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Address for Correspondence

Selimiye Mah. Tıbbiye Cad. 34668 Üsküdar, İstanbul

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E-mail: tipfakultesi@sbu.edu.tr

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LETTER TO THE EDITOR

ORIGINAL ARTICLE

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The Importance of Low E-cadherin Expression for Epithelial Mesenchymal Transition (EMT) in Pulmonary Pleomorphic Carcinoma

Pulmoner Pleomorfik Karsinomda Epitelyal Mezenkimal Geçiş (EMT) için Düşük E-cadherin Ekspresyonunun Önemi

Nurcan Ünver[1], Nur Büyükpınarbaşılı[2]

[1]*Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Başakşehir Çam ve Sakura State Hospital, Clilnic of Pathology, İstanbul, Turkey*

ABSTRACT

Background: Epithelial-mesenchymal transition is an important step in the invasion and metastasis of cancer cells in various cancer types. The aim of this study is to evaluate immunohistochemical staining with E-cadherin in patients with pleomorphic carcinoma (PC), which is a group of advanced lung tumors, to decide the correlation between clinicopathological parameters and to determine the prognostic significance of the results.

Materials and Methods: Materials and data of 56 cases diagnosed with PC between January 2011 and December 2018 were evaluated. Expressions of E-cadherin applied to tumor sections of resection materials were evaluated. Immunohistochemically, data were collected under two groups as low and high according to E-cadherin staining results. The results obtained were compared with clinicopathological findings and prognostic factors.

Results: Forty-five of the fifty-six cases were male (80.36%) and 11 were female (19.64%), their age ranged from 44 to 83 years and the average age was 64.12 years. When expressions of E-cadherin were evaluated, loss of expression of E-cadherin (low expression) was observed in 47 (83.9%) cases. When the disease-free survival time was examined, it was found that the mean time (12 months) in 35 cases was below. No statistically significant correlation was found between the immunohistochemically E-cadherin expressions and other clinicopathological parameters. Our study showed that low E-cadherin expression or loss of E-cadherin expression in spindle and/or giant cell areas has a poor prognostic factor on disease-free survival (p=0.001).

Conclusion: E-cadherin loss has been observed in cases of PC, especially in spindle and/or giant cell areas, and has been associated with shorter disease-free survival. Expression loss of E-cadherin was accepted as a poor prognostic factor. Expression of E-cadherin can be used to evaluate the prognostic potential in PCs with poorly progressive groups.

Keywords: E-cadherin, pulmonary pleomorphic carcinoma, epithelial mesenchymal transition

ÖZ

Amaç: Epitelyal mezankimal geçiş (EMT), çeşitli kanser tiplerinde kanser hücrelerinin istilası ve metastazında önemli bir aşamadır. Bu çalışmanın amacı, ileri akciğer tümörü olan pleomorfik karsinomlu (PC) hastalarda E-kaderin ile immünohistokimyasal boyamayı değerlendirmek, klinikopatolojik parametreler arasındaki korelasyona karar vermek ve sonuçların prognostik önemini belirlemektir.

Gereç ve Yöntemler: Ocak 2011 - Aralık 2018 tarihleri arasında pleomorfik karsinom tanısı alan 56 olguya ait materyaller ve bu olgulara ait veriler değerlendirildi. Rezeksiyon materyallerine ait tümör kesitlerine uygulanan E-kaderin ekspresyonları değerlendirildi. İmmünohistokimyasal olarak veriler, E-kaderin boyama sonuçlarına göre düşük ve yüksek olmak üzere iki grup altında toplandı. Elde edilen sonuçlar klinikopatolojik bulgularla ve prognostik faktörlerle karşılaştırıldı.

Bulgular: Elli altı olgunun kırk beşi erkek (%80,36) on biri kadındı (%19,64), yaşları 44 ila 83 arasında değişmekte olup, yaş ortalaması 64,12 idi. E-kaderin ekspresyonları değerlendirildiğinde 47 (%83,9) olguda E-kaderin ekspresyon kaybı (düşük ekspresyon) gözlendi. Hastalıksız sağkalım süresi incelendiğinde, 35 olgunun ortalama sürenin (12 ay) altında olduğu bulundu. İmmünohistokimyasal olarak E-kaderin ekspresyonları ile diğer klinikopatolojik parametreler arasında istatistiksel olarak anlamlı bir korelasyon saptanmamıştır. Çalışmamız iğsi ve/veya dev hücreli alanlarda düşük E-kaderin ekspresyonunun veya E-kaderin ekspresyon kaybının hastalıksız sağkalım üzerinde kötü bir prognostik faktöre sahip olduğu göstermiştir (p=0,001).

Sonuç: E-kaderin pleomorfik karsinom olgularında özellikle iğsi ve/veya dev hücreli alanlarda kaybı gözlemlenmiş daha kısa süreli hastalıksız sağkalımla ilintilendirilmiştir. E-kaderin ekspresyon kaybı kötü bir prognostik faktör olarak kabul edilmiştir. E-kaderin ekspresyonu, kötü gidişli tümör grubu olan PC'lerde prognostik potansiyeli değerlendirmek için kullanılabilir.

Anahtar Kelimeler: E-kaderin, pulmoner pleomorfik karsinom, epitelyal mezankimal geçiş

Address for Correspondence: Nurcan Ünver, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
Phone: +90 505 216 00 18 E-mail: pat.dr.nurcanunver@gmail.com **ORCID ID:** orcid.org/0000-0001-7392-6099

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Introduction

Lung cancer is one of the most common causes of cancer-related deaths in both genders (men and women). Pleomorphic carcinomas (PCs), which are a rare lung cancer, constitute 0.3% of all lung malignancies (1). In the 2015 World Health Organization's (WHO) classification, PCs are a pulmonary malignancy in which spindle cells and/or giant cell tumor (T) are included together with squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma. For diagnosis, more than 10% should be spindle-shaped and/or giant cells (2). The carcinoma component consisting of spindle or giant cells alone is very rare.

Pulmonary PCs are usually seen in smokers, older males. During diagnosis, it usually causes large-scale, chest wall involvement and distant metastases. The most appropriate form of treatment in PC with poor prognosis is surgery if diagnosed at the appropriate stage. In cases of rare and advanced stage lesions (PC), those who have the chance of operation at the time of diagnosis are extremely rare. The principal of the surgery is anatomic resection and mediastinal lymph node dissections. Even if PC is diagnosed early, 5 years survival rates and mean survival time are very low (3,4,5). In cases where surgery cannot be performed on the PC, the treatment is chemotherapy. In operated cases, if lymph node involvement is present (even N1), adjuvant chemotherapy should be added. Chemotherapy should be applied as combined, not as a single drug.

E-cadherin is a protein component that is effective in cell adhesion, cell-cell interaction, and regulation of other cell functions. E-cadherin has been accepted as an important factor for EMT pathway. On the other hand, EMT is an important step in cancer metastases (6). Loss or absence of expression of E-cadherin was detected immunohistochemically in NSCLC of the lung, demonstrating that this may be associated with the control of cell proliferation in carcinogenesis (7).

E-cadherin is not only a protein that regulates intercellular adhesion, cellular functions, cell differentiation, but also an important T suppressor protein involved in carcinogenesis when there is functional disorder. As determined in the literature, it has been reported that dysregulation of E-cadherin leads to carcinogenesis by obtaining invasive and invasive properties of cells through the EMT pathway (6).

Material and Methods

Fifty-six cases of pulmonary PC that were surgically resected were involved from February 2011 to December 2018. These 56 patients (45 male and 11 female, age range 44-83 years; mean age 64.13 years) with pulmonary PC underwent surgery with a radical approach (lobectomy and mediastinum lymphadenectomy). Of the 56 PCs, 32 had adenocarcinoma component, 15 had squamous cell carcinoma, 9 had large cell carcinoma component.

T stages were defined properly according to the 8.TNM classification of the International Union Against Cancer, (8) and the histological types according to the 2015 WHO classification (2). Demographic data of PC cases and pathological findings such as T diameter, T and lymph node stages, metastasis system, lymphatic, vascular and perineural invasions were collected and expressions of E-cadherin were recorded.

Tissue Immunohistochemistry

Four micrometer (4µ) sections of formalin-fixed paraffin-embedded tissues were taken on polylysine-coated slides. Next, the rabbit was stained with polyclonal Biocare Medical E-cadherin antibody (Anti-E-cadherin (36) ouse monoclonal primary antibody according to the manufacturer's protocol). Subsequent procedures were performed with the Ventana BenchMark Ultra (Ventana Medical Systems Inc.) device.

Cytoplasmic and/or membranous staining with E-cadherin antibody was evaluated positively. The estimated percentage of the positively stained T-cells was reported in a scale with four grades: no staining as 0, <10% as 1, 10-50% as +2, and >50% as +3. Grouping was performed considering 0 to 1+ grade as "low" staining and +2 to +3 grade as "high" staining for E-cadherin.

While E-cadherin staining was evaluated by immunohistochemistry, the staining degrees were divided into two categories as "high staining" and "low staining" according to expression levels. E-cadherin expression was compared statistically with clinicopathological data and disease-free survival times.

Statistical Analysis

Chi-square test was used to evaluate the relationship between clinicopathological parameters and E-cadherin expressions. Survival curves were created using the Kaplan-Meier method and the data obtained were compared with the log-rank test. Cox regression analysis was performed, $p<0.05$ value was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (Chicago, IL, USA).

Results

Of the 56 cases, 45 were male (80.36%) and 11 were female (19.64%). The ages of the cases ranged between 44 and 83 years. Twelve patients had pneumonectomy, 20 upper right lobectomy, 10 lower left lobectomy, 6 upper left lobectomy, 5 lower right lobectomy, 2 right middle lobectomy and 1 lower right bilobectomy resection.

T diameters in the resection materials were measured between 1.5 cm and 11 cm (average diameter 6.04 cm). Pathological T-stages were determined as pT1 in four cases, pT2 in nineteen cases, pT3 in twenty-three cases and pT4 in ten cases. The mean clinical follow-up period was 12 months.

Of the 56 PC, 32 had the adenocarcinoma component, 15 had squamous cell carcinoma (Figure 1a,b,c) and 9 had large cell carcinoma component. Forty-four patients had lymphovascular invasion and 12 patients were not detected.

