprednisolone (1 mg/kg i.v. per day Prednol-L ampoule, Mustafa Nevzat Drug Industry, Istanbul, Turkey), with a dose tapering by 10 mg per two days maintained for at least 2 weeks. On the corticosteroids, the patients were administered with the H2 receptor inhibitor ranitidine 1x1 ampoule i.v. (Ulcuran ampoules 50 mg/2 Ml i.v. Yavuz Drug Industry, Istanbul, Turkey), oral vitamin B1 (2×250 mg thiamine hydrochloride) and B6 (250 mg pyridoxine hydrochloride; Nerox B tablet, Abdi İbrahim Pharmaceutical Company, Istanbul, Turkey) for a period of three months. Then, 100 mg pentoxifylline (Vasoplan AMP 100 mg/5 ml Mustafa Nevzat Drug Industry, Istanbul, Turkey) was added into 500 ml Voluven (Fresenius Kabi AG, Oberursel, Germany) and given via intravenous infusion. The dose of pentoxifylline was added every two days and it took eight days to administer the treatment.

The approval of Ethical Committee was received and the study was conducted in accordance with the Helsinki Declaration. Informed consent of all the participants was received.

Meteorological data

The study was conducted for three years (March 2015 to June 2017) in the province of Sivas, being located in Northeastern Turkey and having a population of about

621,224 people. Meteorological data including monthly ambient temperature, relative humidity, atmospheric pressure, rainfall, and maximum and minimum temperatures obtained at observation station of the Central Weather Bureau of Sivas were used.

Being a relatively small city, Sivas has a total surface area slightly larger than 28,619 km^2. Therefore, meteorological data in a period of 10 days before onset of the disease (the day on which patient stated their complaints started was considered as the day 1) and in a period of 21 days since the beginning of the treatment (to cover the whole period of medical treatment) were used to investigate the relationship between climatic data and ISSNHL.

During the study period, temperature ranged from -21°C (February) to 38.1°C (July) and relative humidity was between 96% (January) and 24.9% (April). Pressure ranged from 853.1 hPa (February) and 880.4 hPa (February). Since Sivas province is geographically located in a high region, pressure less than 1000 hPa is considered as normal. Maximum rainfall during the study period was 24.1 kg/m^2 (May).

Also in the present study, each year was divided into four seasons in order to obtain seasonal distribution of ISSNHL: spring (March 1 – May 31), summer (June 1 – August 31), autumn (September 1 – November 30), and winter (December 1 – February 28/29).

Audiological assessment

Hearing data of all of 68 cases were obtained by using AC-40 Interacoustics Clinic Audiometer (Interacoustics, Assen, Denmark) at baseline and after the treatment (at the end of the 4th week) and they were recorded in the audiological evaluation form of each patient.

All of the ISSHL patients were subject to a standard evaluation including a pure-tone speech audiometry. Pure tone thresholds were obtained for air conduction at 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, and 6 kHz and for bone conduction at 250 Hz, 500 Hz, 1 kHz, 2 kHz, and 4 kHz, respectively. Audiologic data were reported via the methods suggested by the Hearing Committee of the American Academy of Otolaryngology Head and Neck Surgery. Based on Siegel's criteria,[16,17] a classification was made in accordance with the treatment success and pure tone averages were observed during the follow-ups one month later. ISSNHL patients were divided into four subgroups by considering whether their pure tone averages (PTA) pointed out complete, partial, slight and no recovery or not. Complete recovery was defined as a final pure tone audiometry result <25 dB, and partial recovery as an improvement of >15 dB, but final hearing of 25–45 dB. Slight recovery was defined as an improvement of >15 dB, but final hearing >45 dB; and no recovery was defined as a hearing improvement of <15 dB and final hearing of >75 dB.

Statistical analysis

The data were analyzed by using the Statistical Package of Social Science (SPSS Inc., Chicago, IL, USA) for Windows version 23.0.

Additionally, SSNHL values of patients as well as periodical climatic data were also added in data set used in the study. At the application stage of analyses, normality was tested via Kolmogorov-Smirnov Z test. Because variables met normal distribution, independent samples t-test and related samples t-test were performed in order to test the mean differences between two categorical variables. F-test was performed for testing multiple categorical variables. Presentations were also prepared with the aid of demographic and disease data of the patients. The tests carried out were interpreted at confidence level of 95%.

Results

Sixty-eight ISSNHL patients who had a mean age of 46.81±16.045 (range: 13 to 78) years were included in the study.

Thirty-one patients were male (45.6%) and 37 were female (54.4%). The mean age was 51.46±15.70 (range: 15 to 78) years in female patients and 41.26±14.85 (range: 13 to 75) in male patients.

All the cases had a unilateral hearing loss [right ear was 45.6% (n=31) and left ear was 54.4% (n=37)]. Pre-treatment and post-treatment PTA values of ears with hearing loss in patients with ISSNHL were 47.89±28.95 and 40.19±29.93 ($p<0.001$) for the left ear and 59.16±24.83 and 51.10±27.76 ($p<0.001$) for the right ear, respectively.

According to Siegel's criteria, complete recovery was observed in 30 (44.12%) patients, slight recovery in 14 (20.59%) patients, and no recovery in 24 (35.29%) patients.

When examining the distribution of 68 patients, included in the study, by months in a 3-year period, it was observed that patients with ISSNHL were observed almost every month ($n_{max(March)}=14$; $n_{min(September)}=1$) (**Fig. 1**). When distribution of the patients with ISSNHL was evaluated by seasons, 23.52% ($n_{wint}=16$) patients were observed in winter months, 39.70% ($n_{spring}=27$ in spring months, 26.47%

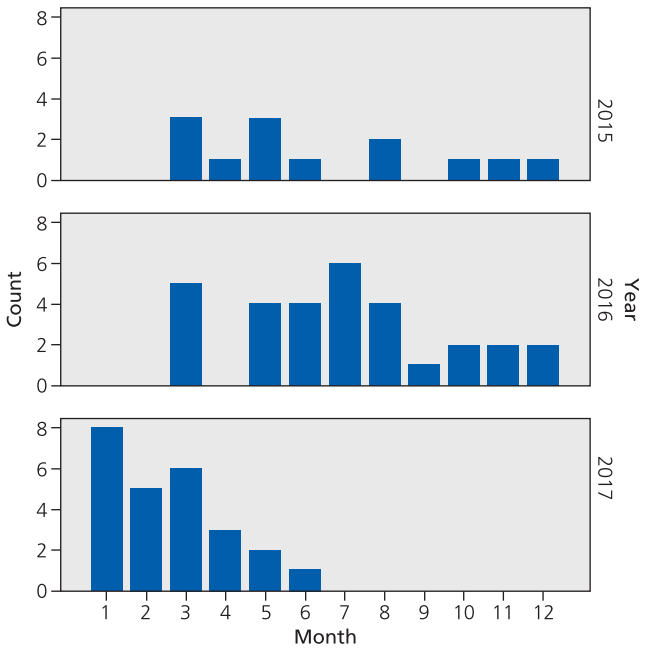

Fig. 1. The distribution of ISSNHL by months and years.

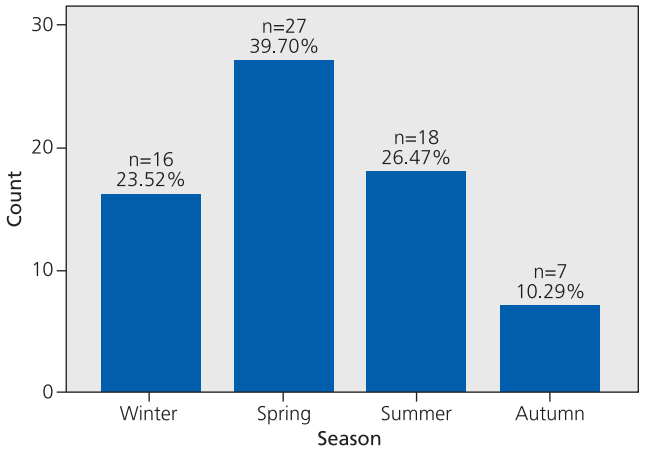

Fig. 2. The seasonal distribution of ISSNHL.

(n_{summ}=18) in summer months, and 10.29% (n_{autumn}=7) in autumn months, respectively. When distribution of the patients by seasons was assessed statistically, it was observed that there was a statistically significant correlation between ISSNHL and seasons (p<0.05; p=0.008) (**Fig. 2**).

When hearing recovery level of the patients with ISSNHL by seasons was assessed according to Siegel's criteria, it was remarkable that those with complete recovery were rather in summer and spring months; on the other hand, those with no recovery were intense among the patients diagnosed during winter. This variation between Siegel's criteria and the season was statistically significant (p<0.001) (**Table 1**).

Based on the day when complaints of the patients with ISSNHL started, meteorological parameters included 10 days before the onset of symptoms and in the 21-day treatment period by accepting that the starting day of the treatment was the first day were summarized in **Table 2**. As it can be seen in the table, there was a statistically significant difference between 10-day period before the onset of symptoms and 21-day treatment period in meteorological parameters in the period evaluated (p<0.001).

When hearing recovery of the patients with ISSNHL according to Siegel's criteria and meteorological parameters were evaluated, a statistically difference was determined between minimum, maximum and mean weather temperatures, minimum pressure and rainfall during pretreatment 10-day period. Additionally, there was a statistical correlation between only the rainfall among meteorological parameters and recovery of the patients based on Siegel's criteria during 21-day treatment period (p<0.005) (**Table 3**).

Table 1. The distribution of the patients with ISSNHL by seasons based on Siegel's criteria.

Seasons	On the basis of Siegel's criteria			p-value
	Complete recovery n (%)	Slight recovery n (%)	No recovery n (%)	
Winter	1 (6.25%)	3 (18.75%)	12 (75.0%)	**0.002**
Spring	15 (55.6%)	1 (3.7%)	11 (40.7%)	**0.003**
Summer	12 (66.7%)	5 (27.8%)	1 (5.6%)	**0.006**
Autumn	2 (28.6%)	5 (71.4%)	0 (0%)	0.257
	<0.001	0.370	**0.010**	

Table 2. Mean value of each meteorological parameter on the 10-day period prior to the onset of symptoms and the 21-day period from the start of medical treatment.

Meteorological parameter		Mean±SD	Minimum	Maximum	p-value
T_{min} (°C)	Before	3.70±7.30	-9.98	16.39	**<0.001**
	After	3.80±7.91	-10.28	15.70	
T_{max} (°C)	Before	15.92±10.12	.11	33.03	**<0.001**
	After	16.52±10.44	-2.26	32.46	
T_{mean} (°C)	Before	9.30±8.65	-5.27	23.90	**<0.001**
	After	9.60±9.10	-6.54	23.06	
RH	Before	61.04±10.30	42.97	80.01	**<0.001**
	After	60.92±9.27	48.08	77.92	
Rf	Before	1.34±1.34	.00	5.29	**<0.001**
	After	1.22±1.17	.00	5.41	
P_{min}	Before	869.73±2.30	865.47	874.93	**<0.001**
	After	870.25±2.35	866.03	877.16	
P_{max}	Before	873.31±2.31	869.44	878.95	**<0.001**
	After	873.72±2.42	87.30	880.27	
P_{mean}	Before	871.71±2.24	867.61	876.86	**<0.001**
	After	872.12±2.32	868.64	878.79	

P_{max}: maximum atmospheric pressure; P_{mean}: mean atmospheric pressure; P_{min}: minimum atmospheric pressure; **RH:** relative humidity; **Rf:** rainfall; T_{max}: minimum temperature; T_{mean}: mean temperature; T_{min}: maximum temperature.

Table 3. Mean values of meteorological parameters and difference analysis results based on Siegel's criteria.

Meteorological parameter		Siegel's criteria	N (%)	Minimum	Maximum	Mean±SD	p-value
T_{min} (°C)	Before	1	30 (44.11%)	-6.88	16.07	6.43±6.91	0.017[a]
		3	14 (20.58%)	-9.13	16.39	2.46±7.56	
		4	24 (35.29%)	-9.98	13.49	1.01±6.66	
T_{max} (°C)	Before	1	30 (44.11%)	1.43	33.03	19.51±10.01	0.028[b]
		3	14 (20.58%)	1.36	32.73	14.08±10.32	
		4	24 (35.29%)	.11	29.98	12.51±9.00	
T_{mean} (°C)	Before	1	30 (44.11%)	-2.91	23.81	12.46±8.43	0.021[c]
		3	14 (20.58%)	-4.42	23.90	7.76±8.84	
		4	24 (35.29%)	-5.27	21.20	6.24±7.73	
Rf	Before	1	30 (44.11%)	.00	5.18	1.16±1.35	0.039[d]
		3	14 (20.58%)	.02	1.99	.83±.77	
		4	24 (35.29%)	.07	5.29	1.88±1.46	
Rf	After	1	30 (44.11%)	.00	3.53	.87±.85	0.016[e]
		3	14 (20.58%)	.02	3.54	1.03±.91	
		4	24 (35.29%)	.00	5.41	1.76±1.47	
P_{min}	Before	1	30 (44.11%)	866.47	873.62	869.60±1.86	0.037[f,g]
		3	14 (20.58%)	866.58	874.10	871.06±2.19	
		4	24 (35.29%)	865.47	874.93	869.11±2.62	

P_{min}: minimum atmospheric pressure; **Rf:** rainfall; T_{max}: minimum temperature; T_{mean}: mean temperature; T_{min}: maximum temperature.