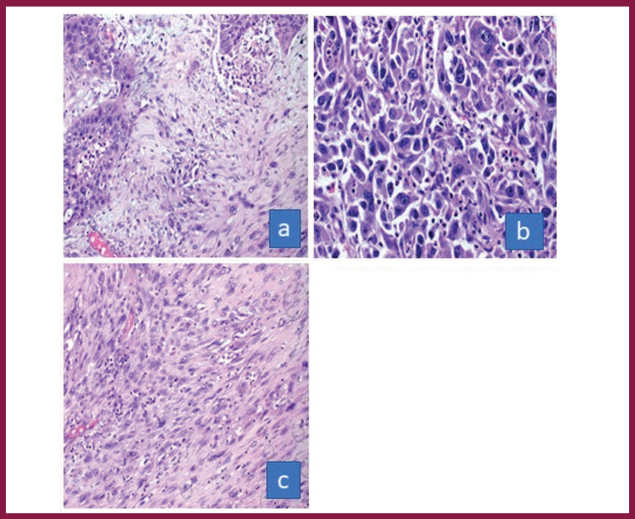

Figure 1. Tissue sections from one of our pleomorphic carcinoma cases containing epithelial and spindle and/or giant cell components. Hematoxylin and eosin staining. Magnification, x400 (a) The epithelial area is accompanied by the presence of squamous cell carcinoma (a) giant cells and (b) spindle cell component (c)

According to the nodal involvement, 33 (58.9%) of the cases were classified as pN0, 20 patients (35.7%) as pN1, and 3 patients (5.3%) as pN2. Twenty-seven patients were perineural invasion and 34 (60.7%) patients were pleural invasion positive. T necrosis was detected only in two cases. Low level of staining (low expression) with E-cadherin was observed in 47 (83.9%) of the cases, and in thirty-five of these cases, the mean disease-free survival time was less than 12 months (Figure 2). in the study of the pathological stages of cases, 10 were stage T4, 19 were stage T3, 16 were stage T2, and 2 were stage T1. When the staining pattern of E-cadherin was evaluated, positive staining was observed in 11 cases (19.6%) in spindle and/or giant cell carcinoma area, whereas 47 (83.9%) cases were detected in the epithelial component (Figure 3a,b). Low and non-staining E-cadherin expression in giant cell and/or spindle cell area were detected in all PC cases (Figure 3c,d,e,f).

The low and high staining results of E-cadherin were compared with the clinicopathological data obtained from the patients and presented in a table (Table 1). Statistically,

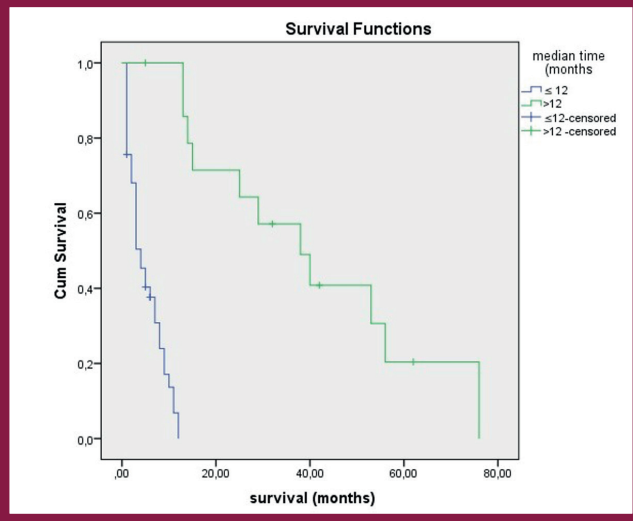

Figure 2. Kaplan-Meier mean disease-free survival time analysis by staining E-cadherin

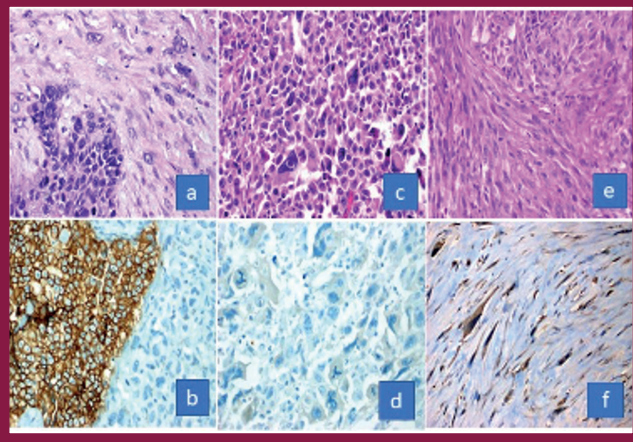

Figure 3. Immunohistochemical examples for Low and High staining of E-cadherin. Magnification, x400. High staining for E-cadherin in in epithelial cell components of PCs, (a, b). No staining was detected for the giant cell component (c,d) low staining for the spindle cell area (e,f)

no significant correlation was found between low and high staining patterns of E-cadherin and clinicopathological parameters.

Loss of E-cadherin expression was statistically significantly correlated with spindle and giant cell T area (p=0.001) (Figure 4). No significant correlation was found between loss of expression of E-cadherin in other T areas.

Discussion

PC is a very rare histological type of non-small lung cell carcinoma. When diagnosed, there are difficulties in

Table 1. E-cadherin expression and clinicopathological data of cases (and=56)

E-cadherin			
Parameteres	**High**	**Low**	**p***
Age (years)	-	-	0.469
⩽65	5	27	-
>65	4	20	-
Gender	-	-	0.430
Male	8	37	-
Female	1	10	-
Diameter (cm)	-	-	0.594
⩽6	5	25	-
>6	4	22	-
pT	-	-	0.908
T1	1	3	-
T2	3	16	-
T3	4	19	-
T4	1	9	-
Lymph node metastasis	-	-	0.551
Yes	19	4	-
No	28	5	-
Lymphovascular invasion	-	-	0.626
Yes	7	37	-
No	10	2	-
Necrosis	-	-	0.702
Yes	9	45	-
No	0	2	-
Perineural invasion	-	-	0.547
*Chi-square test			

determining the prognostic factors of these advanced and metastatic Ts. We evaluated the PC cases which were immunohistochemically E-cadherin expression loss and/or negativity. In addition to ongoing research on whether E-cadherin expression loss is the cause or effect of EMT, functional loss of E-cadherin has often been associated with poor prognosis and survival in various cancer types (7,9,10,11,12,13).

In some studies, the staining rate of E-cadherin in lung carcinomas has been documented as 41-78% (14,15,16). Our study showed that a large proportion (83.9%) of PC cases lost and or decreased E-cadherin expression.

Our results showed that low E-cadherin expression could be evaluated as a poor prognostic factor among disease-free survival. In similar studies, it has been observed that down-regulation of E-cadherin is significantly associated with the stimulation of differentiation from the direction of the T and

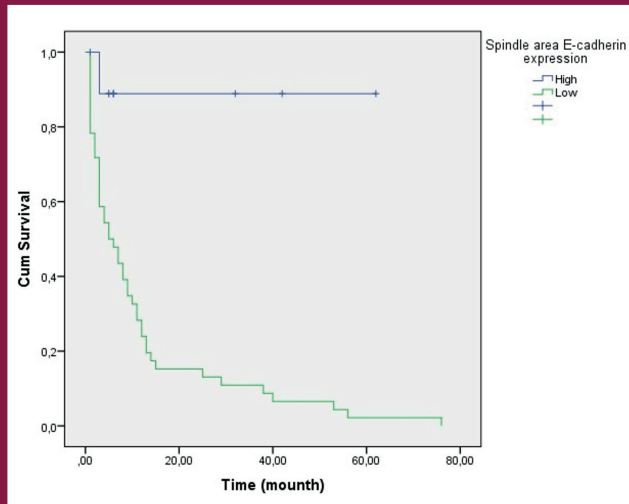

Figure 4. Kaplan-Meier median disease-free survival time analysis by E-cadherin staining pattern in spindle cell area

infiltration (13,14,15). For example, Yang et al. (17) showed that low E-cadherin expression was associated with an increase in lymph node metastasis rate, high grade, vascular invasion, and poor survival. However, our study showed that there was no significant relationship between decreased E-cadherin expression and most parameters such as stage, grade, lymph node involvement, necrosis, and diameter. This can be explained by the small number of PC cases in the subclass of non-small cell carcinoma in our study. Similar results were found in some studies conducted for NSCLC (18).

In our study, a higher E-cadherin staining was detected in the epithelial area of the T, while a reduced in expression was found in the spindle and/or giant cell area. Okimura et al. (19), similar to our study, found a higher rate of staining with E-cadherin in the epithelial area of the T in cases of pulmonary PC.

The loss of expression of E-cadherin in the spindle and giant cell epithelial component in resection materials may explain the invasive potential and increase of their metastases of these Ts.

TKI (Tyrosine Kinase Inhibitors) is frequently used in the treatment of NSCLC and EMT is believed to play an important role in resistance to these drugs (20,21). Some studies have shown that EMT is involved not only in determining the prognosis of patients with NSCLC, but also in response to specific treatments such as anti-EGFR treatments used for this type of T (22). TKI were not used in our cases.

Our results were obtained as a result of a limited number of retrospective studies based on the existing archive screening of our hospital. However, while a relatively small

number of patients have been analyzed, patient data have been meticulously collected and recorded.

Conclusion

As shown in studies, loss of expression of E-cadherin has an important role in carcinogenesis and T progression as a result of EMT increase. In different studies made with different types of Ts, it is shown that E-cadherin expression loss is related to poor prognosis. Future studies with different T types may contribute to the development of new therapeutic agents and the determination of prognostic factors.

Ethics

Ethics Committee Approval: The study design was approved by the appropriate ethic review board Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number and date: 2085/2019; 12/06/2019).

Informed Consent: Informe consent were obtained from all patients before surgery.

Peer-review: Internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: N.Ü., N.P., Concept: N.Ü., Design: N.Ü., Data Collection or Processing: N.P., Analysis or Interpretation: N.Ü., Literature Search: N.P., Writing: N.Ü.

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Demographic Characteristics of Electronic Cigarette Users: A Survey Study

Elektronik Sigara Kullanıcılarının Demografik Özellikleri: Bir Anket Çalışması

Ayşe Turan[1], Pelin Duru Çetinkaya[2], Mehmet Atilla Uysal[3]

[1]*Adana Seyhan State Hospital, Adana, Turkey*

[2]*University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Chest Diseases, Adana, Turkey*

[3]*University of Health Sciences Turkey, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases, İstanbul, Turkey*

ABSTRACT

Background: Electronic cigarette (e-cigarette) use is on the rise in Turkey, even though e-cigarettes have been banned since 2013. In this study, the demographic characteristics of e-cigarette users and their reasons for starting and then stopping e-cigarette smoking were investigated.

Materials and Methods: A total of 234 e-cigarette users were selected from social groups using the snowball sampling method in the city of Adana. E-cigarette users were questioned about their demographic characteristics, regular smoking status, reasons for starting e-cigarettes, areas of use, and health symptoms regarding e-cigarette use.

Results: Of the 234 participants, 89.74% were male, and the mean age was 34.84±10.15 (18-63) years; 85.89% had high school or above education. The participants' three most frequently stated reasons for starting e-cigarettes were a desire to quit smoking completely (74.79%), the absence of a foul smell (73.93%), and the wish to avoid the harm of smoking (67.10%). Of the 234 e-cigarette users, 170 reported that they also quit using e-cigarettes. The top three most frequently cited reasons for quitting e-cigarettes were a failure to help to quit traditional cigarettes (26.47%), the risks of using e-cigarettes (22.35%), and concerns about the safety of the product (22.35%). Responses to the question of how to get e-cigarette devices or liquids were as follows: 45.31% of users obtained the product from friends, 23.93% ordered it online, and 30,76% purchased it from tobacco shops.

Conclusion: Our data show that the most frequent reason to switch from traditional cigarettes to e-cigarettes was quitting smoking. It is worrisome that the users who have made this critical smoking cessation decision, instead of distancing themselves from tobacco, have shifted to yet another tobacco product. This information is an important warning for those in the smoking cessation area to question the availability and comprehensibility of the public's services to help them quit tobacco.

Keywords: Electronic cigarette, smoking cessation, demographic analyses, tobacco use

ÖZ

Amaç: Türkiye'de elektronik sigara (e-sigara) kullanımı 2013 yılından itibaren e-sigara yasaklanmasına rağmen artmaktadır. Bu çalışmada, e-sigara kullanıcılarının demografik özellikleri ve e-sigara içmeye başlama ve sonra bırakma nedenleri araştırılmıştır.

Gereç ve Yöntemler: Adana'da e-sigara kullanmış 234 kişiye sosyal gruplarından kartopu yöntemi ile ulaşılmış ve anket çalışması yapılmıştır. Ankette demografik özellikler, sigara, e-sigara kullanım bilgileri, e-sigaraya başlama/bırakma nedenleri, kullanıldığı alanlar ve e-sigara kullanım esnasında veya sonrasında oluşan sağlık semptomları sorgulanmıştır.

Bulgular: Çalışmaya dahil olan 234 kişinin %89,74'ü erkek, %85,89'u lise ve üzeri eğitime sahip, yaş ortalamaları 34,84±10,15 (18-63) idi. Katılımcıların e-sigaraya başlama nedenleri sorulduğunda, en sık belirtilen üç neden; sigarayı tamamen bırakma isteği (%74,79), kötü kokunun olmaması (%73,93) ve daha az zararlı olarak algılanması (%67,10) olmuştur. Çeşitli nedenlerle e-sigara kullanımını sonlandıran 170 katılımcının belirttiği en sık nedenler; konvansiyonel sigarayı bırakmaya yardımcı olmaması (%26,47), e-sigaranın riskleri ile ilgili (%22,35) ve e-sigaranın güvenliği ile ilgili endişelerdir (%22,35). E-sigara veya likitlerini sıklıkla (%45,31) arkadaşlarından/tanıdıklarından, (%23,93) internetten, (%30,76) çeşitli tütün dükkanından temin ettikleri bilinmektedir.

Sonuç: Bu çalışmada klasik sigaradan e-sigaraya geçişte belirtilen en önemli nedenin sigarayı bırakma isteği olduğu görülmektedir. Bu durum "sigara bırakma" noktasına gelmiş kullanıcıların tütünden tamamen uzaklaşmak yerine yeni bir tütün ürününe kayıyor olmaları tütün kontrolünde kaygı vericidir. Bu bilgi aynı zamanda, halkımıza sağladığımız bilgilendirme ve bırakma hizmetlerini gözden geçirmemiz için önemli bir uyarı niteliğindedir.

Anahtar Kelimeler: Elektronik sigara, sigara bırakma, demografik özellikler, tütün kullanımı

Address for Correspondence: Pelin Duru Çetinkaya, University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinic of Chest Diseases, Adana, Turkey
Phone: +90 532 707 75 06 E-mail: pelindurucetinkaya@hotmail.com **ORCID ID:** orcid.org/0000-0002-4428-8590

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Introduction

Electronic cigarettes (e-cigarettes) were introduced to the market in 2004. The product was introduced to the European and American markets in 2006 as a "lower risk" alternative to smoking (1,2). E-cigarettes are battery-powered devices heated below the burning point to generate steam and contain many chemical substances, such as liquid propylene glycol and/or a vegetable glycerin solution. Disposable and refillable types are available (3). Nicotine can be added to the liquid solution in varying concentrations and frequencies, depending on the consumer's requirements.

A wide variety of chemicals, including propylene glycol, glycerol, ethylene glycol, polyethylene glycol (PEG400), diacetyl, diethylene glycol, amino-tadalafil, rimonabant, cannabinoid, nitrosamines, formaldehyde, acetaldehyde ketone, mercury, tetramethylpyrazine, lead, nickel, chromium, nicotine, and artificial flavors, have been identified in e-cigarettes (4,5,6,7). Nitrosamines, known to be carcinogenic, including N-Nitrosonornicotine, 4-(nitroso methyl-amino)-1-(3-pyridyl)-butanone, and nitroso-anatabine, have also been found in e-cigarettes (8). Moreover, diethyl glycol, anabasine, myosmine, and beta-nicotryine, proven to be harmful to human health, have been found in e-cigarettes (6,7,8,9,10).

In the United States of America, the prevalence of e-cigarette use among adults was estimated to be 3,2% (11). In Canada, the prevalence of use was 2,9% in 2017 (12). In Turkey, e-cigarettes entered the market in 2007-2008, but a 2008 circular of the Ministry of Health banned its sales. Since 2013, the product has been accepted as a tobacco product and included in indoor smoke-free laws (13,14,15). Since e-cigarettes are not legal for sale in Turkey, there has not been a study to report their consumption frequency in the country. However, the use of e-cigarettes is increasing in Turkey as well as in the world. Although electronic cigarettes are not legally available in Turkey, it has been reported that there are 96 active websites that market these products over the internet (7,16). In studies conducted in Turkey, it has been shown that online sales of e-cigarettes and their usage are commonly available (17). Because the increasing prevalence of e-cigarettes raises concerns about possible health risks, it is important to know the user profile to combat population-wide e-cigarette use.

This study investigated the demographic characteristics of e-cigarette users and their reasons for starting and then stopping e-cigarette smoking.

Material and Methods

Approval for the study was obtained from the Adana Numune Training and Research Hospital Local Ethics Committee (protocol no: 26.04.2017-57). Verbal consent was obtained from the patients for the questionnaire. E-cigarette users in Adana were recruited from several e-cigarette social groups via the snowball sampling method. Due to the fact that it is a prohibited product, a group not suitable for systematic sampling methods was selected by the snowball sampling method. The prevalence of e-cigarette use in a metropolitan city in the Mediterranean region attracted the attention of researchers, and it was decided to start the study there. Verbal information was given to e-cigarette users about the subject, purpose, and method of the study after 36 patients who came to a state hospital's Smoking Cessation Polyclinic to quit smoking reported their use of e-cigarettes; other e-cigarette users were reached through social networks/media by asking, "who or whom would you recommend contacting" regarding the subject of the research, conveying that personal information would be kept confidential. When the number of 234 was reached, the research was terminated when there were repetitions. The study included 253 individuals aged ⩾18 years, who had used e-cigarettes for at least one month. However, 12 people did not want to participate for various reasons, and seven people with psychiatric disorders (diagnosis of schizoaffective disorder, bipolar disorder, and major depressive disorder) were not included in the scope. At the time of the study, there was no reliable or valid questionnaire about e-cigarettes. For this reason, the questions of this survey were formed by the researchers based on the literature.

In the first part of the questionnaire, 10 questions about demographic information, smoking and e-cigarette use, and frequency of use were asked. In the second part, the participants were asked to choose the appropriate option from "I disagree," "I partially agree," and "I totally agree" for 13 areas where the reasons for starting e-cigarettes were listed. The time of use of e-cigarettes, the third part, which included information about where it was used, and the 14 areas in which the reasons for discontinuing e-cigarette use were listed, were searched with the options of "disagree," "partially agree," and "completely agree." In the last part of the questionnaire, 18 health symptoms that might occur during or after e-cigarette use were questioned. Eighteen items of categorical data, including health symptoms occurring during or after e-cigarette use, were evaluated. On average, it took about 8-10 minutes to complete the survey.

Statistical Analysis

Statistical data analysis was performed with the SPSS 16.0 (Statistical Package for the Social Sciences) program. Only descriptive statistics were used in the analysis of the data. In evaluating the data, mean and standard deviation

were used to describe continuous data, while categorical variables were presented as frequencies and percentages.

Results

Descriptive analysis showed that 89.74% of the participants were male, 52.99% were married, 40.59% were civil servants, and 85.89% had a high school or higher education (Table 1). The mean age for e-cigarette users was 34.84±10.15 years (18-63).

The mean package-year of traditional cigarette users was 14.75±8.29. When asked about their tobacco use habits, the average e-cigarette use duration was 3.81±2.52 months. E-cigarette users in this group consumed 28.90±18.9 mL vials and finished a vial in 13.67±14.9 days on average.

The aromas preferred by the participants were fruit (47.86%, n=112), "other" (pastry, coffee, spices, etc.; 24.80%, n=58), tobacco (14.10%, n=33), and mint/menthol (13.24%, n=31). The mean nicotine use of e-cigarette users was 4.82±2.04 mg/mL.

The smoking status of the participants before starting e-cigarettes was questioned: 56.41% (n=132) reported that they smoked regularly, 38.46% (n=90) were ex-smokers, and 5.12% (n=12) had never smoked. The change in smoking status after starting e-cigarettes was questioned: 15.38% (n=36) smoked only e-cigarettes, 39.74% (n=93) smoked only traditional cigarettes, 11.97% (n=28) were dual users (use both e-cigarettes and traditional cigarettes), and 32.91% (n=77) did not use tobacco products.

Table 1. Sociodemographic characteristics and smoking history of the participants in the study

Sociodemographic characteristics	n (%)
Gender	
Male	210 (89.74)
Female	24 (10.26)
Marital status	
The married	124 (52.99)
Single	110 (47.01)
Education status	
Illiterate	4 (1.71)
Primary school	6 (2.56)
Middle school	23 (9.83)
High school	89 (38.04)
University	102 (43.59)
Postgraduate	10 (4.27)
Job	
Worker	46 (19.65)
Officer	64 (27.35)
Retired	4 (1.71)
Housewife	4 (1.71)
Student	30 (12.82)
Self-employment	50 (21.37)
Health employee	31 (13.25)
Other	5 (2.14)

Responding to the question, "Where do you get your e-cigarettes?", 45.31% (n=106) stated they obtained the product from friends/acquaintances, 23.93% (n=56) ordered online, 30.76% (n=72) purchased from tobacco shops, 22.65% (n=53) obtained from "other" sources (various shopping centers).

When asked about the type of symptoms they may have experienced during or after using e-cigarettes, the most commonly mentioned symptoms were a feeling of dryness in the mouth/throat and cough (reported by 36.75%, n=86), increased sputum (reported by 26.15%, n=61), and excessive smoking desire (reported by 13.67%, n=32). The majority, 70.08% (n=164) of the participants, reported using e-cigarettes in their homes' indoor spaces, 44.44% (n=104) in the indoor spaces of their workplaces, and 4.70% (n=11) in public vehicles, while 31.20% (n=73) of the users reported that they used e-cigarettes in the home while children were present.

The reasons given for using e-cigarettes differed according to smoking status. When participants' stated reasons for starting e-cigarettes were evaluated, the top three most frequently cited reasons were a desire to quit smoking completely at a rate of 74.79% (n=175), the absence of a foul smell at a rate of 73.93% (n=173), and being perceived as less harmful than smoking at a rate of 67.10% (n=157) (Table 2).

Of the 234 e-cigarette users, 170 reported that they also had quit using e-cigarettes. The top three most frequently cited reasons for quitting e-cigarettes were: Not helping to quit traditional cigarettes [26.47% (n=45)], the risks of using e-cigarettes [22.35% (n=38)], and concerns about the safety of the product [22.35% (n=38)] (Table 3).

Discussion

We have found that the most common reason for e-cigarette usage was trying to quit smoking or to reduce the health risks of regular smoking and, 30.76% of e-cigarette users could buy e-cigarettes easily, although the sale is prohibited in our country.