[a]The difference was caused by Siegel 1–4 groups (p=0.006). [b]The difference was caused by Siegel 1–4 groups (p=0.011). [c]The difference was caused by Siegel 1–4 groups (p=0.008). [d]The difference was caused by Siegel 1–4 groups (p=0.048). [e]The difference was caused by Siegel 1–4 groups (p=0.005). [f]The difference was caused by Siegel 1–3 groups (p=0.047). [g]The difference was caused by Siegel 3–4 groups (p=0.012).

Discussion

The aim of the present study was to investigate if climatic conditions and meteorological parameters of the region where we have been living had any effect on development of ISSNHL and/or recovery level of patients' hearing or not. Therefore, primarily the change between the diagnosis and treatment periods of the cases with ISSNHL in terms of parameters obtained from meteorology unit was revealed statistically. The results obtained from the present study indicate that when considering the climatic conditions of our region, the patients with ISSNHL were observed almost every month during the 3-year period; however, the patients were observed more frequently in especially spring, and when the patients were classified by Siegel's criteria in terms of recovery in hearing levels, complete recovery was observed mostly in the patients diagnosed and treated in summer and spring months (Siegel 1), while the worst outcomes of treatment were observed in the patients diagnosed and treated in winter months (Siegel 4).

SSNHL is a type of hearing loss with no exact reason developing in a relatively short time and is a common otolaryngologic entity. It has an unclear etiology. The pathogenesis of this disease has been suggested by different theories such as inflammatory, vascular, traumatic, metabolic, neoplastic, and ototoxic.[16] Thus, once all other possible pathological entities causing SSNHL were excluded, ISSNHL is most often diagnosed.

Since the argument suggested by Hippocrates in the 5th Century for the first time, studies have been conducted for centuries indicating that climatic changes may have effects on human health. Because its etiology has not been known exactly yet, the effects of climate on etiology, incidence, and prognosis in patients with ISSNHL have become subject in various studies in the literature. The first study, which we could access upon literature review on this issue, was published by Mess et al.,[8] in 1984. This study was conducted retrospectively on more than 500 patients with SSNHL living in the region of Munich and a statistically significant correlation with the data of weather condition was shown. The results obtained from the study of Hebert et al.[9] on a possible relationship between weather condition and Bell's palsy, acute unilateral vestibular disorder, Meniere's disease, and sudden hearing loss, abstract of which we accessed via PubMed database, pointed out that these diseases were observed more frequently in low pressure conditions. The present study included the patients living in Sivas province. Due to geographical location, Sivas is located in a low pressure area. When minimum, maximum, and mean pressure values of pre-diagnosis 10-day period and 21-day treatment period were compared, pressure values in the period of the disease onset were observed to be lower in a statistically significant way. These results are similar to the results of the study of Herbert et al.[9] Mizukoshi et al.[10] pointed out in their study that there was no relationship between cold weather and incidence of SSNHL. When an evaluation was made in terms of weather temperature and recovery in hearing level of patients, the results obtained from our study revealed that mean, minimum, and maximum temperatures in the 10-day period before the disease were high, which led to better recovery rates.

In the study performed by Preyer[11] to investigate the correlation between incidence, degree of hearing loss, remission and atmospheric pressure and temperature in 128 patients with ISSNHL for a 12-month period, it was observed that while the minimum differences were observed for atmospheric pressure and temperature in the patient group with completely recovered hearing threshold, the same parameters were higher for the patients with hearing loss. However, the disease did not have a statistically significant correlation with pressure and temperature. In addition, a correlation between disease and season was not revealed. When considering the results obtained from the present study, they were different from the results of this study. For example, disease was observed mostly in spring in our patient group. The results of the present study were also remarkable regarding the fact that the rates of complete recovery were higher in patients who were diagnosed with ISSNHL mostly in summer and spring compared to those diagnosed in other seasons. Nonetheless, the rates of complete recovery were also higher in patients having high minimum, maximum, and mean temperature values in the period when they were diagnosed with ISSNHL. In conclusion, the results obtained from the present study were not similar to the results of the study of Preyer.[11]

In the study conducted by Danielides et al.[12] to investigate the effects of seasonal distribution of ISSNHL and variations and covariations of meteorological parameters such as temperature, humidity, atmospheric pressure on incidence of disease, the authors drew attention that there was no correlation between prevalence of disease and seasons and the incidence could not be significantly associated with any meteorological parameter or any weather type. According to our opinion, the most remarkable point of this study was that their results were only for the regions involving meteorological conditions dominating in Northwestern Greece. For example, although there was a relationship between disease and seasons in the present study, we con-

ducted it in a geography completely dominated by continental climate. Therefore, results of the present study were not compatible with the results of the study of Danielides et al.[12]

Lin et al.[13] investigated the relationship between specific weather conditions such as ambient temperature, relative humidity, atmospheric pressure, rainfall, and percentage of total sunshine in Taiwan and incidence of ISSNHL by using 5-year population data. Even though their results indicated that there were significant correlations between ambient temperature, relative humidity and incidence of ISSNHL for the total population, they determined that the significant relationship between incidence of ISSNHL and climatic parameters disappeared after arrangements made by seasonality, months, and trends. Consequently, the theory suggesting that weather is a triggering factor for pathogenesis of ISSNHL was not supported by this study.

In the study conducted by Ryu et al.[14] to evaluate whether prognosis of ISSNHL was associated with the initial season as well as the factors that may influence the prognosis in every season or not, they revealed that recovery rates of hearing of 318 patients did not show a significant difference by months and there was no correlation between mean temperature and daily temperature range in onset period of disease and recovery rates. This study revealed that recovery rates did not show a significant difference among patients with onset during these four seasons. The results of their study and the results of the present study did not support each other. However, while weather temperature was -6 to -3°C (January) in the coldest month, it was 23–27°C (August) in the hottest month in the region where Ryu et al.[14] conducted their study. During the three years of period when the present study was conducted, the coldest temperature in Sivas was -21°C observed in January, whereas the hottest temperature was 38.1°C observed in June. We are of opinion that the main reason why the results of two studies did not show similarity was different climate conditions. In the study of Narozny et al.,[17] the rates of hearing recovery were indicated to be higher in patients for whom disease developed in spring, which supports the results of the present study.

The last study in the literature which evaluated the effect of meteorological factors on ISSNHL and we could access was the one by Seo et al.[18] This study was conducted in a 6-year period and on 607 patients. The largest series of patients studied about this issue was included in this study. Analysis was also performed to evaluate the weather conditions occurring 1–7 days before ISSNHL onset and possible delayed effects of meteorological factors regarding the onset of disease. When the results of the study were evaluated, it was reported that mean and maximum wind velocity was higher in days when ISSNHL developed than the days that were not onset of ISSNHL, but a distinct relationship could not be established between any meteorological factor and onset of ISSNHL following the adjustment of multiple comparison value. In addition, maximum wind velocity had a distinct difference 5 days before onset of ISSNHL and it was pointed out that stronger wind velocity was likely to be associated with onset of ISSNHL.

Consequently, when the results of the present study were assessed with higher weather temperature in the pre-diagnosis period when the patients with ISSNHL were detected as well as the lower precipitation and the lower rainfall also in the 21-day treatment period, the rate of recovery in hearing loss was higher. The most important results making the present study different from other related studies in the literature are that it is the first study indicating that there might be a relationship between temperature in 10-day period before ISSNHL diagnosis, the rainfall in both pre-diagnosis and treatment periods and the prognosis of disease, and there might be a relationship between rainfall and both the pathogenesis and prognosis of ISSNHL.

Conclusions

The relationship between weather condition, meteorological parameters and diseases has become the subject in studies for long years. ISSNHL is also one of these diseases. The results obtained from the limited number of studies evaluating etiology, incidence, and prognosis of disease and meteorological parameters in the literature are different from the results of the our study. It was thought that these differences might be arising from the differences between both geographical locations and climatic conditions of the regions where the studies were conducted. However, we are of the opinion that the relationship between ISSNHL and temperature, pressure, rainfall and season obtained from some of previous studies and similarly from the present study should not be ignored. Therefore, we think that further multicenter studies including several regions and climatic conditions, and large case series are needed in order to evaluate the relationships between ISSNHL and season and meteorological parameters. In addition, it would not be right to assert that season and meteorological parameters have or do not have a possible role as a triggering factor in prognosis or pathogenesis of ISSNHL by only a single study without conducting a study involving wide geographical regions.

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Neutrophil to lymphocyte and platelet to lymphocyte ratios as an indicator of inflammation in patients with recurrent aphthous stomatitis

Mustafa Kule[1], Asude Kara Polat[2], Aslı Akın Belli[3], Zeynep Gökçen Kule[1]

[1]*Department of Otorhinolaryngology, Muğla Sıtkı Koçman University Training and Research Hospital, Muğla, Turkey*
[2]*Department of Dermatology, Istanbul Training and Research Hospital, Istanbul, Turkey*
[3]*Department of Dermatology, Muğla Sıtkı Koçman University Training and Research Hospital, Muğla, Turkey*

Abstract

Objective: Recently, the ratios of neutrophil to lymphocyte (NL) and platelet to lymphocyte (PL) have been used as an indicator of inflammation. We aimed to investigate the relation of recurrent aphthous stomatitis (RAS) to inflammation by analyzing the ratios of NL and PL.

Methods: We conducted a case-control study on 143 patients with RAS and 134 healthy control cases between February 2015 and March 2016. Age, sex, neutrophil count, platelet count, lymphocyte count, and the ratios of NL and PL of the participants were recorded.

Results: One hundred and forty-three RAS patients and 134 control cases were included in the study. The ratios of NL and PL of RAS group were significantly higher than in the control group (p=0.004 and p=0.010, respectively). The NL ratio was the only independent predictor of RAS in multivariate logistic regression analysis (p=0.014). The cut-off value of NL ratio for predicting RAS was 3.49 with 13.3% sensitivity and 99.9% specificity (p=0.010).

Conclusion: We have found that the ratios of NL and PL were higher in RAS group than the control group. The results of our study support that inflammation has an important role in the pathogenesis of RAS.

Keywords: Lymphocyte, neutrophil, platelet, recurrent aphthous stomatitis.

Özet: Rekürren aftöz stomatitli hastalarda enflamasyon göstergeleri: Nötrofil/lenfosit ve trombosit/lenfosit oranları

Amaç: Son zamanlarda, nötrofil/lenfosit (NL) ve trombosit/lenfosit (TL) oranları enflamasyonun bir göstergesi olarak kullanılmaktadır. Bu çalışmada NL ve TL oranlarını değerlendirerek rekürren aftöz stomatitin (RAS) enflamasyon ile ilişkisini incelemeyi amaçladık.

Yöntem: Şubat 2015 ile Mart 2016 tarihleri arasında 143 RAS hastası ve 134 sağlıklı kontrol üzerinde bir olgu-kontrol çalışması yürüttük. Çalışmada katılımcıların yaş, cinsiyet, nötrofil, trombosit ve lenfosit değerleri ve NL ve TL oranları kaydedildi.

Bulgular: Yüz kırk üç RAS hastası ve 134 kontrol çalışmamıza dahil edildi. RAS grubunun NL ve TL oranları kontrol grubundakinden anlamlı olarak yüksekti (sırasıyla p=0.004 ve p=0.01). Çok değişkenli lojistik regresyon analizinde, NL oranı RAS için tek bağımsız prediktör olarak bulundu (p=0.014). RAS'ı tahmin etmede NL oranının kesme değeri %13.3 duyarlılık ve %99.9 spesifite ile 3.49 olarak tespit edildi (p=0.01).

Sonuç: NL ve TL oranları RAS grubunda kontrol grubundan yüksek bulundu. Çalışmamızın sonuçları RAS patogenezinde enflamasyonun önemli bir role sahip olduğunu desteklemektedir.

Anahtar sözcükler: Lenfosit, nötrofil, platelet, rekürren aftöz stomatit.

The most common cause of oral ulcers is recurrent aphthous stomatitis (RAS) in adults and children.[1] The prevalence of RAS varies from 5% to 60%.[2] Pathogenesis of RAS is multifactorial that trauma, stress, hormonal status, family history, food hypersensitivity, infectious factors, and immunological factors have a role in the development of RAS.[1] RAS can appear in three forms: minor aphthous ulcers, major aphthous ulcers, and herpetiform ulcers.[2] It has been considered that there are some changes in cellular immunity of RAS patients. It has been found that the rate of

Correspondence: Mustafa Kule, MD. Department of Otorhinolaryngology, Muğla Sıtkı Koçman University Training and Research Hospital, Muğla, Turkey.
e-mail: mustafakule@hotmail.com

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CD8+/CD4+ of peripheral blood increased in RAS patients.[3] In oral ulcers, whereas the levels of interleukin (IL)-2, IL-6, IL-8, the tumor necrosis factor-α (TNF-α), which are pro-inflammatory cytokines, are increased, the level of IL-10, which is an anti-inflammatory cytokine, is decreased.[3-6]

Recently, the ratios of neutrophil to lymphocyte (NL) and platelet to lymphocyte (PL) have been noticed to be an indicator of inflammation for some cardiovascular or non-cardiovascular diseases.[7] Moreover, these ratios have been used as an indicator of poor prognosis in various cancers.[8,9]

To our knowledge, there are a few studies reporting the NL and PL ratios as inflammation predictors in RAS patients. In this study, we aimed to investigate the relation of RAS to inflammation by analyzing the ratios of NL and PL.

Materials and Methods

We conducted a case-control study on 143 patients with RAS and 134 healthy control cases between February 2015 and March 2016 in the Dermatology and Otorhinolaryngology Outpatient Clinics. The approval of Ethics Committee was obtained for this study from the Ethics Committee of Muğla Sıtkı Koçman University. We had age- and sex-matched subjects in RAS and the control groups. Diagnosis of RAS was based on the typical clinical findings and only the patients with minor aphthous stomatitis were included in the study.

The patients with diabetes mellitus, hypertension, coronary artery disease, connective tissue disease, vasculitis, inflammatory bowel disease, chronic renal insufficiency, chronic liver failure, malignancy, Bell's palsy, vertigo, tinnitus, and obesity were excluded from the study.

Complete blood count was analyzed in the RAS patients with active ulcers. Age, sex, neutrophil count, platelet count, lymphocyte count, and the ratios of NL and PL of the participants were recorded.

The statistical software "SPSS for windows 20.0" (SPSS Inc., Chicago, IL, USA) was employed for the data analysis. The chi-square test was used for the qualitative data. The distribution of quantitative variables was checked with Kolmogorov-Smirnov test. Independent samples T test for normal distributed variables and Mann-Whitney U test for abnormal distributed variables were used. Logistic regression analysis was performed to identify independent risk factors for RAS. The factors with the p<0.10 significance level in the univariate analysis were entered into multivariate regression analysis. A p-value <0.05 was considered significant.

Results

One hundred and forty-three RAS patients (46 male, 97 female; mean age 41.54 years) and 134 control cases (47 male, 87 female; mean age 38.36 years) were included in the study.

The ratios of NL and PL of the RAS group were significantly higher than those of the control group (p=0.004 and p=0.010, respectively). Lymphocyte count of the control group was significantly higher than those of the RAS group (p<0.05) (**Table 1**). The neutrophil count, lymphocyte count, NL ratio, and PL ratio levels were correlated with each other (p<0.001).

The NL ratio was the only independent predictor of RAS in multivariate logistic regression analysis (p=0.014) (**Table 2**). The cut-off value of NL ratio was 3.49 for predicting RAS with 13.3% and 99.9% specificity (p=0.010) (**Fig. 1**).

Table 1. Comparison of the demographic and hematologic parameters in RAS and the control groups.

	RAS group n (%) or mean ±SD	Control group n (%) or mean ±SD	p-value
Female	97 (67.8)	87 (64.9)	0.609
Male	46 (32.2)	47 (35.1)	
Age	41.54±15.88	38.36±13.65	0.076*
Neutrophil count (K/mL)	3.96±1.33	3.76±1.33	0.271†
Lymphocyte count (K/mL)	1.91±0.56	2.10±0.56	**0.004†**
Platelet count (K/mL)	260.22±58.61	262.04±63.11	0.804*
NL ratio	2.25±1.07	1.85±0.64	**0.004†**
PL ratio	145.89±48.33	131.56±41.65	**0.010†**

Chi-square test, Independent T test (*), and Mann-Whitney U test (†). **NL:** neutrophil/lymphocyte; **PL:** platelet/lymphocyte; **RAS:** recurrent aphthous stomatitis; **SD:** standard deviation.

Table 2. Predicting the presence of RAS in the participants with multiple regression analysis.

Independent variables	p-value	Odds ratio (95% CI)
Lymphocyte count	0.370	1.305 (0.729–2.337)
NL ratio	0.014	0.632 (0.438–0.912)
PL ratio	0.898	0.999 (0.992–1.007)

CI: confidence interval; **NL:** neutrophil/lymphocyte; **PL:** platelet/lymphocyte; **RAS:** recurrent aphthous stomatitis.

Discussion

RAS is a disease characterized by recurrent round/oval ulcers with erythematous halo and yellow/gray base.[10] Etiopathogenesis of RAS is still unclear while trauma, stress, family history, and immunological factors have been attribute to be responsible for oral ulcers.[1,11] In the differential diagnosis, there are traumatic lesions, malign lesions, drug reactions, vesiculobullous diseases, hematological disorders, gastrointestinal system diseases, vasculitidis, and infections.[3]

It has been demonstrated that levels of some pro-inflammatory cytokines (IL-2 and TNF-α) are high and level of IL-10, an anti-inflammatory cytokine, is low in the oral ulcers of RAS patients. In recent years, the NL ratio is gaining importance as an easy and cost-effective method to identify systemic inflammation.[7] The increased NL ratio levels have been demonstrated to be related to cytokines involving TNF-α, IL-6, IL-7, IL-8, IL-12, and IL-17. [12] Calculation of NL ratio is an easier and cheaper method than the measurement of these inflammatory cytokines.[12,13]

In various studies, the NL ratio levels have been reported increased in the patients with cardiovascular or non-cardiovascular diseases. However, studies investigating hematological ratios in RAS are scarce. Firstly, Soylu Özler et al. have demonstrated a relationship between the NL ratio and RAS.[14] Seçkin et al. have investigated the effect of colchicine treatment on hematologic inflammatory parameters in the patients with RAS and showed significant decrease in the levels of NL ratio, leukocyte count, and red cell distribution width after the colchicine treatment.[15] In another study, Terzi et al. have reported an increased NL ratio in 80 patients with RAS compared to 80 healthy control cases and supported the role of inflammation in the pathogenesis of RAS.[16] Hypertension and diabetes mellitus have been found associated with high NLR levels.[7] Moreover, the NL ratio has been demonstrated as an predictor of morbidity and mortality in the patients with acute coronary syndrome.[12] Among cutaneous diseases, the NL ratio has been noticed significantly increased in the psoriasis patients.[17] Torun et al. have reported that the NL ratio may be a promising marker to indicate disease severity in ulcerative colitis.[18] Ozbay et al. have reported that mean NL ratio levels were significantly increased in the patients with tinnitus and peripheral vertigo.[19,20] In another study, the NL ratio has been found higher in the patients with a sudden hearing loss than healthy control cases.[21] Atan et al. have reported that both NL and PL rates were significantly higher in the patients with Bell's palsy than the control group.[22]

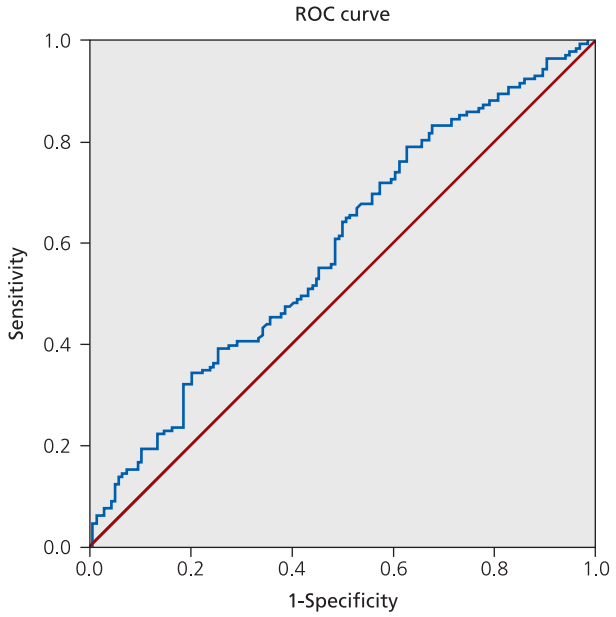

Fig. 1. Receiver operating characteristics curve of NL ratio for predicting recurrent aphthous stomatitis in the participants.

In conclusion, we found that increased NL and PL ratio levels are the inflammation predictors in the patients with RAS. To our knowledge, there are a few studies demonstrating the relation of RAS to inflammation by using the NL and PL ratios. Since the current study was conducted on the patients with minor aphthous stomatitis, further studies are needed involving patients with major and herpetiform aphthous ulcers to show differences in the pathogenesis.

Conflict of Interest: No conflicts declared.

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An investigation of the prevalence of indoor and outdoor inhalant allergens in children with allergic rhinitis

Ahmet Hamdi Kepekçi[1,2], Mustafa Yavuz Köker[3], Ali Bestemi Kepekçi[4,5]

[1]*Department of Audiometry, Health Vocational High School, Yeniyüzyıl University, Istanbul, Turkey*
[2]*Otolaryngology Clinic, Meltem Hospital, Istanbul, Turkey*
[3]*Department of Immunology, Faculty of Medicine, Erciyes University, Kayseri, Turkey*
[4]*Department of Anesthesia, Health Vocational High School, Yeniyüzyıl University, Istanbul, Turkey*
[5]*Department of Anesthesiology, Meltem Hospital, Istanbul, Turkey*

Abstract

Objective: The aim of the present study was to determine the prevalence of the aeroallergens sensitivity among children with allergic rhinitis in the province of Istanbul in Turkey, based on skin prick test (SPT) reactivity.

Methods: This study, including 729 AR patients with positive SPT, was conducted in three age groups. SPT with extracts including pollens, house dust mites (HDMs), animal dander's (ADs) and molds was performed on these patients. All these patients have a positive reaction to at least one allergen with SPT.

Results: The allergen prevalence of 729 patients with positive SPT results was 33% for HDMs, 31% for pollen, 19% for molds and 17% for ADs. The sensitivity to aeroallergens significantly decreased as the age increased ($p<0.01$). Both outdoor and indoor allergen positivity in preschool children (Group 1) were 89 (43.4%) and in adolescent children (Group 3) were 32 (15.6%), and also sensitivity to allergens significantly decreased according to increase of age ($p<0.01$).

Conclusion: We provided regional allergens profile of children with AR in Istanbul. Avoiding exposure to allergens and finding the best formulation of allergen immunotherapy for AR are important steps in the clinical management of patients.

Keywords: Aeroallergen, allergic rhinitis, children, skin prick test.

Özet: Allerjik rinitli çocuklarda indoor ve outdoor inhalen alerjen prevalansının araştırılması

Amaç: Bu çalışmanın amacı, İstanbul'da allerjik rinitli (AR) çocuklarda deri prick testi (DPT) reaktivitesine dayanan aeroallerjen duyarlılığının prevalansının belirlenmesidir.

Yöntem: Pozitif DPT olan 729 AR'li hastanın dahil edildiği bu çalışma, üç yaş grubu halinde incelendi. Bu hastalar üzerinde polen, ev tozu akarları, hayvan epiteli ve mantarlar içeren ekstraktlarla birlikte DPT yapıldı. Araştırmaya dahil olan hastalar DPT'de en az bir alerjene karşı pozitif olan bir tepkiye sahiptir.

Bulgular: Pozitif DPT sonuçları olan 729 hastanın alerjen prevelansı, ev tozu akarları için %33, polen için %31, mantarlar için %19 ve hayvan epiteli için %17 idi. Aeroalerjenlere karşı duyarlılık, yaş arttıkça belirgin olarak azaldı ($p<0.01$). Okul öncesi çocuklarda (Grup 1) outdoor ve indoor alerjen pozitifliği 89 (%43.4), ergen çocuklarda (Grup 3) 32 idi (%15.6) ve alerjenlere duyarlılık da yaş artışına göre belirgin olarak azaldı ($p<0.01$).

Sonuç: Bu çalışma ile İstanbul'daki AR'li çocukların alerjen profili elde edildi. AR'li hastaların klinik yönetiminde sorumlu alerjenlere maruz kalmaktan kaçınma ve AR için en iyi alerjen immünoterapi formülasyonunu bulma önemli adımlardır.

Anahtar sözcükler: Aeroallerjen, allerjik rinit, çocuklar, deri prick testi.