The high proportion of e-cigarette users were male, and over 85.89% of the cases had a high school education. Of the cases, 83.76 % had ordinary income jobs. The most common reason to commence using e-cigarettes was the desire to quit smoking completely, followed by a disturbing bad smell being perceived as less harmful than smoking.

Table 2. The reasons for using/choosing e-cigarette

E-cigarette use/reasons to choose	Disagree n (%)	Partially agree n (%)	Totally agree n (%)
Starting e-cigarettes out of curiosity	103 (44.02)	53 (22.65)	78 (33.33)
More pleasurabl than smoking	131 (55.98)	40 (17.10)	63 (26.92)
Thinking it as less harmful than smoking	44 (18.80)	33 (14.10)	157 (67.10)
The thought of not exposing those around me to smoke	59 (25.22)	44 (18.80)	131 (55.98)
Its being cheaper than cigarettes	114 (48.71)	50 (21.37)	70 (29.92)
Thinking it will reduce stress better than smoking	114 (48.71)	51 (21.80)	69 (29.49)
Thinking it will help reduce the number of cigarettes smoked	51 (21.80)	30 (12.82)	153 (65.38)
Wanting to quit smoking completely	37 (15.81)	22 (9.40)	175 (74.79)
My friends' using it	113 (48.29)	42 (17.95)	79 (33.76)
Liking taste of e-cigarette	69 (29.49)	48 (20.51)	117 (50.0)
Its having no bad smell	40 (17.10)	21 (8.97)	173 (73.93)
Its being able to be used indoors	72 (30.77)	32 (13.68)	130 (55.55)

Table 3. Reasons for stopping e-cigarettes

Reasons for stopping e-cigarettes	Disagree n (%)	Partially agree n (%)	Totally agree n (%)
Its being costly, expensive	155 (91.18)	9 (5.29)	6 (3.53)
Disliking the taste	152 (89.42)	9 (5.29)	9 (5.29)
Its being too complicated to use, impractical	137 (80.59)	18 (10.59)	15 (8.82)
Being concerned about the risks	119 (70.0)	13 (7.65)	38 (22.35)
Not feeling like smoking	116 (68.24)	20 (11.76)	34 (20.0)
Its not reducing the number of cigarettes smoked	120 (70.59)	13 (7.65)	37 (21.76)
Its not helping to quit smoking	116 (68.24)	9 (5.29)	45 (26.47)
Being ashamed to use	158 (92.94)	5 (2.94)	7 (4.12)
Worrying about being addicted to e-cigarettes	138 (81.18)	14 (8.24)	18 (10.59)
Its having too much smoke	146 (85.89)	9 (5.29)	15 (8.82)
Being tired of carrying the e-cigarette tool	132 (77.65)	16 (9.41)	22 (12.94)
Difficulties in liquid supply	129 (75.88)	8 (4.71)	33 (19.41)
Having concerns about its safety	121 (71.18)	11 (6.47)	38 (22.35)

A wide variety of chemicals in e-cigarettes, including propylene glycol, glycerol, ethylene glycol, polyethylene glycol (PEG400), amino-tadalafil, rimonabant, cannabinoid, nitrosamines, formaldehyde, acetaldehyde ketone, mercury, tetramethylpyrazine, nicotine, artificial flavors, and various other carcinogenic chemicals, have been identified in e-cigarettes. Multinational tobacco companies claim that e-cigarettes are a "safer," "less harmful" alternative to regular cigarettes and an "adequate" method for smoking cessation (4,6,8).

Nicotine concentration peaks within five minutes of inhaling an e-cigarette (18). Acute exposure to nicotine can cause headache, dizziness, nausea, and vomiting. Liquid nicotine in the cartridge of an e-cigarette can cause acute poisoning. The repeated use of the cartridge can raise the level of nicotine to toxic levels (19). This activity commonly causes oral and throat irritation, dry cough, dry eye, gastrointestinal symptoms, and local irritation. An increase in heart rate, short-term shortness of breath, headache, and sore throat are also reported. Nitrosamines contained in the product are known to be carcinogens. There are also studies showing that it may cause decreased respiratory function (18,19,20,21). In humans, e-cigarette use has been associated with multiple cases of acute lung injury and acute respiratory distress syndrome (ARDS) (22).

Although there are many questions about the efficacy of e-cigarettes as a smoking cessation tool or the long-term health effects of the product, multinational tobacco companies have managed to split those who oppose the use of e-cigarettes for tobacco control (23). Legal regulations regarding e-cigarettes differ among countries. Some countries entirely ban electronic cigarettes, while others have no regulations.

For instance, in the United Kingdom, it is not forbidden to sell, use, and advertise e-cigarettes. However, in Turkey, following an amendment made to the law in 2013, the advertisement of e-cigarettes, sales, and smoking in indoor places is prohibited.

Despite this ban, the use of e-cigarettes in Turkey and the world has increased in recent years. Worldwide, 3.7% of adults use e-cigarettes every day or several days a week. More than 20% of adults aged 18-20 years have tried e-cigarettes (5).

The device's stylish designs, the perception that it is harmless or less harmful than traditional cigarettes, and

the presentation of different flavors have contributed to the increase in the prevalence of e-cigarette use among young adults (24). When the sociodemographic characteristics of e-cigarette users are examined in systematic reviews, it is seen that it is prevalent in males, adolescents, young adults, and people with relatively higher education levels (25). This situation is compatible with the study data.

In a study conducted in European Union countries, 70.9% of non-smokers, 63.1% of ex-smokers, and 45.7% of smokers reported that they supported the ban on e-smoking in public places (26). Despite the ban on tobacco and products in closed areas in Turkey, in our study, 70.08% of e-cigarette users continued to use e-cigarettes at home, 44.44% at work, and 4.70% in public vehicles. This situation suggests that tobacco controls have been insufficient.

In this study, the first reason for using e-cigarettes was the desire to quit smoking. In another study, the reason for starting e-cigarettes was stated as being curious (27).

Although the participants stated that the most compelling reason for starting smoking was to give up traditional smoking, it is known that they continue to smoke. Switching to another tobacco product to quit smoking may result in low motivation for making other attempts to quit. This information was an important warning for us to review the services we provide to the public to quit smoking.

In a study conducted with 3,878 e-cigarette users, among the most common reasons for starting e-cigarettes, curiosity was reported to be the first with the rate of 53%, the suggestion of friends or family members to be the second with the rate of 34%, while 30% had the idea to quit smoking (27). It was observed that the thoughts of quitting smoking, not having a foul odor, and being less harmful than smoking were dominant when starting e-cigarettes. In the literature about e-cigarettes, it is seen that people often initiate e-cigarette use to quit or reduce traditional smoking, which is consistent with our study (28,29).

Doran et al. (30) studied whether e-cigarette use reduced smoking or not. They found that e-cigarette usage sustained smoking habits and even increased smoking. The fact that using e-cigarettes may sustain or even increase a person's smoking rather than decrease may explain the same behavioral effect of e-cigarette use and smoking. E-cigarette users continue their behavioral dependence, and to reach the same nicotine level, they overuse e-cigarettes, which have less nicotine than traditional cigarettes, or use both e-cigarettes and traditional cigarettes (dual use) (31). Our study consisted of 11.97% (n=28) of dual users.

Study Limitations

This is a survey study; the proportions of smoking, e-cigarette use, quitting smoking, and restarting are based on the participants' statements. Since the people reached through the social platform were surveyed, the data may not include all e-cigarette users. The questions were constructed according to current data by researchers because there was not an available validated questionnaire about e-cigarette usage. So, this survey cannot represent the complete characteristics of e-cigarette users.

Conclusion

In this study, it was seen that the most important reason for starting to use e-cigarettes was the desire to quit smoking. For this reason, we think it is essential to inform the public about that e-cigarettes are not a smoking cessation method.

The tobacco industry mainly targets young people and users who want to quit smoking with e-cigarette ads. It should be explained to the public that e-cigarettes are harmful and are yet another kind of tobacco product. We should fight against the increased usage of e-cigarettes to avoid losing the gains obtained in tobacco control.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Adana Numune Training and Research Hospital Local Ethics Committee (protocol no: 26.04.2017-57).

Informed Consent: Verbal consent was obtained from the patients for the questionnaire.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.T., P.D.Ç., M.A.U., Concept: A.T., P.D.Ç., M.A.U., Design: A.T., P.D.Ç., M.A.U., Data Collection or Processing: A.T., P.D.Ç., M.A.U., Analysis or Interpretation: A.T., P.D.Ç., M.A.U., Literature Search: A.T., P.D.Ç., M.A.U. Writing: A.T., P.D.Ç., M.A.U.

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The Profile and Severity of Causal Factors in Symptomatic Epilepsies

Semptomatik Epilepsilerde Altta Yatan Nedenler ve Ağırlık Dereceleri

Hülya Ertaşoğlu Toydemir[1], Vildan Yayla[1], Dilek Bozkurt[1], Filiz Azman[2], Hayriye Örnek[1]

[1]*University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey*

[2]*Kayseri City Hospital, Clinic of Neurology, Kayseri, Turkey*

ABSTRACT

Background: The purpose of this study was to identify the profile of causal factors, to estimate severity of causal factors, and to evaluate the relationship between them and the clinical features of our patients with symptomatic epilepsy.

Materials and Methods: We retrospectively analyzed demographic, clinical, electroencephalographic and radiological findings and causal factors of 128 patients. Patients were grouped in three according to the number of causal factors which were hypothesized to represent the severity. The relationships between the severity of causal factors and clinical, electroencephalographic or radiological findings were evaluated.

Results: The most frequent causal factors were head trauma, prenatal/perinatal/postnatal problems, mesial temporal sclerosis and central nervous system infections. Group 1 consisted of 73 patients (57%) having one causal factor. In group 2, 32% had two causal factors and in group 3, 11% had more than two causal factors. There were no significant differences between the severity of causal factors and age, sex, delivery problems, mental status, radiological or electroencephalographic findings. There existed a significant difference only in terms of encephalomalacia (p=0.008) Encephalomalacia was more frequently detected in patients having more than two causal factors.

Conclusion: A wide variety of one or more causal factors may be detected in patients with symptomatic epilepsies. The severity of the causal factors may not be easily evaluated. The number of causal factors may represent the severity of the insult and may have influences on the electro-clinical or radiological findings. Future studies are required for the prediction of the severity of the underlying causes and the type of pathological process.

Keywords: Symptomatic epilepsy, causes of epilepsy, risk factors

ÖZ

Amaç: Çalışmamızda semptomatik epilepsisi olan hastalarda altta yatan nedenleri tanımlamak, bu nedenlerin ağırlık derecelerini tayin etmek ve hastaların klinik özellikleri ve bu nedenler arasındaki ilişkiyi değerlendirmek amaçlandı.

Gereç ve Yöntemler: Yüz yirmi sekiz hastanın demografik, klinik, elektroensefalografik, radyolojik bulguları ve epilepsi nedenleri retrospektif olarak analiz edildi. Hastalar, epilepsinin altta yatan nedenlerinin ağırlık derecesini yansıttığı düşünülerek bu nedenlerin sayısına göre üç gruba ayrıldı. Epilepsi nedenlerinin ağırlık dereceleri ile hastaların klinik, elektroensefalografik ve radyolojik bulguları arasındaki ilişki değerlendirildi.