Hypersensitivity and allergic disorders of the immune system which occur through allergic inflammation induced by an allergen-specific immunoglobulin E (IgE) mediated response.[1,2] Today, homes have been insulated for energy efficiency, carpeted, heated and cooled especially in developed countries and indoor allergens have increased in

Correspondence: Ahmet Hamdi Kepekçi, MD. Department of Audiometry, Health Vocational High School, Yeniyüzyıl University, Istanbul, Turkey.
e-mail: ahmethamdi.kepekci@yeniyuzyil.edu.tr

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homes, where is an ideal habitat for the production of indoor allergens.[3,4] Globally, the most abundant indoor allergens include those derived from house dust mites (HDMs), cats, and cockroaches.[4,5] The principal HDM species are the pyroglyphid mites *(Dermatophagoides pteronyssinus*, *dermatophagoides farina*, and others), which usually account for 90% of mite species in house dust in temperate regions.[6,7] Grass pollen are clinically important sources of outdoor aeroallergens and is recognized as an important trigger for allergic rhinitis.[8,9] People are exposed to outdoor allergens that directly or through penetrate the interior throughout life. The most abundant source of outdoor aeroallergens and the most commonly known ones are pollen grains and fungus spores.[10]

In fact, aeroallergens play an important role in the pathogenesis of respiratory allergic diseases. Pollen, mold, house dust mites (HDMs) and animal dander's (ADs) are the most common allergens.[11,12] Allergic disorders are diagnosed by performing a physical examination and epidermal skin testing. Skin prick test (SPT) in the assessment of allergic response continues to be the most appropriate in vivo diagnostic test applied.[1] Any bubble greater than 3 mm at 15 minutes is considered a positive response when there is no response to the negative control.[13] It is also important to identify common allergens in the environment to avoid exposure to allergens and to find the best allergen immunotherapy formulation.[12] So far, there has been no information regarding the common aeroallergens according to outdoor and indoor classification. The aim of this study was to investigate the prevalence of various aeroallergens in Istanbul and their involvement in sensitizing children with AR.

Materials and Methods

This retrospective study was performed on the patients who admitted to otolaryngology clinic between March 2008 and August 2015 and the data from 2–16 years old patients with symptoms of rhinitis were collected in this study.

The diagnosis of allergic rhinitis is in line with "Allergic rhinitis and its Impact On Asthma (ARIA)" guidelines.[14] To avoid false-negative skin tests, patients using antihistamine medications, immune suppressive drugs, and antidepressants were not included in the study groups because antihistamines suppress the skin test results.[15] The study was conducted with the data from ENT clinic. The age range of these patients was 2–16 years and they were divided into three groups, 2–6 years of age were preschool children (Group 1), 7–11 years of age were school children (Group 2) and 12–16 years of age ones were adolescent (Group 3). The results of SPT in these patients were evaluated from their files in this study. SPT was also used for allergens (Allergopharma, Reinback, Germany; Stallergenes SA, Antony, France), which were investigated in terms of both individual responses and in groups. The groups were as follows: outdoor allergens; pollen allergens (tree pollen mix, olive tree, red oak, grass pollen, grain pollen, weed pollen), fungal allergens *(Alternaria alternata*, *Aspergillus fumigatus)* and indoor allergens; house dust allergens *(Dermatophagoides farinae*, *Dermatophagoides pteronyssinus)* and animal dander's (dog epithelium, cat epithelium).

Statistical analysis was performed using SPSS for Windows, Version 21.0 (SPSS Inc., Chicago, IL, USA). A difference in the mean number of siblings between the categories of each index of exposure was tested by Kruskal-Wallis test. A p value <0.05 was considered significant.

Results

Demographic data

In our study, the results of SPT in 1210 patients who had clinical findings for rhinitis were evaluated. Patient's medical history and physical examination findings (sneezing, nasal congestion, frequent and transparent watery runny nose, nasal itching, burning in the eyes, with symptoms such as itching) had been used to diagnose rhinitis. Of them, 729 (60.2%) had at least one or more allergen-positive SPT responses, and this group was accepted as AR patients and their results were evaluated in this study. Remaining 481 (39.8%) patients had no allergen sensitization with SPT and these rhinitis patients were excluded from the study.

The age of patients was between 2 and 16 years and the male/female ratio and the mean age of subjects were 1.03 and 8.25±3.61 years, respectively. The average age of the girls was 8.54±3.66 years, while that of boys was 7.99±3.54 years. These patients were grouped into 3 age groups in 5-year brackets and the Groups 1, 2 and 3 included 276, 307 and 146 patients, respectively.

The prevalence of allergens in SPT positive children with allergic rhinitis

In children with AR living in the Istanbul, the positive SPT allergens consist of 33% house dust allergens, 31% pollen allergens, 19% fungal allergens, and 17% ADs (**Fig. 1**).

SPT reactivity to outdoor and indoor aeroallergens in our patients' groups

The data of SPT positive patients (who had at least one of the house dusts, pollens, fungi, or ADs allergens) were cal-

culated and outdoor allergens were positive in 261 patients (35.80%) from all groups and 96 (36.8%) were in Group 1, 101 (38.7%) were in Group 2 and 64 were (24.5%) in Group 3 (p>0.05) (**Table 1**). Indoor allergens were positive in 263 patients (36.08%) from all groups and 91 were (34.6%) in Group 1, 122 were (46.4%) in Group 2 and 50 were (19.0%) in Group 3 (p>0.05) (**Table 1**).

Both indoor and outdoor allergens were positive in 205 patients (28.12%) from all groups and 89 were (43.4%) in Group 1, 84 were (41.0%) in Group 2 and 32 were (15.6%) in Group 3 (p=0.001) (**Table 1**). However, preschool children (Group 1) showed high sensitivity, while teenager group (Group 3) showed lower sensitivity to all allergens (p<0.01) (**Table 1**).

The distribution of allergens reactivity in our patients with AR

In children with AR living in the Istanbul region, the positive SPT allergens consist of 33% house dust allergens, 31% pollen allergens, 19% fungal allergens, and 17% ADs (**Table 2**). No significant differences between men and women in the distribution of allergen species were observed.

Sensitivity to indoor allergens such as house dust, fungus, and animal allergens decreased inversely with increasing age (p<0.05) (**Table 2**). Especially, the sensitivity to animal allergens decreased more significantly in the adolescence group (Group 3) (p<0.01) (**Table 2**). There was no statistically significant correlation between pollen allergens and age groups (p>0.005) (**Fig. 2**). When each outdoor allergens were examined one by one, poplar, red oak, and weed pollen sensitivity were seen more frequently in the Group 1 and the sensitivity decreased with age (Group 3) (p<0.01) (**Table 2** and **Fig. 2**).

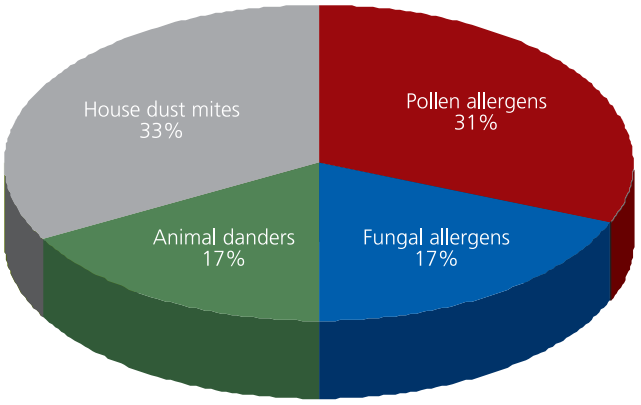

Fig. 1. The prevalence of allergens in SPT positive children with allergic rhinitis.

When the indoor allergens were examined one by one, dermatophagoides farinae, dog epithelium and cat epithelium sensitivity was more frequent in the preschool children (Group 1) and sensitivity decreased in the adolescence group (Group 3) (p<0.01). HDMs were highly positive in the Group 2 and sensitivity decreased in the adolescence group (Group 3) (p<0.01) (**Table 2**). The fungal allergen sensitivity was higher in preschool children (Group 1), whereas it was found lower in the adolescence group (Group 3) (p<0.05) (**Table 2** and **Fig. 2**).

There was male predominance in the percentage of preschool children with allergic rhinitis (male 21.40% and female 16.46%), there was also male predominance in the percentage of school children with allergic rhinitis (male 22.09% and female 20.03%) and there was female predominance in the percentage of adolescent children with allergic rhinitis (female 11.25% and male 8.78%) (**Fig. 3**).

Table 1. The prevalence of outdoor, indoor and both allergen-positive groups for patients with allergic rhinitis.

Allergens	All groups		Group 1	Group 2	Group 3	p-value
Type	100%	N=729	n=276	n=307	n=146	
Outdoor	35.80%	N=261 100%	96 (36.8%)	101 (38.7%)	64 (24.5%)	0.207
Indoor	36.08%	N=263 100%	91 (34.6%)	122 (46.4%)	50 (19.0%)	0.069
Outdoor & Indoor	28.12%	N=205 100%	89 (43.4%)	84 (41.0%)	32 (15.6%)	0.001

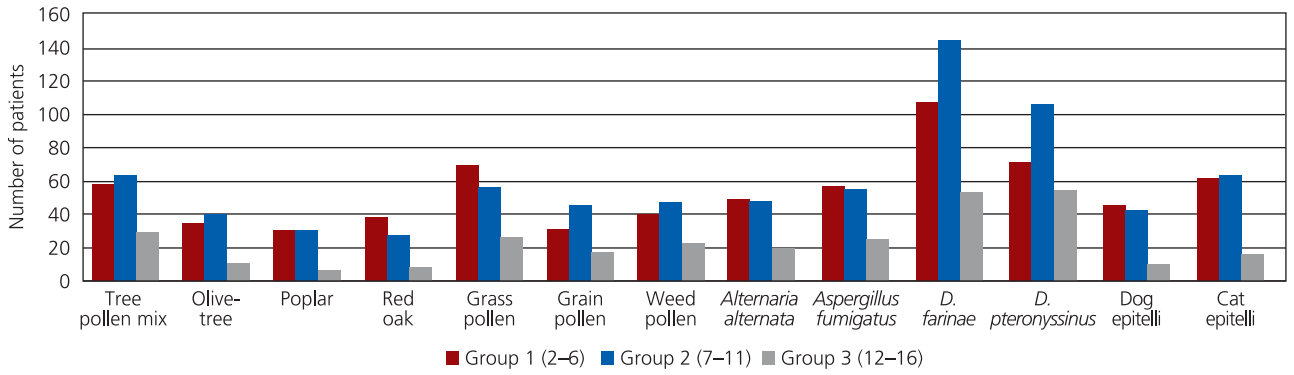

Fig. 2. Allergen distribution in three age groups of patients with allergic rhinitis.

Discussion

In this study, the characteristics of allergen causing AR and their prevalence in the children living in Istanbul were investigated. Characteristics of allergen types were important for the evaluation of allergic rhinitis. So the prevalence of indoor and outdoor allergens among children was investigated according to the age groups. The result showed that the sensitizing aeroallergens among our patients with AR were including 33% house dust allergens, 31% pollen allergens, 19% fungal allergens, and 17% ADs (**Table 1**) (**Fig. 1**). HDMs (33%) were the most common aeroallergens in our patient's groups. Moreover, HDMs' percentage is mostly dependent on ambient humidity and high temperature in environmental condition. Likewise, the incidence of HDMs sensitization in Singapore, Malaysia, and Thailand was as high as our study.[16,17]

It was also observed that the percentage of indoor allergens (36.08%) including HDMs and ADs were similar with outdoor allergens (35.80%) like pollens and fungal allergens (**Table 1**). Additionally, both indoor and allergens were positive in 28% of the patients. It has been observed that outdoor allergens in AR patients are more prevalent in different cities where dry climate prevails,

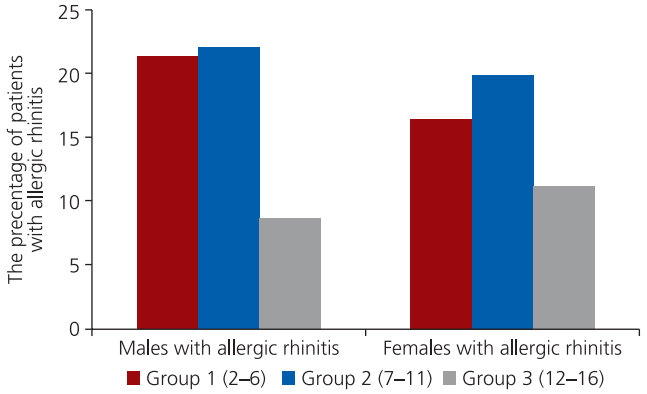

Fig. 3. Gender of patients and percentage of allergic rhinitis in preschool (Group 1), school (Group 2) and adolescent (Group 3) children.

Table 2. The percentage of allergens in age groups and statistical significance in patients with allergic rhinitis.

Allergens	Group 1	Group 2	Group 3	Total	p-value*
	Positive value				
	n (%)	n (%)	n (%)	N† (%)	
HDMs	131 (30.46%)	169 (34.28%)	74 (25.78%)	374 (30.90%)	**0.045**
Pollen allergens	135 (31.39%)	143 (29.01%)	70 (24.39%)	348 (28.76%)	**0.126**
Fungal allergens	91 (21.63%)	86 (17.44%)	40 (13.94%)	217 (17.93%)	**0.044**
Animal dander's	89 (20.69%)	83 (16.84%)	22 (7.66%)	194 (16.03%)	**0.000**
Total	276 (37.86%)	307 (42.11%)	146 (20.03%)	729 (100%)	

unlike our study.[18,19] Indoor allergens are seen more frequently in preschool children but less in adolescents (p<0.01) (**Table 1**). We observe these results because children spend more time at home in their early ages. Additionally, outdoor allergens were more frequent in preschool children, but less in adolescents (p<0.01) (**Table 1**). We associate this with our region which is very dense in terms of pollen levels.