Bulgular: En sık epilepsi nedenleri kafa travması, prenatal/perinatal/postnatal problemler, mezial temporal skleroz ve merkezi sinir sistemi enfeksiyonlarıydı. Tek neden saptanan 73 hasta (%57) grup 1'i oluştururken, iki neden saptanan %32 hasta grup 2'de, ikiden fazla neden saptanan %11 hasta grup 3'te bulunuyordu. Epilepsi nedenlerinin ağırlık dereceleri ile yaş, cinsiyet, doğum problemleri, mental durum ve elektroensefalografik bulgular arasında anlamlı ilişki saptanmadı. Sadece ensefalomalazi ile epilepsi nedeninin ağırlık derecesi arasında istatistiksel anlamlı ilişki mevcuttu (p=0,008). Ensefalomalazi, ikiden fazla neden saptanan hastalar arasında daha sıktı.

Sonuç: Semptomatik epilepsisi olan hastalarda iki veya daha çok neden, çok geniş çeşitlilikte saptanabilmektedir. Nedenlerin ağırlık dereceleri kolay saptanamayabilir. Altta yatan nedenlerin sayısının, hasarın ağırlık derecesini yansıtabileceği ve elektro-klinik, radyolojik bulgular üzerine etkisi olabileceği düşünülmüştür. Gelecekte, epilepsi nedenlerinin ağırlık derecesini ve patolojik sürecin tipini öngörebilmeye yönelik başka çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Semptomatik epilepsi, epilepsi nedenleri, risk faktörleri

Address for Correspondence: Hülya Ertaşoğlu Toydemir, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey

Phone: +90 505 374 33 69 E-mail: hulyatoydemir@hotmail.com **ORCID ID:** orcid.org/0000-0002-2024-1181

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Introduction

Symptomatic epilepsy (SE) is the epilepsy in which convulsions are due to a central nervous system (CNS) insult that may be metabolic, toxic, structural, infectious, or inflammatory (1). SE has been described as "an epilepsy predominantly due to a gross neuroanatomical or neuropathological abnormality or a relevant systemic disease, which can be acquired or genetic in origin" (2). Underlying etiologies, investigations and treatment of symptomatic seizures are different from that of unprovoked seizures (3).

Symptomatic epilepsies are not always acquired. Genetic or developmental causation may be detected for some of the symptomatic epilepsies, such as progressive myoclonic epilepsies, neurocutaneous syndromes, disorders of chromosome structure and developmental anomalies of cerebral structure. Symptomatic epilepsies of acquired causation consist of hippocampal sclerosis, perinatal and infantile causes, cerebral trauma, tumor, infection, cerebrovascular disorders, cerebral immunologic disorders and degenerative conditions (2). In the majority of cases, epilepsy is multifactorial and has contributions from genetic, acquired and precipitating causes (4). The concepts of proximate and remote causes underlying symptomatic epilepsies were evaluated in previous studies (2,5). A proximate cause was considered to be an actual cellular disturbance at the epileptic focus and remote causes were defined to be those which triggered this disturbance (5).

Causal factors, remote or proximate, are extremely important in the concept of symptomatic epilepsy. Sometimes there may be difficulties in defining the causal factors or there may be more than one causal factor underlying symptomatic epilepsies. Moreover, recognition of the severity of insult required to precipitate seizures and the determination of a temporal relationship might have influences on the understanding of the concept of SE. The severity of the insult might be understood with four conceptual models: 1- acute disease model in which multiple insults are needed to provoke a seizure; 2- chronic disease model in which seizures happen after a single insult in the context of a chronic disease; 3- unique insult model in which seizures occur due to high-magnitude insult; and 4- genetic predisposition in which seizures happen after an insult of low intensity (5,6). The purpose of this study was (i) to identify the profile of causal factors, (ii) to estimate severity of causal factors, and (iii) to evaluate the relationship between the severity of causal factors and the clinical features of our patients with symptomatic epilepsy.

Material and Methods

A retrospective analysis was performed to 128 patients with SE attending to our epilepsy outpatient clinic in a 3-year-period. The inclusion criteria were the presence and the documentation of a CNS insult. Patients with acute or chronic setting were both included in the study. Patients with inadequate data or the patients whose causal factor could not be defined were excluded. Besides demographic findings of the patients, causal factors, radiologic and electro-clinical features were recorded.

Epileptic seizures were classified according to the ILAE classification as simple partial seizures, complex partial seizures, absence, myoclonic seizures, generalized tonic clonic seizures, secondary generalized tonic clonic seizures and status epilepticus (7).

Cranial magnetic resonance imaging (MRI) according to epilepsy protocol was undertaken to investigate the presence of structural brain abnormality. All of our patients had at least one cranial MRI during their follow-up.

Electroencephalographic (EEG) findings were grouped in five as focal epileptogenic focus, generalized epileptiform activity, focal slowing in fronto-temporal region, non-specific paroxysmal activity and generalized slowing.

We categorized head trauma as minor (<30 min amnesia and no skull fracture) or major head trauma (>30 min amnesia and/or skull fracture and/or intracranial traumatic lesions).

Prenatal/perinatal/postnatal problems were not evaluated separately. Problems during pregnancy such as infections and trauma, delivery problems such as difficult and prolonged labor, complicated labor, problems after birth such as prolonged neonatal jaundice, kernicterus were termed as prenatal/perinatal/postnatal problems. Information about prenatal/perinatal/postnatal problems was obtained from patients, parents, care givers, previous medical documents or the medical records of the hospital.

A wide variety of causal factors in our study population and the presence of more than one causal factor in the same patient allowed us to make a hypothesis that the number of causal factors might represent the severity of the insult and might have influences on the electro-clinical or radiological findings of the patients. For this reason, causal factors underlying the seizures were listed and then patients were categorized in three groups according to the number of causal factors. Patients presenting with only one causal factor belonged to group 1, patients with two causal factors were in group 2 and the ones with more than two causal factors constituted group 3. These groups were defined to represent the level of severity of causal factors. The relationship between the severity of causal factors and the clinical features of our patients with SE were evaluated.

Statistical Analysis

We performed statistical analysis by NCSS (Number Cruncher Statistical System) 2007 software program (NCSS, LLC Kaysville, Utah, USA). Besides descriptive statistical methods (mean, standard deviation, median, frequency and ratio), data were analyzed by using the One-Way ANOVA test for qualitative variables with normal distribution between the groups. The Pearson's chi-square test (χ^2) and Fisher Freeman Halton test were used for the analysis of quantitative variables. Data were evaluated within a 95% confidence interval and a p-value<0.05 was considered significant.

Results

Among the 128 patients included in this study, 71 patients (55.5%) were male and 57 patients (44.5%) were female. The mean age of the patients was 31.91±13.76 (12-81) years. Ages at seizure onset were between the first year of life and 80 years (mean: 18.17±13.91 years). The mean latent period between the insult and the age at seizure onset was 11.81±9.85 years (min-max: 6 months-46 years). Causal factors underlying symptomatic seizures of our patients are listed in Table 1. The most frequent causal factors were head trauma, prenatal/perinatal/postnatal problems, mesial temporal sclerosis (MTS) and CNS infections.

Patients were grouped in three according to the number of causal factors. Group 1 consisted of 73 patients (57.0%) with one causal factor, group 2 included 41 patients (32.0%) with two causal factors and in group 3, 14 patients (11.0%) had more than two causal factors. Neurological examination was unremarkable in 72 (56.3%) patients, 15 (11.7%) patients had motor-mental retardation, 13 (10.2%) had hemiparesis, 12 (9.4%) had mental retardation, and the rest had other neurological deficits including tremor, vision loss, dysmetria, ataxia, dysarthria and hemihypoesthesia.

Seizure types in our study population consisted of 7 subtypes: generalized tonic clonic (52.3%), complex partial (49.2%), simple partial (23.4%), secondary generalized (6.6%), absence (2.3%), myoclonic seizures (2.3%) and status epilepticus (7.0%).

Neuroimaging modalities revealed pathological findings in 101 patients (78.9%). Pathological findings were encephalomalacia (32.8%), MTS (12.5%), periventricular ischemic-gliotic lesions (8.6%), cortical dysplasia (6.3%), periventricular leukomalacia (5.5%), global atrophy (4.7%), hemiatrophy (3.9%), infarction (2.3%), tumor (2.3%), diffuse white matter lesions (2.3%), arachnoid cyst (2.3%), and aneurysms (0.8%).

Pathological EEG findings, which were detected in 72.7% of the patients, were grouped in five: focal epileptogenic focus (58.1%), focal slowing in fronto-temporal region (39.8%), generalized slowing (20.4%), generalized epileptiform activity (15.1%) and non-specific paroxysmal activity (10.8%).

Analysis revealed no significant differences between the severity of causal factors and sex or age (p=0.320 and p=0.299).

There were no significant differences between the severity of causal factors and problems of delivery or mental status (p=0.699 and p=0.453).

We did not find any significant differences between the severity of causal factors and radiological findings globally (p=0.599). There existed a significant difference only in terms of encephalomalacia (p=0.008). Encephalomalacia was more frequently detected in patients who had more than two causal factors underlying their symptomatic seizures (group 3) (Table 2).

Analysis of the relationship between the severity of causal factors and pathological EEG findings showed no significant difference between the groups (p=0.409). In addition, there was no significant difference between the subgroups of EEG pathological findings (Table 3).

Table 1. Causal factors of symptomatic seizures in our patients

	n	%
Trauma (head)	46	35.9
Minor	21	51.2
Major	20	48.8
Prenatal, perinatal postnatal problems	32	25.0
Mesial temporal sclerosis	30	23.4
Right-sided	10	33.3
Left-sided	15	50.0
Bilateral	5	16.7
Central nervous system infections	19	14.8
Brain operations	12	9.4
Congenital malformations	12	9.4
Cerebrovascular diseases	7	5.5
Ischemic	4	57.1
Hemorrhagic	3	42.9
Arteriovenous malformations/aneurysms	6	4.7
Brain tumor	5	3.9
Other causal factors	11	8.6
Cavernous angioma	3	33.3
Tuberous sclerosis	2	22.2
Neuroepithelial cyst	1	11.1
Coroid fissure cyst	1	11.1
Epidermoid cyst	1	11.1
DNET	1	11.1

DNET: Dysembryoblastic neuroepithelial tumor

Table 2. The relationship of the severity of causal factors with radiological findings

		Severity of causal factors			p
		Group 1 (n=55)	Group 2 (n=34)	Group 3 (n=12)	
Encephalomalacia	No	39 (70.9)	17 (50.0)	3 (25.0)	**0.008****
	Yes	16 (29.1)	17 (50.0)	9 (75.0)	
Periventricular ischemia	No	48 (87.3)	30 (88.2)	12 (100.0)	**0.599**
	Yes	7 (12.7)	4 (11.8)	0	
Tumor	No	54 (98.2)	33 (97.1)	11 (91.7)	**0.356**
	Yes	1 (1.8)	1 (2.9)	1 (8.3)	
Aneurysms	No	55 (100.0)	34 (100.0)	11 (91.7)	**0.122**
	Yes	0	0	1 (8.3)	
Diffuse white matter lesions	No	54 (98.2)	32 (94.1)	12 (100.0)	**0.701**
	Yes	1 (1.8)	2 (5.9)	0	
Periventricular leukomalacia	No	50 (90.9)	32 (94.1)	12 (100.0)	**0.746**
	Yes	5 (9.1)	2 (5.9)	0	
Hemiatrophy	No	52 (94.5)	33 (97.1)	11 (91.7)	**0.671**
	Yes	3 (5.5)	1 (2.9)	1 (8.3)	
Cortical dysplasia	No	52 (94.5)	31 (91.2)	10 (83.3)	**0.312**
	Yes	3 (5.5)	3 (8.8)	2 (16.7)	
Global atrophy	No	52 (94.5)	31 (91.2)	12 (100.0)	**0.709**
	Yes	3 (5.5)	3 (8.8)	0	
Infarction	No	52 (94.5)	34 (100.0)	12 (100.0)	**0.515**
	Yes	3 (5.5)	0	0	
Mesial temporal sclerosis	No	48 (87.3)	25 (73.5)	12 (100.0)	**0.077**
	Yes	7 (12.7)	9 (26.5)	0	

Fisher Freeman Halton test, **p<0.01, *p<0.05

Discussion

Our study demonstrates that a wide variety of causal factors may be detected in patients with symptomatic epilepsies. The most frequent causal factors are listed as head trauma, prenatal/perinatal/postnatal problems, MTS and CNS infections. Although clinical and laboratory findings vary according to the underlying causal factors in symptomatic epilepsies, more than one causal factor may be found in the same patient. It may not be easy to evaluate the severity or intensity of the causal factor needed to provoke a seizure. We aimed to find out whether the number of causal factors has an influence on the electro-clinical or radiological findings of the patients.