A study conducted on 5080 children with asthma in Istanbul region has shown allergen sensitivities to house dust mite for 50%, cat feathers for 15% and dog feathers for 10%.[20] A study from Ankara in preschool children with respiratory problems showed that the sensitivity to HDMs and A. Alternaria were 46.3% and 29.9%, respectively.[21] Our study has similar results and the sensitivity to both outdoor and indoor allergens in preschool children was (43.4%) and it was significantly higher than adolescents 15.6% (**Table 2**). Therefore, the allergen sensitivity decreased depending on the age (p<0.01) (**Tables 1** and **2**).

In our study, there was a male predominance for allergic rhinitis (21.3%, female 16.4%) in the preschool group and there was a female predominance for allergic rhinitis (11.2%, male 8.8%) in adolescents. The multicenter allergy study followed up 467 children until 13 years of age and showed a similar frequency of rhinitis.[17,22] The reason for this difference may be the lifestyle, and cultural difference of sexes make it possible for a male to expose to antigens more than female children from the environmental conditions in the preschool periods. Thus, the delay of exposure to antigens in the female children could be postponed the allergic reaction and sensitization period in the later ages.

Avoiding exposure to allergens and looking for the best formulation of allergen immunotherapy for AR are important steps in clinical managements of these patients. The eradication of common indoor allergens in domestic living spaces is important in the prevention of symptoms of allergic disease in children groups. Therefore, the prevalence information obtained from our study can be used for the diagnosis and treatment strategies of allergic rhinitis in Istanbul region.

We provide regional allergen profile of AR patients in Istanbul, which is based on the identification of common aeroallergens with the pattern of SPT reactivity.

Conflict of Interest: No conflicts declared.

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Bipolar-assisted tonsil reduction: a simple and inexpensive tonsillotomy technique

Kadir Çağdaş Kazıkdaş, Mustafa Asım Şafak

Department of Otorhinolaryngology, Faculty of Medicine, Near East University, Nicosia, TRNC

Abstract

Objective: This study aims to investigate the novel use of a simple and inexpensive bipolar-assisted tonsil reduction (B-TR) technique in pediatric cases with adenotonsillar hyperplasia by evaluating long-term results, possible complications, need for reoperation and incidence of recurrence.

Methods: We present our long-term retrospective data from 78 consecutive pediatric cases undergoing B-TR combined with adenoidectomy from April 2013 to January 2017. The tonsillar sizes were recorded using the Brodsky grading scale from I to IV, and the patients only with prominant tonsillar sizes (III and higher) and adenoidal sizes exceeding 50% were included in the study group. The tonsil sizes were noted preoperatively, and during the latest follow-up visit after tonsillotomy (min. 9 months postoperatively).

Results: With a mean follow-up period of 18.3 months, the mean tonsillar size preoperatively was 3.47 (±0.50) and mean tonsillar size postoperatively was 1.35 (±0.48). A significant difference ($p<0.001$) was observed between these two groups, excluding the only case who later had undergone tonsillectomy. Minimal uvular edema was noted in 27 children (34.6%), which did not cause any upper airway obstruction in these patients.

Conclusion: We describe herein our B-TR technique in details so that it can be learned relatively quickly and used in pediatric cases with adenotonsillar hyperplasia as a treatment option.

Keywords: Tonsillotomy, tonsillectomy, bipolar diathermy, tonsil reduction.

Özet: Bipolar-destekli tonsil küçültme: Basit ve düşük maliyetli bir tonsillotomi tekniği

Amaç: Bu çalışmada, adenotonsiller hiperplazisi olan pediatrik olgularda basit, ucuz ve yeni bir yöntem olarak bipolar-destekli tonsil küçültme (BTK) tekniğinin, uzun dönem sonuçlarını, olası komplikasyonlarını, revizyon cerrahisi ihtiyacını ve rekürrens insidansını değerlendirerek klinik kullanımını araştırmayı amaçladık.

Yöntem: Nisan 2013 ile Ocak 2017 arasındaki periyotta adenoidektomi ile birlikte BTK uygulanan ardışık 78 çocuk hastamızdan elde ettiğimiz uzun dönem retrospektif verilerimizi sunmaktayız. Tonsil boyutları, I'den IV'e kadar Brodsky dereceleme skalası kullanılarak kaydedildi ve sadece belirgin derecede hipertrofik tonsilleri olan (III ve üstü) ve adenoid boyutları %50'yi aşan hastalar çalışma grubuna dahil edildi. Tonsil boyutları preoperatif olarak ve tonsillotomi sonrasındaki en son takip sırasında (postoperatif min. 9 ay) dosyalarına kaydedildi.

Bulgular: Ortalama 18.3 aylık izlem süresi sonrasında, operasyon öncesi ortalama tonsil büyüklüğü 3.47 (±0.50), operasyon sonrası ortalama tonsil boyutu ise 1.35 (±0.48) olarak kaydedildi. Daha geç dönemde klasik tonsillektomi uygulanan bir hastamız çıkarıldığında, bu iki grup arasında istatistiksel açıdan anlamlı bir fark saptandı ($p<0.05$). 27 çocukta (%34.6) minimal uvula ödemi gözlendi, ancak bu durum hastalarda herhangi bir üst hava yolu obstrüksiyonuna neden olmadı.

Sonuç: Bu çalışma sayesinde BTK tekniğimizi, adenotonsiller hiperplazisi olan pediatrik olgularda, nispeten kolaylıkla öğrenilebilen ve uygulanabilen bir tedavi seçeneği olarak ayrıntılı olarak tarif etmeyi planladık.

Anahtar sözcükler: Tonsilotomi, tonsillektomi, bipolar diatermi, tonsil küçültme.

Tonsillectomy is the most common major otolaryngological procedure performed in pediatric age group, alone or combined with adenoidectomy. Absolute indications for tonsillectomy and adenoidectomy include adenotonsillar hyperplasia with obstructive sleep apnea, failure to thrive, abnormal dentofacial growth; suspicion of malignant disease; acute rheumatic fever or (for tonsillectomy) hemorrhagic tonsillitis.[1] The two major criteria that are most commonly considered to justify surgical intervention are sleep-disordered breathing and recurrent throat infections

Correspondence: Kadir Çağdaş Kazıkdaş, MD. Department of Otorhinolaryngology, Faculty of Medicine, Near East University, Nicosia, TRNC.
e-mail: ckazikdas@gmail.com

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which have a significant impact on children's health and life quality. Hence, adenotonsillectomy for the treatment of adenotonsillar hyperplasia in children is currently the most common indication in our practice. Typical and classical type of surgery in such cases is "extracapsular" tonsillectomy, where the tonsillar tissue and its fibrous capsule coverings are separated from the pharyngeal constrictor muscle as a whole. Exposed peritonsillar tissue containing vessels and muscle fibers can cause significant postoperative pain. Trauma to large extracapsular vessels can result in profuse hemorrhage, with risks of transfusion, further emergent procedures and, in rare cases, even death.[2] In order to decrease the complications and postoperative morbidities, there has been an increasing attention drawn to "intracapsular" tonsillectomy or tonsillotomy lately where the lateral portion of the tonsil and its capsule are preserved.[3] Various methods have been described in the literature and yet there is no consensus on which is the most convenient method, with the most commonly used ones today: radiofrequency, microdebrider, CO_2 laser, thermal welding, bipolar scissors and coblation.[3,4] Despite the reduction in complications due to these techniques, most employ relatively expensive equipment.

Herein, we describe the novel use of our simple and inexpensive bipolar-assisted tonsil reduction (B-TR) technique in 78 consecutive pediatric cases with adenotonsillar hyperplasia by evaluating long-term results, possible complications, need for reoperation and incidence of recurrence.

Materials and Methods

Patients

This is a retrospective chart review of the operated children suffering from snoring and obstructive symptoms due to adenotonsillar hyperplasia with no history of recurrent tonsillitis, who had been referred to our ENT department between April 2013 and January 2017. 78 children (52 f, 26 m) with tonsillar hyperplasia, aged 3–11 (mean age 7.2±2.4) years were included in this study. Exclusion criteria were recurrent tonsillitis, neoplasia, history of peritonsillar abscess or previous tonsillar surgery, comorbidities such as obesity, severe OSA, bleeding disorders and systemic diseases such as pulmonary, cardiac or metabolic abnormalities. Children with elevated titers of anti-streptolysine O, C-reactive protein or rheumatoid factor, and a positive throat culture for group A beta-hemolytic streptococci were also excluded from the study group. Parents were informed about the choices of B-TR technique, classical extracapsular tonsillectomy or conservative management. Written informed consent was obtained from all of the parents. The preoperative consent about B-TR technique included the possibility of tonsillar regrowth, recurrence of preexisting symptoms, occasionally leading to a revision surgery. Only patients treated with B-TR and classical adenoidectomy based upon parents' preferences were included in this retrospective analysis. The tonsil sizes were noted preoperatively, and during the latest follow-up visit (min. 9 months postoperatively). The tonsillar sizes were recorded using the Brodsky grading scale from I to IV, and only patients with prominant tonsillar sizes (III and higher) and adenoidal sizes exceeding 50% were included in this study group. All surgeries were performed by senior surgeons (K.C.K. and M.A.S.).

Surgical technique

Adenoidectomy was performed under general anesthesia at the beginning of the surgery and adrenalin-soaked gauze swaps were routinely inserted into nasopharygeal region to control a possible adenoidal bleeding meanwhile. The uvula was retracted anteriorly by means of a Henke tonsil elevator to avoid injury to anterior and posterior pillars and pharyngeal wall. Bipolar cauterization of the tonsils were initiated starting from the superior pole by inserting the tip of a non-stick bipolar forceps into tonsillar crypts and then activated. The cauterization power was adjusted to 20 W and the energy supply was stopped when blanching of the crypt entrance and neighbouring tonsillar areas occurred and this procedure was repeated multiple times towards to the inferior pole, until the final result was a yellowish residue of the denatured tonsillar tissue (**Figs. 1a–c**). Slight oozing of blood from the surface of the cauterized tonsils and the neighboring pillars could be expected, still these minor hemorrhages were easily managed by further superficial bipolar cauterizations. The entire procedure was brief and lasted between 10–15 minutes depending on the experience of the surgeon. Uvular edema was noted in 27 children (34.6%), most probably caused by pressure applied by the Henke elevator used to protect the operation field, but edema did not cause any upper airway obstruction requiring ICU care in these patients. No secondary hemorrhage occurred and all children were discharged same day. A diet list of soft and cold food was recommended to help resolve the uvular edema for only 3 consecutive days after surgery. We routinely prescribed acetaminophen (15 mg/kg PO q6–8 h) postoperatively for 5 days as our clinic protocol for adenotonsillectomy patients.

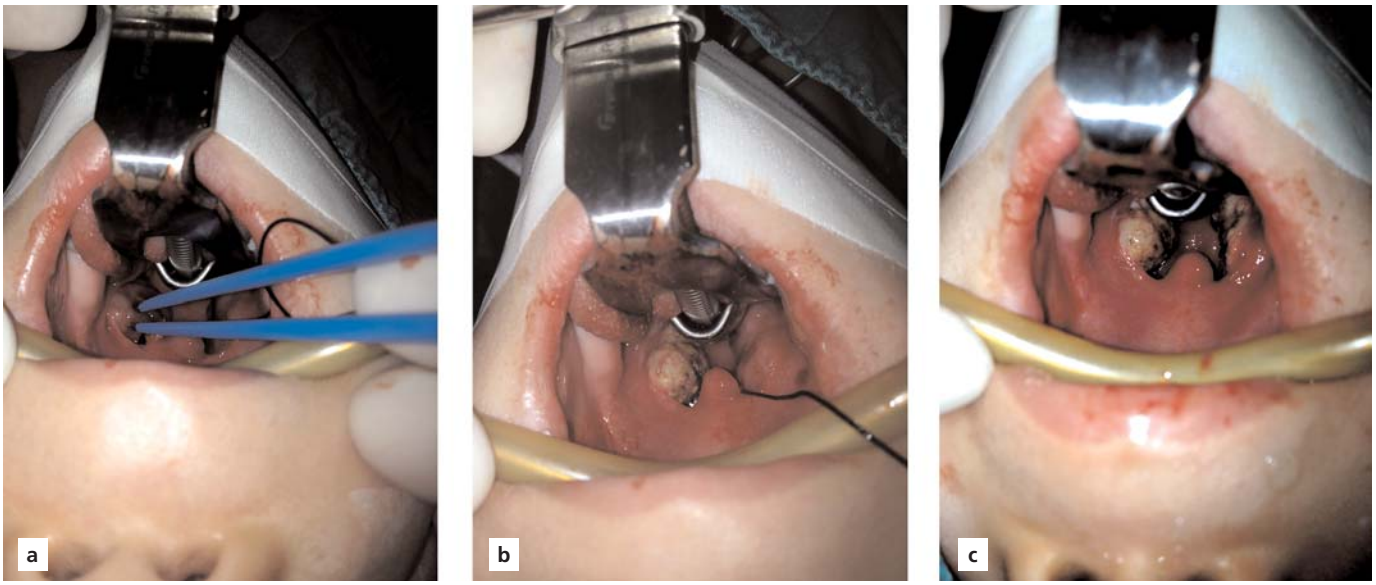

Fig. 1. (**a**) Oral photo documentation of the tonsils before the initiation of the procedure. (**b**) Note the complete blanching of the left tonsil. (**c**) Intraoperative appearance of the tonsils after the completion of the procedure. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

Results

None of our patients had primary postoperative hemorrhage and only one patient (1.3%) suffered from recurrent bacterial tonsillitis symptoms and had to undergo subsequent extracapsular tonsillectomy 16 months after the initial volume reduction operation. There were no technical difficulties during the operation such as adhesions or dissection problems and the histological investigation performed in this revision specimen revealed follicular hyperplasia and signs of chronic inflammation with no evidence of scarring or other signs of previous volume reduction surgery. None of the remaining patients needed reoperation due to tonsillar regrowth.

With a mean follow-up period of 18.3 months, the mean preoperative tonsillar size was 3.47 (±0.50) and mean postoperative tonsillar size was 1.35 (±0.48). A significant difference using Wilcoxon sign rank test ($p<0.001$) was observed between the median tonsil sizes of these two groups, excluding the only case who had undergone tonsillectomy (**Table 1**). As a clinical observation, asymptomatic small-sized tonsils stayed bordered by the palatinal arches (**Fig. 2a** and **b**) and the rest of the children (77/78) did not reveal any signs of recurrent infection or tonsillar regrowth until the last follow-up.

Discussion

In the new millenium, various kinds of methods for tonsil removal and volume reduction have been described to reduce pain and intra- and postoperative bleeding. With the emergence of such novel techniques, partial removal of the tonsil, "the tonsillotomy", has become popular again, whereas the percentage of classical tonsillectomies is rapidly decreasing.[5] For the treatment of non-inflammatory tonsillar hypertrophy resulting in pediatric obstructive symptoms, tonsillotomy combined with adenoidectomy should be considered as the treatment of choice.[5,6] The recent analyses from the national tonsil register in Sweden demonstrate that tonsillotomy + adenoidectomy has become the most commonly administered surgical procedure in pediatric age group of patients with upper airway obstructive symptoms due to tonsillar hyperplasia.[6] Sunnergren et al. claim that this paradigm shift results from the findings that tonsillotomy is superior to tonsillectomy by not only concerning the high rates of postoperative symptom relief, but

Table 1. Mean pre- and postoperative tonsillar sizes (n=77).

	Preoperative	Postoperative
Mean tonsil size	3.47±0.50SD	1.35±0.48SD

Wilcoxon signed rank test $p<0.001$.

Fig. 2. (**a**) Preoperative and (**b**) postoperative 6-month appearances of the tonsils in a different patient. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

also with reduced need for postoperative analgesia, lower rates of postoperative bleeding and reduced number of postoperative infections.[7,8] Leaving a coating layer of semi-viable tonsillar tissue has been shown to reduce exposure of the veins and nerves in the tonsillar plexus and superior constrictor muscle.[3] Additionally, significance of the remaining tonsillar tissue within the lymphoid system, rather than total excision has attracted an increased attention to tonsillotomy techniques.

Vogt et al.[9] presented their results of bipolar radiofrequency cryptolysis in hypertrophic tonsillar tissue and claimed that bipolar technique showed better results when compared to the monopolar method, with emphasis on the fact that lesser lateral heat damage around the bipolar electrodes could be achieved resulting in a hypothetic minor reaction of the tonsillar tissue; however, their results were not supported by a cohort study. Identical results have been observed in bipolar and monopolar applications for the reduction of the lower turbinates, where the energy was delivered by a bipolar double-needle electrode and the epithelium would be preserved, whereas monopolar usage – also known as so-called "coblation tunneling" leads to histological changes similar to CO_2 laser therapy involving the transformation of columnar epithelium into cuboidal or squamous epithelium due to inevitable burn injury. Taneja et al.[10] have demonstrated that intraturbinate bipolar submucosal diathermy prevents mucosal damage, since required intensity of electric current is extremely low compared to monopolar technique, hence the surgical trauma and post-operative pain is less than expected. Thus, bipolar hemostasis is the choice of treatment nowadays for the coagulation of blood vessels in sensitive areas such as the nasal cavity.

Conclusions

Our B-TR can be learned relatively quickly and no tonsillar dissection or incision is warranted in contrast to tonsillar coblation and most of the laser ablation techniques, so no blood vessels are injured, the capsules of the tonsils are left intact, thus postoperative pain is either absent or very minimal. This technique adds only 10–15 minutes to total operation time and is proven to be effective in tonsil size reduction. Another advantage of this method lies in its cost effectiveness. The cost of a single reusable bipolar forceps is $500 but it is autoclavable and can be reused up to 500 times.[4]

Having such advantages, B-TR technique is appropriate to utilize for ambulatory surgery in many cases. B-TR might be recommended as a treatment option in pediatric cases with tonsillar hyperplasia when long-term follow-up results of a larger cohort are analyzed in a prospective study.

Conflict of Interest: No conflicts declared.

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Differential diagnosis of submandibular gland swellings

Demet Yazıcı, Mehmet Yalçın Çöktü, Zekiye Güney, Sanem Okşan Erkan, Orhan Görgülü, İlhami Yıldırım, Osman Kürşat Arıkan

ENT Department, Adana Numune Training and Research Hospital, Adana, Turkey

Abstract

Objective: The differential diagnosis of submandibular triangle swellings can be challenging to the clinician. In this study, we retrospectively analyzed clinical and histopathological characteristics of these swellings referred to our clinic and integrated our results with current literature in terms of various diagnostic aspects.

Methods: A total number of 64 transcervical submandibular gland extirpations were reviewed and evaluated regarding age, gender, fine-needle aspiration biopsy and specimen reports.

Results: This study comprised 34 male (53.1%) and 30 female (46.9%) patients. We classified submandibular triangle swellings clinicopathologically as tumoral and non-tumoral lesions for better evaluation. We had 15 patients with primary epithelial submandibular gland neoplasm, 10 (66.7%) of them were benign cases, all of the benign cases were pleomorphic adenoma with a male to female ratio of 1:2.33 and a mean age of 30.8 years, 5 (33.3%) of them were malignant with a mean age of 55 years. There were also 37(57.8%) patients with chronic sialadenitis associated with sialolithasis, 1 (1.6%) had acute sialedenitis, 2 (3.1%) had granulomatous sialadenitis, 2 (3.1%) had reactive cervical lymphadenopathy and 5 (7.8%) were treated for cystic lesion removal. Ultrasonography and fine needle aspiration cytology were our major diagnostic tools for differential diagnosis. Our institution's sensitivity of fine-needle aspiration cytology for identifying malignancy was 60% and the specificity was 100%.

Conclusion: Submandibular gland excision for primary lesions has relatively low incidence compared with other surgical implications. Although chronic sialadenitis caused by symptomatic sialolithiasisis the most frequent indication for surgery, diverse clinical entities should be ruled out for differential diagnosis of swellings of this region.

Keywords: Submandibular gland, submaxillary gland, salivary gland calculi, submandibular gland neoplasm, pleomorphic adenoma, biopsy, fine-needle.

Özet: Submandibüler bez kitlelerinde ayırıcı tanı

Amaç: Submandibüler üçgen kitlelerinin ayrıcı tanısı klinisyen açısından sıkıntılı olabilmektedir. Biz bu çalışmamızda, kliniğimize submandibüler bez kitlesi ile başvuran hastaların klinik ve histopatolojik bulgularını retrospektif olarak analiz ettik ve bulgularımızı günümüz literatürü ile karşılaştırdık.

Yöntem: Transervikal submandibüler bez eksizyonu yapılan 64 hasta incelendi ve yaş, cinsiyet, ince iğne aspirasyon biyopsisi ve spesimen sonuçları açısından değerlendirildi.

Bulgular: Bu çalışmaya 34 erkek (%53.1) ve 30 kadın (%46.9) hasta dahil edildi. Submandibüler üçgen kitleleri; tümöral ve tümöral olamayan lezyonlar olarak ikiye ayrıldı. 15 hastada primer epitelyal submandibüler bez neoplazmı mevcuttu, bu kitlelerden 10 tanesi (%66.7) benigndi. Benign olanların hepsi plemorfik adenomdu, hastaların ortalama yaşı 30.8 iken, erkek/kadın oranı ise 1:2.33 idi. Kitlelerden 5 tanesi (%33.3) ise maligndi. Malign olanların ortalama yaşı 55 idi. 37 (%57.8) hastada sialolitasise bağlı kronik sialadenit mevcuttu, 1 hastada (%1.6) akut sialadenit, 2 hastada (%3.1) granülomatöz sialadenit, 2 hastada (%3.1) reaktif servikal lenfadenopati mevcuttu. 5 hastada (%7.8) ise kistik lezyon eksizyonu yapıldı. Ultrasonografi ve ince iğne aspirasyon sitolojisi ayırıcı tanıda en sık kullanılan tanısal yöntemlerdi. Malignansi saptamada ince iğne aspirasyon sitolojisinin sensitivitesi %60, spesifitesi %100 idi.

Sonuç: Submandibüler bezin primer eksizyonu, diğer endikasyonlarla karşılaştırıldığında nadirdir. Submandibüler bez eksizyonu en sık nedeni semptomatik sialolitiasise bağlı kronik sialadenit olsa bile, bu bölgenin lezyonlarının ayırıcı tanısında değişik klinik antiteler göz önünde bulundurulmalıdır.

Anahtar sözcükler: Submandibüler bez, submaksiller bez, tükürük bezi taşı, submandibüler bez neoplazmı, pleomorfik adenom, biyopsi, ince iğne.

Salivary glands exhibit a broad spectrum of diseases requiring medical or surgical intervention. The diversity of the diseases varies mainly with the localization of the glands. Bacterial and viral infections, sialolithiasis, systemic diseases such as Sjörgen syndrome and Mikulicz's disease, granulomatous diseases such as tuberculosis and actinomycosis, cys-

Correspondence: Demet Yazıcı, MD. ENT Department, Adana Numune Training and Research Hospital, Adana, Turkey.
e-mail: demetyazici@yahoo.com

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tic lesions and tumoral lesions can all be noted as miscellaneous diseases affecting these glands. As tumors are most frequent lesions of the parotid glands, sialolithiasis and inflammatory diseases are common features of the submandibular glands.[1] The propensity of malignancy increases as the size of the gland decreases, 25% of the parotid gland neoplasms, 43% of the submandibular gland and 82% of the minor salivary gland neoplasms are reported as malignant in the literature.[2]

Plain radiographs, ultrasonography, conventional sialography, sialoendoscopy, computed tomography (CT), magnetic resonance imagining (MRI), MRI sialography, digital subtraction X-ray sialography and fine-needle aspiration cytology (FNAC) may all be used for differential diagnosis of the salivary gland lesions.[3,4] Ultrasonography, conventional or transoral, combined with CT is the most preferred modality for identifying sialoliths of the salivary glands.[5] FNAC is recommended for neoplastic lesions and has a high accuracy for determining malignancy.[6]

The aim of our study is to review our six-year clinical experience with submandibular gland excision and discuss our findings regarding differential diagnosis. We analyzed patients according to their genders, histopathological results, age intervals and complications and correlated our results in the light of the current literature.

Materials and Methods

In this retrospective study, we analyzed 63 patients undergoing 64 transcervical submandibular gland extirpations between January 2011 and December 2016 in our tertiary center. We evaluated patients according to their age, gender, preoperative assessment, fine-needle aspiration biopsy results, specimen reports and complications after the surgery. The ethics committee approval was taken from our own institution's ethics committee (No: 26/2017).

Histopathological, cytological diagnosis and TNM classification of submandibular gland neoplasms were based on the World Health Organization (WHO) classification of tumors: pathology & genetics, head and neck tumors (salivary glands) for benign and malignant neoplasms. 7 We used the statistical package SPSS (version 20.0) for statistical evaluation including χ^2 test and a value of $p<0.05$ was defined as statistical significance.

Results

A total number of 64 submandibular gland excision patients, 34 males (53.1%) and 30 females (46.9%) were enrolled in this study. The ages of the patients raged in between 1 to 75 years with a mean age of 37.5±16.65. Fifty-two percent of the patients had right-sided mass, and fourty-eight percent had left-sided mass. One patient was operated on both sides. We classified submandibular lesions clinicopathologically as tumoral and non-tumoral lesions (**Fig. 1**). Of the 15 (23.4%) primary epithelial submandibular gland tumor patients, there were 10 (66.7%) benign cases and 5 (33.3%) malignant cases and our overall benign/malignant ratio was 2:1. The median age for benign tumors was 30.8 years, for malignant tumors was 55 years with an overall male to female (M:F) of 1:2.75. We also had two male patients diagnosed as having non-Hodgkin lymphoma (NHL). Fourty-seven patients (73.4%) had non-tumoral submandibular gland lesions, 37 of them had (57.8%) chronic sialadenitis associated with sialolithiasis, 1 patient (1.6%) had acute sialedenitis, 2 patients (3.1%) had granulomatous sialadenitis, 2 of them (3.1%) had reactive cervical lymphadenopathy and 5 patients (7.8%) were treated for cystic lesion removal. The median age of 37 chronic sialadenitis associated with sialolithiasis patients was 39.6 years where 23 (62.2%) of them were male and 14 (37.8%) of them were female with a male to female (M:F) ratio of 1.6:1. Of the 5 cystic lesions, 2 had plunging ranula, 1 had benign lymphoepithelial cyst, 1 had epidermal keratinous cyst and 1 patient had salivary duct cyst (**Table 1**).