Epilepsy was stated to develop after an acute brain insult, such as traumatic brain injury (TBI), ischemic stroke, intracerebral hemorrhage, infection, and prolonged acute symptomatic seizures such as complex febrile seizures or status epilepticus in at least 40% of cases (8). Traumatic brain injury, stroke, drug withdrawal and metabolic insults were reported to be the commonest causes among adults in developed countries by Hauser and Beghi (9). The major causes of acute symptomatic seizure were listed as traumatic brain injury, stroke, drug withdrawal and CNS infections by Annegers et al. (10). CNS infections and stroke were found to be the prominent causes of acute symptomatic seizures in Nwani et al. (11). Causes underlying symptomatic seizures may vary according to the developmental status of the countries. In our series, the most common causal factor was head trauma as in line with previous studies. Powell categorized head injury as mild (<30 min amnesia and no skull fracture), moderate (>30 min amnesia and/or skull fracture) or severe (amnesia >24 h, cerebral contusion or intracranial hematoma) in a previous report (3). We categorized head trauma as minor (<30 min amnesia and no skull fracture) or major head trauma (>30 min amnesia and/or skull fracture and/or intracranial traumatic lesions).

Prenatal/perinatal/postnatal problems were the second most common causes of symptomatic seizures in our study

Table 3. The relationship of the severity of causal factors with pathological electroencephalographic findings

		Severity of causal factors			p
		Group 1 (n=50)	Group 2 (n=33)	Group 3 (n=10)	
Focal slowing in fronto-temporal region	No	34 (68.0)	18 (54.5)	4 (40.0)	**0.190**
	Yes	16 (32.0)	15 (45.5)	6 (60.0)	
Generalized slowing	No	41 (82.0)	24 (72.7)	9 (90.0)	**0.483**
	Yes	9 (18.0)	9 (27.3)	1 (10.0)	
Focal epileptogenic focus	No	18 (36.0)	15 (45.5)	6 (60.0)	**0.315**
	Yes	32 (64.0)	18 (54.5)	4 (40.0)	
Nonspecific paroxysmal activity	No	43 (86.0)	30 (90.9)	10 (100.0)	**0.642**
	Yes	7 (14.0)	3 (9.1)	0	
Generalized epileptogenic activity	No	44 (88.0)	26 (78.8)	9 (90.0)	**0.584**
	Yes	6 (12.0)	7 (21.2)	1 (10.0)	

Fisher Freeman Halton test

population. We obtained this medical past information from patients, parents, care givers, previous medical documents or the medical records of the hospital. We noticed that our patients or their primary care givers might have difficulties in reporting causal factors related to birth history definitely. Prematurity, problems related to delivery, metabolic or systemic problems in the postnatal period, febrile seizures and many other conditions might have been all termed as prenatal/perinatal/postnatal problems. This might explain the high frequency of these pathological conditions in our study population.

The most common radiological finding was encephalomalacia followed by MTS. In the literature, encephalomalacia is described as loss of brain tissue after cerebral infarction, cerebral ischemia, infection, craniocerebral trauma, or other injury. The term "encephalomalacia" is usually used for gross radiological abnormalities and many pathological lesions may be named as encephalomalacia. For this reason, our finding was not surprising because our radiologists also reported sequela lesions related to TBI, brain operations, cerebrovascular diseases as encephalomalacia.

Focal epileptogenic focus and focal slowing were the most common EEG findings in our patients. This was consistent with the profile of causal factors which were expected to produce a focal brain injury like head trauma, MTS, brain operations, congenital malformations, cerebrovascular diseases, tumors, aneurysms or other intracranial lesions.

Our analysis did not reveal any significant difference between the severity of causal factors and radiological or EEG findings. There existed a significant difference only in terms of encephalomalacia. Encephalomalacia was more frequently detected in patients who had more than two causal factors underlying their symptomatic seizures. Seizures in the setting of more than two causes were detected in 14 (10.9%) of our patients. It may be argued that encephalomalacia might be caused by the first or the second insults and the third (the most proximate) insult might have highest potential to produce seizures but it might not be easy to determine the exact intensity of each causal factor. This was why we grouped our patients according to the number of causal factors to predict their severity. In addition, the process of epileptogenesis may take a time to develop and physiological basis of epileptogenesis is not well known (2,12,13,14,15,16,17). Löscher concluded that no latent period was needed to acquire epilepsy and stated that currently it was not known when the brain first became "epileptic" (18).

Study Limitations

There are limitations of this study. First limitation is the small sample size. Secondly, we did not investigate the distribution of causal factors according to different age groups. We rather focused on the identification of the profile of causal factors and the estimation of their severity. Further studies with larger patient population and different age groups may strengthen the profile of symptomatic seizures and may contribute to the clinical management of patients with symptomatic epilepsies.

Conclusion

Acute symptomatic seizures should be differentiated from unprovoked seizures (13). Sometimes, causal factors may not be detected easily and this may lead to difficulties in the diagnosis and classification. Epilepsy in most cases has a multifactorial nature. Developments in EEG, histochemical and radiologic investigations might have big impact on the assignment of the causes of epilepsy. Invasive electrophysiological techniques and developed

neuroimaging modalities might assist in detecting the underlying cause of epilepsy, which could not be found with standard investigations.

The severity or intensity of the causal factors may not be easily evaluated. The number of causal factors may represent the severity of the insult and may have influences on the electro-clinical or radiological findings of the patients. Both the severity and the number of causal factors have importance in the assessment of symptomatic epilepsies. Future trials on the prognosis of symptomatic epilepsies are required for the prediction of the severity of the underlying causes and the type of underlying pathological process.

Ethics

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital of Local Ethics Committee (protocol number: 2021/213).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E.T., V.Y., D.B., F.A., H.Ö., Concept: H.E.T., V.Y., D.B., F.A., H.Ö., Design: H.E.T., V.Y., D.B., F.A., H.Ö., Data Collection or Processing: H.E.T., V.Y., D.B., F.A., H.Ö., Analysis or Interpretation: H.E.T., V.Y., D.B., F.A., H.Ö., Literature Search: H.E.T., V.Y., D.B., F.A., H.Ö., Writing: H.E.T., V.Y., D.B., F.A., H.Ö.

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The Public's Knowledge and Compliance with Preventive Measures Related to COVID-19 in Turkey

Türkiye'de Toplumun COVID-19'a Yönelik Bilgisi ve Önlemlere Uyumu

Şemsi Nur Karabela[1], Nesibe Şimşekoğlu[2], Kürşad Nuri Baydili[2], Cemre Özkanca[2]

[1]*University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey*

[2]*University of Health Sciences, Hamidiye Vocational School of Health Services, İstanbul, Turkey*

ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) which emerged in Wuhan City of China at the end of 2020, on March 11, 2020, was declared as a pandemic by the World Health Organization and the first case was seen in Turkey on the same date. With the declaration of the pandemic and the occurrence of the case in Turkey, information was given on the prevention of the disease through the written and visual media. This study aims to determine how the notifications are received in different target groups and to have an idea about the way to be followed for presenting information in the future epidemic diseases such as COVID-19.

Materials and Methods: This research was carried out between 14.11.2020 and 20.11.2020. A questionnaire consisting of 3 parts was used in the research and 3,094 people were included in the sample. The analysis of the data was carried out using the SPSS 25 package program. The total number of correct answers in the questions asked to the participants was accepted as the person's knowledge level of protection from COVID-19 disease. To determine the compliance levels of the participants, they were asked to score their level of compliance with the measures out of 10. Independent sample t-test and One-Way ANOVA were used to compare knowledge and prevention levels with demographic variables.

Results: It was found that the knowledge level of women, who were under 65 years old, single, with at least university education and living in a village/town, about protection from COVID-19 disease was higher than the other categories belonging to the same variables. In terms of compliance with the measures, it was determined that women, who were 36-50 years old, married, and residing in the city had higher scores.

Conclusion: In our country, it has been determined that the level of knowledge of prevention of COVID-19 disease and the level of compliance with measures differ according to various demographic variables. In raising the awareness of societies in epidemic diseases, considering the gender, age group, marital status, education level, and place of residence of the individuals, it is thought that it is of great importance in terms of epidemic management that it is done to different masses with different methods.

Keywords: COVID-19, coronavirus, pandemic, compliance, attitude

ÖZ

Amaç: 2020 yılının sonlarında Çin'in Wuhan Şehrinde ortaya çıkan Koranavirüs hastalığı-2019 (COVID-19) 11 Mart 2020 Tarihinde, Dünya Sağlık Örgütü tarafından pandemi ilan edilmiştir ve aynı tarihte Türkiye'de de ilk olgu görülmüştür. Pandemi ilanı ve Türkiye'de ilk olgunun görülmesiyle birlikte yazılı ve görsel medya üzerinden hastalıktan korunma ile ilgili bilgilendirmeler yapılmıştır. Yapılan bilgilendirmelerin farklı hedef kitlelerde nasıl karşılık bulduğunu tespit etmeyi amaçlayan bu çalışmayla, COVID-19 gibi ileride ülkemizde meydana gelebilecek salgın hastalıklarda yapılacak bilgilendirmelerde nasıl bir yol izleneceği hakkında fikir sahibi olunması hedeflenmektedir.

Gereç ve Yöntemler: Bu araştırma, 14.11.2020 ile 20.11.2020 tarihleri arasında gerçekleştirilmiştir. Araştırmada 3 bölümden oluşan soru formu kullanılmıştır ve örnekleme 3.094 kişi dahil edilmiştir. Verilerin analizi SPSS 25 paket programı kullanılarak gerçekleştirilmiştir. Katılımcılara yöneltilen sorulardaki toplam doğru sayısı, kişinin COVID-19 hastalığından korunma bilgi düzeyi olarak kabul edilmiştir. Katılımcıların uyum düzeylerini belirlemek için, önlemlere uyum düzeylerini 10 üzerinden puanlamaları istenmiştir. Bilgi ve önlem düzeylerinin demografik değişkenlerle karşılaştırılmasında bağımsız örneklem t-testi ve tek yönlü ANOVA kullanılmıştır.