Ultrasonography was our first and major diagnostic tool for evaluating submandibular gland (SG) diseases. Sialolithiasis was detectable with ultrasonography in 82.14% patients and FNAC was performed on patients presenting with SG mass. CT and MRI were used as supplementary diagnostic tools for sialolithiasis, SG masses and cysts. Painful recurrent swelling was the main complaint for sialolithiasis and painless mass in the neck was the major complaint for SG masses.

Our correlation between fine-needle aspiration cytology and final histopathological diagnosis is presented in **Table 2**. The sensitivity of FNAC for identifying malignacy was 60% and the specificity was 100%. Positive predictive value (PPV) was 100% and negative predictive value (NPV) was 83.3%. Malignity prevalence was 33.3% and the overall FNAC accuracy was 86.7%.

Additional to submandibular gland excision, we performed supraomohyoid neck dissection and functional neck dissection for the malignant tumors. Our most common postsurgical complication was temporary marginal mandibular nerve palsy which developed in 3 (4.6%) patients. Moreover, one (1.6%) patient with orocutaneous

fistulareoperated three months after surgery. One patient was treated for neck abscess and one for sialocele after SG excision.

Discussion

Granulomatous lymphadenopathy caused by tuberculosis and sarcoidosis, various cystic entities such as branchial cleft cysts and ranula, primary neoplastic and metastatic tumors, lymphomas, suppurativesialedenitis caused by sialolithiasis should all be evaluated for the differential diagnosis of the submandibular triangle swellings.[8,9] In this study, we classified submandibular gland diseases as tumoral and non-tumoral lesions for better assessment (**Fig. 1**).

Chronic sialadenitis caused by symptomatic sialolithiasis is the most commonly encountered indication for submaxillectomy.[1,10] In our study, our sialolithiasis rate was 57.8%, comprised of mainly male patients between 4th and 6th decades of life. Our youngest sialolithiasis patient was a 14-year-old male, the oldest one was a 58-year-old male and one male patient was operated for bilateral sialolithiasis (2.7%). The higher incidence of SG sialolitheasis between 3rd to 6th decades of life is also mentioned in the literature which was also consonant with our study's results.[11,12] 80% to 90% of salivary stones are formed in the submandibular glands instead of parotid glands because of the anatomical properties of the Wharton duct and biochemical properties of saliva excreted by the glands.[12,13] The more viscous saliva of the SG having higher pH and higher calcium concentration compared with parotid gland (pH 6.5 vs pH 5.8) and the longer course of the Wharton duct against gravity causing stasis of the salivary flow lead to predisposition of the formation of stones.[12–14] Our M:F ratio was 1,6:1 demonstrating male predilection in this study. Although there are conflicting reports, the male predominance is a consensus on the SG sialolithiasis.[11,12,15,16] Besides the general concept of no side predilection in SG sialolithiasis, our sialolithiasis patients showed a higher right-sided incidence (59.5% vs 40.5%) which is also remarked in literature.[12,13,15] Our bilaterality incidence was 2.7% which was in concordance with the literature.[12,13] Ultrasonography was our major diagnostic tool to avoid radiation exposure.[4] Transoral and transcervical

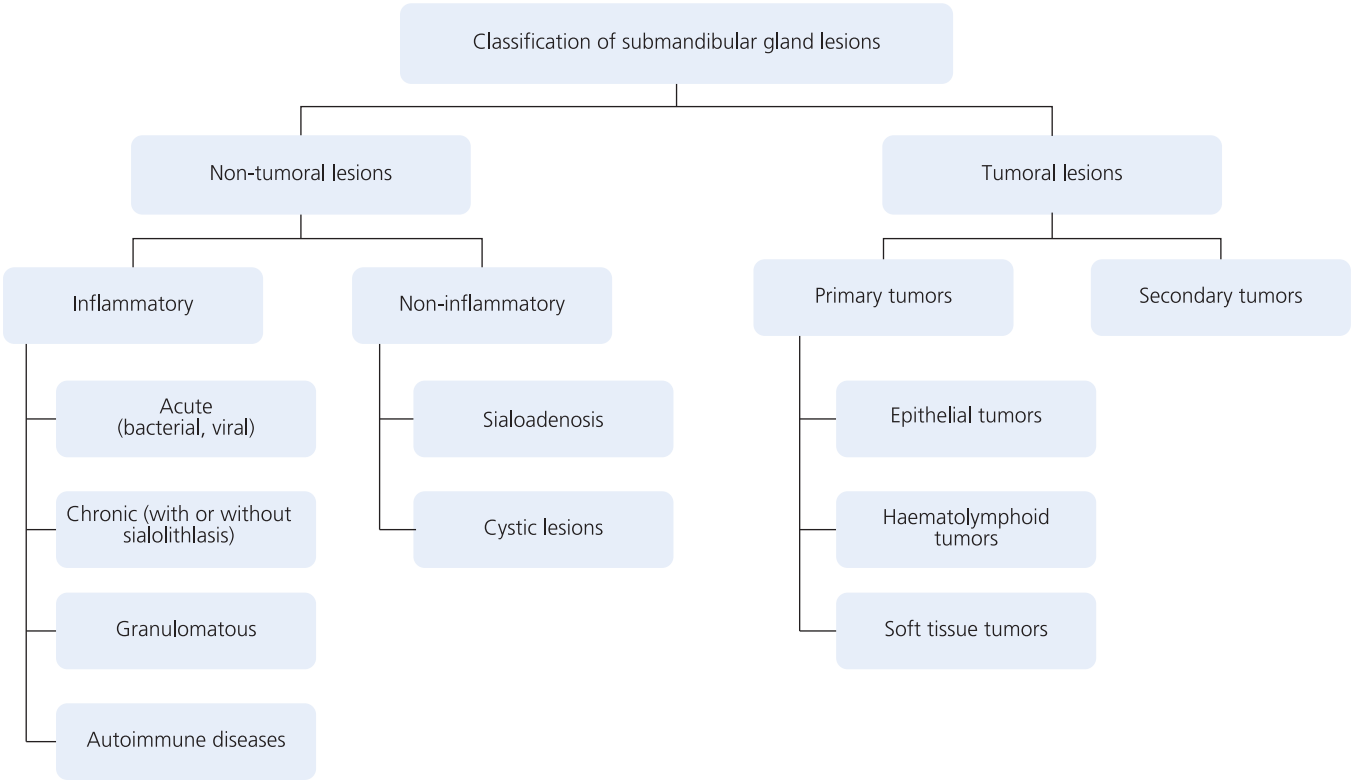

Fig. 1. Classification of submandibular gland lesions.

Table 1. Histopathological classification of the submandibular gland lesions and their distribution according to frequency, median age, percentage and gender.

Histopathological classification of submandibular gland lesions	Frequency	Percentage in total	Median age (range)*	Gender	
				Male	Female
Pleomorphic adenoma	10	15.6	30.8 (10–61)	3 (30%)	7 (70%)
Adenoid cystic carcinoma	2	3.1	42 (40–44)	1 (50%)	1 (50%)
Squamous cell carcinoma	1	1.6	75	0	1 (100%)
Malignant mixt tumor	1	1.6	60	0	1 (100%)
Carcinoma ex-pleomorphic adenoma	1	1.6	56	0	1 (100%)
Chronic sialadenitis associated with sialolithiasis	37	57.8	39.6 (14–58)	23 (62.2%)	14 (37.8%)
Acute sialadenitis	1	1.6	1	1 (100%)	0
Granulomatous sialadenitis	2	3.1	14 (12–16)	1 (50%)	1 (50%)
Plunging ranula	2	3.1	13.5 (13–14)	0	2 (100%)
Salivary duct cyst	1	1.6	19	1 (100%)	0 (100%)
Epidermal keratinous cyst	1	1.6	18	1 (100%)	0
Benign lymphoepithelial cyst	1	1.6	63	1 (100%)	0
Non-Hodgkin lymphoma	2	3.1	64.5 (64–65)	2 (100%)	0
Reactive cervical lymphadenopathy	2	3.1	33 (29–37)	0	2 (100%)
Total	64	100	37.5±16.65 (1–75)	34 (53.1%)	30 (46.9%)

*Years.

extirpation of the submandibular gland, intraoral excision of the sialolith and sialoendoscopy are the general methods for treating submandibular sialolithiasis, but in this study we only included patients with transcervical extirpation.

Pleomorphic adenoma was the most prevalent tumor of our review and adenidcyctic carcinoma was the most common malignant tumor which were all consistent with the literature.[1,8] All of our patients presenting with SG mass had fine-needle aspiration cytology before the final operation. We had 10 pleomorphic adenoma patients which were all diagnosed correctly with FNAC. Overall, FNAC specified 86.7% correct diagnosis. Of our five primary malignant SG patients, one carcinoma ex-pleomorphic adenoma patient and one malignant mixt tumor patient were misdiagnosed with FNAC and reported as having pleomorphic adenoma. These two tumors are the two different forms of malignant transformation of pleomorphic adenomas and repeated aspirations from different areas of the mass should be performed in case of malignancy suspicion for avoiding misdiagnosis. In our study, our sensitivity of FNAC for malignant lesions was 60% and our specificity was 100%. Despite wide range of outcomes in the current literature, the specificity of FNAC of salivary glands for identifying malignancy is predominantly higher than the sensitivity which was also consistent with our findings.[17,18]

Table 2. Our institution's correlation between fine needle aspiration cytology results and final histopathological diagnosis for primary epithelial submandibular gland neoplasms.

	Histopathologically malignant	Histopathologically benign	
FNA malignant	3 (true positive)	0 (false positive)	Positive predictive value 100%
FNA benign	2 (false negative)	10 (true negative)	Negative predictive value 83.3%
	Sensitivity 60%	Specificity 100%	Malignity prevalence (33.3%) FNAC accuracy (86.7%) Total = 15

Our malignancy rate was 33.3% in this study. Also, for primary submandibular gland neoplasms, our M:F ratio was 1:2.75 demonstrating a female prominence. Our mean age of patients with pleomorphic adenoma was 30.8 years and with malignant tumors was 55 years. Our youngest pleomorphic adenoma patient was a 10-year-old female and the oldest one was a 61-year-old female (**Table 1**). Unfortunately, our study group for primary submandibular gland neoplasms was too small to end up with any conclusions, but our findings were consistent with the literature. The malignancy rate of SG lesions varies from 40% to 70% in miscellaneous studies demonstrating higher malignancy rate compared with parotid lesions.[1,2,19] The female predominance for benign SG lesions and male predominance for malignant lesions are also implied in various series.[19,20]

Besides sialolithiasis and neoplastic lesions, non-neoplastic cystic lesions such as lymphoepithelial cysts, mucus retention cysts and epidermal cysts should also be considered as differential diagnosis. Various neoplastic diseases such as Warthin's tumor, pleomorphic adenomas with cystic degeneration, acinic cell carcinomas, mucoepidermoid carcinomas, cystadenoma malignant mixed tumors and cystadenocarcinomas may also demonstrate cystic changes and may cause misinterpretation of FNAC.[21,22]

We also had two patients with granulomatous sialadenitiscaused by tuberculosis. In addition to mycobacterial infections, ductal obstruction caused by calculi or carcinoma, sarcoidosis, cat-scratch disease, tularemia, toxoplasmosis and systemic diseases such as Wegener's granulomatosis and Crohn's disease may also cause granulomatous sialadenitis and should not be overlooked both by the clinician and the pathologist.[23,24]

Two of our elderly male patients in their seventh decade were diagnosed with non-Hodgkin lymphoma. Primary haematolymphoid tumors of the salivary gland are rare neoplasms consisting mainly of B-cell NHLs. One of our patients was diagnosed with diffuse large B-cell lymphoma and the other with mantle cell lymphoma. The majority of NHLs affect the parotid gland (75%), and the rest mainly arise in the submandibular gland. Adjuvant chemoradiotherapy is the treatment of choice for these patients where the survival rate is lowest for diffuse large B-cell lymphoma.[25,26]

In this current study, all our patients diagnosed with sialolithiasis and benign tumors had undergone trancervical extirpation of the submandibular gland. Additional prophylactic neck dissection had been performed on patients during the surgery when FNAC indicated malignancy or after the surgery when the final specimen report was malignant. Patients received adjuvant radiotherapy and/or chemotherapy by the oncologists. Due to the close relationship between the gland and the lingual, hypoglossal and the marginal mandibular branch of the facial nerve, facial artery, anterior facial vein and lingual artery, meticulous care should be taken during extirpation of the submandibular gland to avoid complications such as transient or permanent paralysis of marginal mandibular nerve, lingual nerve and hypoglossal nerve, hematomas, seromas, salivary fistulas and sialoceles.[27] Of our six patients with complications, 3 (4.7%) of them had transient palsy of the mandibular branch of the facial nerve, one patient (1.6%) with malignant lesion had permanent paralysis of marginal mandibular nerve, one patient (1.6%) who had undergone functional neck dissection developed neck abscess, one patient (1.6%) with salivary fistula was re-operated for fistula excision and developed transient marginal mandibular nerve palsy, one patient (1.6%) was treated for sialocele. We didn't have any complications considering lingual or hypoglossal nerve. Our total complication rate was 9.4% which was in concordance with literature.[1,27]

Conclusion

In the 6-year retrospective study, we analyzed patients undergoing transcervical excision of submandibular gland according to their age, gender, FNAC findings, final specimen reports and surgical complications and discussed our findings with the current literature. Chronic sialadenitis caused by symptomatic sialolithiasiswas the most common indication for gland surgery prevail among males in 4th and 6th decades of life, followed by pleomorphic adenoma of the gland which was prevalent in females starting from the 2nd decade of life. Ultrasonography and FNAC were our two major methods for diagnosis of gland lesions. We performed FNAC before all neoplastic lesions and our FNAC was 86.7%. Our high malignity rate (33.3%) of primary tumors was consistent with current literature. Transient palsy of the marginal mandibular nerve was the main complication of our surgery.