Address for Correspondence: Nesibe Şimşekoğlu, University of Health Sciences Turkey, University of Health Sciences, Hamidiye Vocational School of Health Services, İstanbul, Turkey

Phone: +90 553 931 97 91 E-mail: nesibe.simsekoglu@sbu.edu.tr **ORCID ID:** orcid.org/0000-0002-6461-7961

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ÖZ

Bulgular: Kadın, 65 yaş altı, bekar, en az üniversite düzeyinde eğitim almış ve köy/kasabada yaşayan katılımcıların COVID-19 hastalığından korunmaya yönelik bilgi düzeyleri aynı değişkenlere ait diğer kategorilere göre daha yüksek bulunmuştur. Önlemlere uyum düzeyleri bakımından ise kadın, 36-50 yaş aralığında, evli ve şehirde ikamet eden katılımcıların daha yüksek puanlara sahip olduğu tespit edilmiştir.

Sonuç: Ülkemizde, COVID-19 hastalığından korunma bilgi düzeyleri ve önlemlere uyum düzeylerinin çeşitli demografik değişkenlere göre farklılık gösterdiği saptanmıştır. Salgın hastalıklarda toplumun bilinçlendirilmesinde; bireylerin cinsiyet, yaş grubu, medeni durum, eğitim düzeyi, yaşadığı yerleşim yeri gibi durumlarının göz önünde bulundurularak, farklı kitlelere farklı yöntemlerin uygulanmasının salgın yönetimi açısından büyük önem taşıdığı düşünülmektedir.

Anahtar Kelimeler: COVID-19, koronavirüs, pandemi, uyum, tutum

Introduction

The Coronavirus disease-2019 (COVID-19) epidemic, which was first seen in the city of Wuhan in China in December 2019, soon became a serious public health problem and was declared a pandemic on March 11, 2020 (1). The first case was seen in Turkey on the same date, and by October 2021, the number of cases exceeded 2 million. Unfortunately, the disease affects individuals' daily lives, working lives, and social and economic development, and threatens their physical and mental health and even their life security (2).

The importance of preventing infection has increased together with the increasing need for intensive care and the increase occurring in the number of deaths. As in all pandemics, until an effective vaccine is made available to the public, the most effective method is to prevent the spread of the effects of COVID-19 disease. To bring the present epidemic under control in Turkey, comprehensive measures have been taken for preventing or reducing infection in vulnerable groups, primarily children, healthcare providers, and the elderly. Among the strategies used, early diagnosis, isolation, supportive treatment, guidance towards correct information sources, reporting, and contact tracing practices are included (3,4,5,6). During the crisis, human knowledge and behaviors are also critical for efforts to bring the epidemic under control. In this regard, educational activities implemented to inform the public are assumed to have an important role. Scientific and reliable information given on time by health authorities will prevent the spread of incorrect information that may appear especially in visual and printed media organs (2,7,8). Since the first days of the pandemic, besides the posters, brochures, and billboards prepared by the Health Ministry of the Turkish Republic, educational materials such as the COVID-19 dictionary and COVID-19 Pandemic Management and Working Directory have been presented to the public and authorities via the internet and updated. With all these practices, it is expected that the individuals who make up society will carry out their responsibilities for preventing the epidemic, implement standard protective measures aiming at hand hygiene and droplet isolation, and warn those around them about this issue (8,9,10).

The public's knowledge levels, protection methods, and compliance with preventive measures related to the disease may differ regionally according to education and traditional value judgments. Determining these differences is important for increasing correct information, enabling changes in attitudes and permanent behavior, and preventing and controlling the pandemic. This study aims to define the public's knowledge levels regarding preventive measures aiming at protection from the disease and to determine and interpret their levels of compliance with these measures during the active struggle with the second wave of COVID-19, which is still in progress.

Material and Methods

Research Design

This research is a descriptive, cross-sectional type of study.

Study Universe and Sample

The study universe consisted of individuals living in Turkey who used the internet and mobile phones. According to the research by the Turkish Statistical Institute (TUIK) into household information technology use, the percentage of individuals using the internet in Turkey is 79% (11). According to the 2019 results of the TUIK address-based population system, the number of individuals who use the internet is estimated to be 63,114,643 (12). To determine the number of individuals who needed to be included in the sample of the research, first of all, a pilot implementation was carried out. Calculations of the data obtained as a result of the pilot implementation were made by substituting them into the formula $n=(\sigma^2 Z^2_{\alpha})/d^2$ (13). As a result of the calculations, it was concluded that it was necessary to include 2,526 individuals in the sample α=0.05; d=0.25; σ=6.41). In the study, responses to the online questionnaire were obtained from 3,200 individuals, and 3,094 of these were considered suitable for statistical evaluation.

Data Collection Tools

A questionnaire form consisting of 3 sections was used in the study. In the first section, personal information questions consisting of 8 items are included. The second section

concerns preventive measures with correct and incorrect options and consists of 27 items aiming at measuring participants' levels of knowledge related to the COVID-19 disease and its prevention (Ad. 1). For some of the preventive measures, the correct answer is the "correct" option, while for the other preventive measures, the correct answer is the "incorrect" option. The reliability of the items intended to measure knowledge levels related to protection from the COVID-19 disease was examined with the Cronbach alpha test, and a coefficient of α=0.863 was found. To determine content validity, the views of 5 different domain experts were obtained. For logical validity, the questions were revised according to the views of the same domain experts. The third section of the questionnaire form includes a question that can be scored on a scale from 1 to 10 and was created to determine individuals' levels of compliance with the preventive measures.

Data Collection

The research data were gathered using an online application and the responses were also recorded via the online system. The data collection was made between the dates 14.11.2020 and 20.11.2020. This period represents the second wave of the pandemic when a high number of cases were seen and the vaccine had not yet arrived in Turkey.

Statistical Analysis

The data analysis was carried out using the SPSS 25 software program. For comparisons made between scale scores and demographic variables and for comparison with scale scores of variables including two categories, independent samples t-test was used. On the other hand, for comparison with scale scores of variables including more than two categories, one-way analysis of variance (One-Way ANOVA) was used. In the case of identifying differences resulting from One-Way analysis of variance, the Bonferroni test post-hoc method was employed to determine which category or categories the differences originated from . A type I error of 0.05 was accepted in the study.

Ethical approval was obtained from the Hamidiye Scientific Research Ethics Committee for the conduct of the study (date and number: 05 May 2020; 46418926-050.03.04). The aim of the research was explained to the volunteers and informed consent for participating in the research was obtained.

Results

When the demographic data obtained from the participants were examined, it was seen that 42.8% (n=1,292) were aged 20-35 years, 64.9% (n=2,009) were women, 65% (n=2,010) were single, 49.5% (n=1,533) were high school graduates, 55.7% (n=1,724) were from the Marmara Region, 61% (n=1,886) lived in big cities, and 87.4% (n=2,703) did not have any chronic diseases (Table 1).

The participants' demographic characteristics were compared regarding their knowledge scores for protection from the COVID-19 disease by using independent samples t-test and one-way analysis of variance (Table 2). As a result of the comparison, it was determined that scores were lower for participants in the group at the age of 65 years and over compared to the other age groups, for male participants

Table 1. Demographic characteristics of the participants

	n	%
Age (years)		
20 and under	995	32.2
Between 20-35	1,292	41.8
Between 36-50	581	18.8
Between 51-64	140	4.5
65 and over	86	2.8
Gender		
Male	1,085	35.1
Female	2,009	64.9
Marital status		
Married	1084	35.0
Single	2,010	65.0
Education status		
Middle school and lower	458	14.8
High school	1,533	49.5
University	929	30.0
Postgraduate	174	5.6
Region		
Mediterranean region	134	4.3
Eastern anatolia region	382	12.3
Aegean region	192	6.2
Southeastern anatolia region	139	4.5
Central anatolia region	225	7.3
Black sea region	298	9.6
Marmara region	1,724	55.7
Residential area		
Greater city area	1,886	61.0
Downtown	562	18.2
District center	493	15.9
Village/Town	153	4.9
Chronic illness		
No	2,703	87.4
Yes	391	12.6

Table 2. Comparison of the demographic characteristics of the participants in terms of their knowledge of protection from COVID-19 disease

Age group (years)		F	p
20 and under	23.07±2.78	248.672	<0.001*
Between 20-35	22.86±2.95		
Between 36-50	22.83±2.46		
Between 51-64	22.41±2.77		
65 and over	11.43±11.34		
Gender		T	p
Male	21.54±5.47	-9.222	<0.001*
Married	23.15±2.37		
Marital status		T	p
The married	21.91±5.07	-6,262	<0.001*
Single	22.95±2.90		
Education status		F	p
Middle school and lower	22.19±3.79	9,141	<0.001*
High school	22.37±4.59		
University	23.03±2.43		
Postgraduate	23.22±2.23		
Residential area		F	p
Greater city area	23.01±2.74	50,206	<0.001*
Downtown	20.84±6.74		
District center	22.89±2.34		
Village/Town	22.83±2.61		
Chronic illness		T	p
No	22.54±3.98	-2,299	0.022
Yes	22.90±2.63		

*p<0.05, COVID-19: Coronavirus disease-2019

compared to females, for married participants compared to single participants, and for participants living in city centers compared to participants living in other areas (p<0.001). On the other hand, it was determined that participants with bachelor's and postgraduate education levels had higher scores than participants who had other levels of education (p<0.001). No significant difference was found in knowledge level scores in terms of the chronic disease status category (p=0.022).

The participants' demographic characteristics were compared regarding their scores for level of compliance with preventive measures taken against the COVID-19 disease by using independent samples t-test and one-way analysis of variance (Table 3), and it was determined that scores were higher for participants aged 36-50 years compared to those aged 20-35 years (p=0.001), for female participants compared to males (p<0.001), for married participants compared to

Table 3. Comparison of the demographic characteristics of the participants in terms of their level of adjustment scores

Age group (years)		F	p
20 and under	8.65±1.48	4.415	0.001*
Between 20-35	8.52±1.50		
Between 36-50	8.79±1.30		
Between 51-64	8.85±1.39		
65 and over	8.52±1.54		
Gender		T	p
Male	8.33±1.61	-8.102	<0.001*
Female	8.79±1.34		
Marital status		T	p
Married	8.78±1.29	4.458	<0.001*
Single	8.55±1.53		
Education status		F	p
Middle school and lower	8.64±1.53	0.026	0.994
High school	8.62±1.44		
University	8.64±1.45		
Postgraduate	8.64±1.48		
Residential area		F	p
Greater city area	8.70±1.42	6.074	<0.001*
Downtown	8.54±1.54		
District center	8.59±1.39		
Village/Town	8.23±1.70		
Chronic illness		T	p
No	8.62±1.43	-1.304	0.192
Yes	8.72±1.63		

*p<0.05

single participants (p<0.001), and for participants living in city centers compared to those living in villages and towns (p<0.001). No significant difference was found in compliance level scores in terms of the chronic disease status (p=0.192) or the education status (p=0.994) categories.