Conflict of Interest: No conflicts declared.

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Case Report

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Bilateral and multicentric Warthin's tumor primarily presented with cervical lymph node involvement

Muammer Melih Şahin[1], Alper Ceylan[1], Mehmet Düzlü[1], Erolcan Sayar[2]

[1]*Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey*
[2]*Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey*

Abstract

Papillary cystadenoma lymphomatosis (Warthin's tumor) is the second most common benign neoplasm of the parotid gland. Although the tumor usually presents as a slowly growing mass in the tail of the parotid gland, extraparotid involvements such as the cervical lymph nodes may be observed rarely. In this article, we aimed to report a Warthin's tumor case with atypical presentation. A 68-year-old male patient with the history of smoking was admitted to our clinic with the complaint of right-sided neck lump. After physical examination and imaging, excisional biopsy was performed with an initial diagnosis of cervical lymphadenopathy. Pathology result was reported as Warthin's tumor. Five months later, multicentric Warthin's tumor in the contralateral parotid gland was diagnosed and operated. With this case report, we want to emphasize that Warthin's tumors may rarely present as a neck lump outside the parotid gland, and we want to review relevant literature data.

Keywords: Warthin's tumor, cervical lymph node, papillary cystadenoma lymphomatosum, extraparotid.

Özet: Primer olarak servikal lenf nodu tutulumu gösteren bilateral multisentrik Warthin tümörü

Papiller kistadenoma lenfomatozum (Warthin tümörü), parotis bezinin ikinci en sık görülen benign neoplazisidir. Tümör parotis bezi kuyruğunda, yavaş büyüyen kitle olarak kendini gösterir. Sıklıkla parotis bezinde gözlense de, servikal lenf nodları gibi ekstraparotidal tutulumlar da gözlenebilir. Biz de bu çalışmamızda atipik yerleşimli bir Warthin tümörü olgusunu sunmayı planladık. Sigara içme öyküsü olan 68 yaşında erkek hasta bir yıldır olan boyunda şişlik şikayeti ile kliniğimize başvurdu. Fizik muayene ve görüntüleme sonrası servikal lenfadenopati ön tanısı ile eksizyonel biyopsi yapıldı. Patoloji sonucu Warthin tümörü olarak raporlandı. Beş ay sonra karşı parotis bezinde multisentrik Warthin tümörü tanısı kondu ve opere edildi. Bu olgu sunumu ile Warthin tümörlerinin nadiren de olsa ekstraparotidal yerleşimli görülebileceğini vurgulamayı ve ilgili literatür verilerini derlemeyi amaçladık.

Anahtar sözcükler: Warthin tümörü, servikal lenf nodu, parotis dışı Warthin tümörü, papiller kistadenoma lenfomatozum.

Warthin's tumor (WT) is a benign salivary gland tumor frequently arising from the parotid gland. It is the most common salivary gland tumor after pleomorphic adenoma.[1] WT may be seen bilateral (5–14%) and multicentric (12–20%).[2] Although WT is often originated from parotid gland, it may be encountered in extraparotid tissues such as nasopharynx, oral cavity, larynx, and cervical lymph nodes.[3,5] Histopathologically, there are encapsulated lesions containing cystic and solid components. The tumor occurs more commonly in male patients (10:1) and develops more often in the sixth and seventh decades.[3] Patients often complain slow but progressively growing masses around the jawbone. In this article, we aimed to present a case of WT with an atypical presentation and location and to compare it with literature data.

Case Report

A 68-year-old male patient admitted to our clinic with the complaint of swelling on the right side of his neck approximately for one year. The medical history revealed that the neck mass has enlarged in the last four months, despite the empiric antibiotic treatment. In addition, the patient was in the remission period of bladder tumor without any problems

Correspondence: Muammer Melih Şahin, MD. Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Gazi University, Ankara, Turkey.
e-mail: mlhseda@gmail.com

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in the follow-up. The low-grade bladder epithelial tumor was treated surgically without adjuvant treatment for about 3 years ago. The patient had one packet/day smoking history for 40 years. On physical examination, approximately 4×3 cm hard, mobile, painless mass was observed on the right side of the neck. Comprehensive otorhinolaryngologic examination was normal except this right sided neck mass. The USG examination revealed heterogeneous-hypoechoic multifocal lymph nodes-mass appearance with locally cystic areas with the largest size of 4.1×4.7 cm in the right cervical zone 3. Due to the patient's age and previous medical history, excisional biopsy was planned considering bladder tumor metastasis or lymphoma. A 4 cm horizontal incision was made approximately 2 cm below the right mandibular angle. The tumor was exposed after dissection in sub-platysmal plane and the mass was entirely excised from the surrounding tissues. Marginal mandibular nerve not recognized. The submandibular gland was observed in natural location and no relation was noticed between the mass and the parotid gland tail. The mass was observed to be about 6×4 cm in size, with hard-nosed, necrotic, lobule, and somewhat cystic areas (**Fig. 1**). There were no complications during the operation. The cervical lymph node pathology was reported as WT (**Fig. 2a**).

In the post-operative follow-up, a secondary neck mass formation was noticed on the contralateral (left) parotid gland five months later. USG imaging revealed a deep lobe mass with a size of 25×10 mm. The subsequent fine needle aspiration was reported as non-diagnostic. Parotidectomy was planned with WT diagnosis. In the operation, both the superficial and the deep lobes of the parotid gland were observed to be involved, meaning that multicentricity of the tumor is present. Therefore, total parotidectomy was performed. Pathology result was compatible with WT (**Fig. 2b**). There were no complications. No residual or recurrence was encountered in control examinations in the post-operative second year control.

Fig. 1. Macroscopic view of the mass.

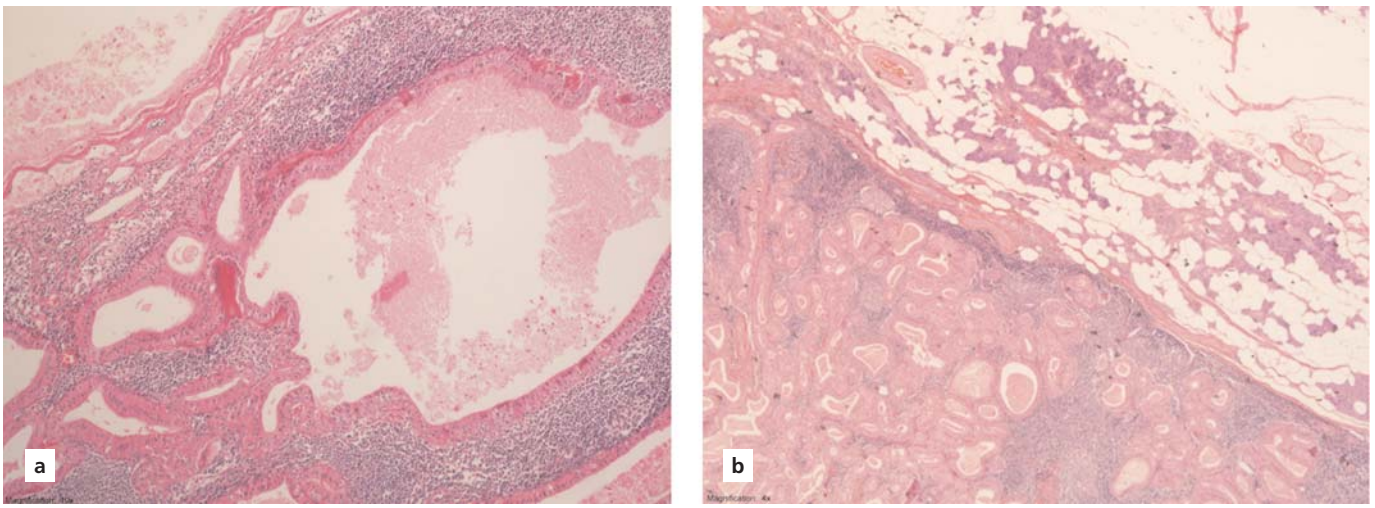

Fig. 2. (**a**) Lymph node. Oncocytic columnar cells lining the surface epithelium in the dense lymphoid stroma and epithelial elements composed of the basal cell layer (H&E ×100). (**b**) Parotid gland. In the dense lymphoid stroma, oncocytic columnar cells lining the surface epithelium, epithelial elements composed of the basal cell layer and surrounding normal salivary gland tissue (H&E ×40). [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

Discussion

Warthin's tumor is the second most common benign neoplasm in salivary gland tumors and it is accounted for about 6–10% of all salivary gland tumors. It was first described by Hillebrand in 1985 as "adenolenoma" and was described by Warthin in 1929 as "papillary cystadenoma lymphomatosis".[4] It often occurs in the parotid gland, especially in the tail part of the gland. However, it is rarely seen outside the parotid gland in various locations like submandibular salivary glands, cervical lymph nodes, larynx, nasal and oral cavity, minor salivary glands, upper lip, and nasopharynx.[5–7]

In patients with complaints of neck mass, inflammatory lesions are considered primarily, and antibiotic treatment is frequently administered. Especially in patients over forty years of age, neck masses should be considered primarily as a neoplastic formation unless proved to be non-neoplastic.[8] WT is often seen in the sixth decade and is rarely seen before fourth decade. Several theories have been proposed in the histopathogenesis of extraparotid WT. Most commonly accepted theories are, delayed encapsulation of the parotid gland in the embryological process and development of the salivary ductal inclusions located in the lymph nodes. Macroscopically, it contains cystic and necrotic areas filled with brown gelatinous fluid, and histologically it is surrounded by an oncocytic epithelium of cystic and papillary structures around the dense lymphoid stroma.[9] It is known to be closely related to smoking. The risk of WT development was shown to be eight times higher in smokers than in non-smokers.[10] Our case had one packet/day smoking story for 40 years. WT's recurrence (2%) and malignant transformations (1%) are very rare. For this reason, the World Health Organization (WHO) should consider it as "tumor-like lesions" and discuss whether it is a true neoplasm.[11]

After reviewing medical history and detailed physical examination, USG is the first imaging modality for diagnosis. CT and MRI studies can be performed in the presence of recurrences, multicentric formation, contact with neighboring structures and presence of concomitant neoplastic lesions.[12] In parotid tumors, some studies suggest that fine-needle aspiration (FNA) shows high specificity and sensitivity, but some authors argue that the main goal of FNA is the distinction between malignant benign neoplasms and the definitive result can only be revealed by excisional biopsy.[13] In this case, we planned excisional biopsy considering malignant lesion.

WT is often caused by the superficial lobe of the parotid gland (90%), and therefore superficial parotidectomy is considered necessary and adequate. However, total parotidectomy is recommended if the mass is originated from deep lobe or extends toward deep lobe. The most important complication after surgery is facial paralysis. Temporary paralysis is seen between 16% and 47%, and permanent paralysis between 0% and 9%.[14]

Although WT frequently originates from the parotid gland, it may also be located on the cervical lymph nodes with bilateral and multicentric involvement as is our case. Cervical lymph node involvement of WT may be the first apparent tumor focus for the patients. Therefore, these patients should be closely followed both parotid glands and other extraparotid fields for possible disease in postoperative routine examinations. In the surgery of benign salivary gland tumors with heterotypic placement, local excision and close follow-up are recommended.

In conclusion, WT often originates from parotid gland; however, it may also be seen in extraparotid tissues. Extraparotid presentation of WT, such as cervical lymph node involvement, may also be a sign of a primary tumor located in the ipsilateral or contralateral parotid gland.

Conflict of Interest: No conflicts declared.

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