Discussion

In Turkey, notifications about the pandemic began before the pandemic had arrived in the country and continue to be made using audio and visual media and digital platforms. According to the data of the Supreme Board of Radio and Television, television is mostly watched by individuals aged 45 years and over, and it is stated that people aged 50 years and over find health-related television programs to be an important source of information (14,15). According to the TUIK research into household information technology use, while the rate of computer usage during the last three months by people aged 65 years and over was 8.5%, the internet

usage rate was 19.8%. The fact that knowledge levels related to protection from the disease were lowest in the group aged 65 years and over may be due to the limitations such as inability to access up-to-date information by individuals in this age group. According to the January 2020 report by We Are Social and Hootsuite, in terms of social media usage rates, this group represents the smallest population, with the rate of 1% in women and 1.8% in men (16). While social media and other internet tools such as search engines have an inquiry feature, television programs and printed magazines follow a certain flow. In people aged 65 years and over, besides adapting to new information, carrying out new behaviors other than the habits they have acquired may also be difficult. When memory, sight, and hearing faculties are also taken into consideration, this sensitive group may also require repetition of information in audio and visual publications, or retention of this information by their family. In a study examining knowledge and attitudes related to protection from the COVID-19 disease by the Egyptian public, it was similarly reported that knowledge levels in individuals aged 65 years and over were low. It should be recommended that for this age group, more accessible communication tools are used, or that their families behave more responsibly (17).

The volunteers included in this study, in which people's knowledge and compliance levels related to methods of protection from COVID-19 disease were evaluated, were predominantly made up of individuals aged 20-35 years who were female, single, and high school graduates, and who lived in the city. In terms of scores for levels of compliance with preventive measures taken against the disease, it was seen that participants aged 36-50 years had higher scores than participants aged 20-35 years. This situation may be since people in this age group are still active in society, they have more health-related knowledge and experience due to age, and their health and social anxieties increase due to these experiences. Moreover, studies report that the knowledge that mortality is lower in young people decreases their compliance with preventive measures (18). In terms of the age variable, assuming that they are not in the risk group may make individuals think that compliance with preventive measures is unnecessary. According to the results of research examining the levels of compliance related to protection from COVID-19 disease by young participants and males, it was reported that these groups had lower scores than other participants (19,20).

In the study by Pan et al. (21), it was stated that patients' mean age was 56 years and that while the rate of critical cases in diagnosed individuals aged 20-39 years was 12.1%, this rate increased to 41.3% in individuals aged over 80 years (21). Similarly, the mean age of patients included in the study by Li et al. (22) was 59 years. These data support the hypothesis that the prognosis of the disease becomes more severe with age and reveal that intense efforts are required to protect this sensitive group and to prevent the severity of the disease from worsening. In the literature, studies report that among the factors having a positive effect on the levels of compliance with preventive measures aiming at protection from COVID-19 disease are perceived risk, motivation, and high health-related anxiety levels (19,22,23,24). Saurabh and Ranjan (25) determined that levels of knowledge and compliance with preventive measures related to protection from COVID-19 disease in India were low and argued that this situation could be improved by offering financial support for efforts to inform the public about the pandemic, and by enabling the public to access information sources (25).

Several studies that examine society's knowledge and attitude levels regarding the COVID-19 disease support the finding obtained in this study that female participants were in a better position than male participants concerning both knowledge and compliance levels related to protection against the disease (20,26,27,28). The higher levels of compliance in women can be explained by their greater anxieties related to the disease. Indeed, Vesga-López et al. (29) stated that the probability of suffering from an anxiety disorder, which is a psychological illness, was greater in female individuals compared to male individuals (29). Anxiety can assist in avoiding situations that are dangerous to health (30). According to the research by Erdoğdu et al. (31), it was reported that women's anxiety levels towards the COVID-19 disease were higher than men's.

In several studies, it is reported that the Severe Acute Respiratory syndrome-Coronavirus-2, which causes the COVID-19 disease, is caught by both genders, but that mostly males contract the disease (20,32,33,34). The reasons why men are more affected by the pandemic can be explained by the fact that men are more inclined towards risky behavior and more prone to chronic diseases, and that their smoking habits are more common (6,20,21,35). The fact that the disease is more severe in males can be explained by several potential factors, such as the higher expression of the angiotensin-converting enzyme-2 (coronavirus receptors) in men than in women, and gender-based immunological differences and differences due to the X chromosome. It is considered that a part of this difference is due to gender behaviors (lifestyle), that is, that rates of tobacco and alcohol use are higher in men than in women (36). Although it is known that the disease is more mortal in men, in this study, unfortunately, men's knowledge and compliance levels were found to be lower, concerning gender behaviors.

In terms of knowledge and compliance with preventive measures related to protection from the disease, the fact that in the "marital status" variable, single participants had

greater protection knowledge but lower compliance levels than married participants suggests that they were unable to convert their knowledge into behavior. In a study examining knowledge and attitude levels related to the COVID-19 disease in the Chinese public, it was reported that single individuals' knowledge levels were lower (20).

The findings of the study reveal that in terms of education status in Turkey, as expected, participants with bachelor's and postgraduate education had better knowledge about protection from COVID-19 disease. Studies support this finding in the literature (17,20,37). Due to reporting of information about the disease via official sources and effective warnings by healthcare authorities, the effective use of the internet, contract tracing and family practice implementations, protection knowledge scores of participants with bachelor's and postgraduate education were, as expected, higher than those of the others. However, levels of compliance with preventive measures did not differ from those of participants with other education levels.

Our data show that in Turkey, the knowledge levels of participants living in villages and towns were higher, whereas compliance levels of those living in city centers were higher.

Addition 1. Questionnaire Used in the Research

Please tick the "correct" column next to the items that you think as correct, and the "false" column next to the items that you think as incorrect.

Sequence No.	Question	Sequence No.	Question
1	We must wash our hands when entering and leaving the toilet.	15	We should change the surgical mask every 2 hours or when it gets damp/dirty.
2	We should wash our hands after coughing and sneezing.	16	There is no harm in touching the mask while using the mask.
3	We do not need to wash our hands before and after preparing food.	17	It is possible to wash and reuse the masks, their protective properties do not disappear with washing.
4	There is no need to wash our hands after coming from outside.	18	When we have fever, cough, shortness of breath and other cold symptoms, we should apply to the nearest health facility.
5	We must wash our hands for at least 10 seconds.	19	After the trip, we must comply with the 14-day rule by not leaving the house.
6	We should not touch our mouth, nose and eyes with our dirty hands.	20	We need to access information about the coronavirus from reliable sources.
7	When our hands are visibly dirty, it will be sufficient to use an alcohol-based hand sanitizer.	21	While coughing and sneezing, we should cover our mouth and nose with the inside of our elbow or a tissue.
8	We need to wait at least 25-30 seconds for the alcohol-based hand sanitizer to dry.	22	We need to maintain a distance of at least 1.5-2 meters between us and people.
9	We should avoid shaking hands and hugging.	23	There is no harm in using public transport.
10	We need a balanced and healthy diet.	24	There is no harm in using accessories such as rings, earrings and watches.
11	Before consuming raw foods, we need to wash them thoroughly.	25	There is no harm in choosing short-sleeved clothes.
12	We do not need to ventilate our room and common areas frequently.	26	We need to continue our personal hygiene habits.
13	Desk, phone, keyboard etc. There is no need to disinfect our belongings.	27	Bathing with high-temperature water protects people against infection.
14	We do not need to use a surgical mask before leaving the house.		

Rate your level of compliance with the measures related to COVID-19 from 1 to 10. (How much do you sleep within your means? For example, going out due to your commute doesn't mean you don't fit)

1	2	3	4	5	6	7	8	9	10

COVID-19: Coronavirus disease-2019

It is thought that the knowledge of participants living in city centers was affected by different sources of information and that the difference in compliance that was formed could be related to an increase in compliance with compulsory bans and restrictions in crowded areas. Some studies report that knowledge and compliance levels of individuals living in villages or towns related to COVID-19 disease are lower (17,20). In the study by Wolf et al. (18), it was stated that individuals, living in areas where transport to healthcare services was inadequate, believed that they would not catch the COVID-19 disease and that they felt unprepared for the pandemic (18). The fact that those residing in villages and towns had less compliance than those in other settlement areas can be associated with the unfounded confidence they felt to the effect that the pandemic would not reach the area where they lived. Moreover, these results that we obtained are significant in terms of revealing that the correlation between knowledge and compliance with preventive measures can change according to an area of settlement. It is seen that in Turkey, urbanization and marital status are important for the conversion of knowledge into behavior.

In several studies, it is reported that severe COVID-19 patients have additional chronic diseases (32). For this reason, those with chronic diseases must have correct knowledge regarding the protection and pay attention to preventive measures. According to the findings of this study, the presence of the chronic disease did not make a difference compared to those without chronic disease. In the study by Ergün et al. (38), however, levels of compliance with preventive measures were higher in participants who did not have a chronic disease. This situation may stem from the fact that due to protection facilities offered by the state (supply of medicine, communication with family practitioner, exemption from work), those with chronic diseases do not feel the need for extra precautions. Those with chronic diseases should be included as a target group in extra programs related to knowledge and compliance and should possess higher levels of knowledge and compliance than healthy individuals.

Conclusion

In conclusion, levels of knowledge related to protection from the COVID-19 disease were higher in participants who were below the age of 65 years, female, single, and university graduates, and who lived in villages or towns. On the other hand, levels of compliance with preventive measures aiming at protection from the disease were higher in participants who were aged between 36 and 50 years, female, and married, and who lived in the city center. The findings we have obtained reveal that there are differences in levels of knowledge and compliance in society and therefore, information needs to be repeated. It is stated that as people's knowledge levels related to the COVID-19 increase, they display more positive compliance with preventive measures. However, our findings reveal that in some groups in which knowledge levels were high, it could not always be inferred that their compliance levels were also high. It is seen that in Turkey, urbanization and marital status are important for the conversion of knowledge into behavior. Our results may serve as a guide for public health planners and healthcare administrators, especially by serving the purpose of determining groups whose levels of knowledge and compliance are low and of creating COVID-19 training and behavior programs for target groups.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Hamidiye Scientific Research Ethics Committee for the conduct of the study (date and number: 05 May 2020; 46418926-050.03.04).

Informed Consent: Informed consent for participating in the research was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ş.N.K., N.Ş., C.Ö., Design: Ş.N.K., K.N.B., N.Ş., C.Ö., Data Collection or Processing: Ş.N.K., K.N.B., N.Ş., C.Ö., Analysis or Interpretation: Ş.N.K., K.N.B., N.Ş., Literature Search: Ş.N.K., K.N.B., N.Ş., C.Ö., Writing: Ş.N.K., N.Ş., C.Ö.

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Investigation of Myalgia and Related Factors in COVID-19 Quarantine Center Patients- A Retrospective Study

COVID-19 Karantina Merkezi Hastalarında Miyalji ve İlişkili Faktörlerin İncelenmesi-Retrospektif Çalışma

Aysun Özlü[1], Gamze Ünver[2], Hasan Hüseyin Gökpınar[1], Gülsüm Bakçepınar[1], Can Özlü[3]

[1]*Kütahya Health Sciences University Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Kütahya, Turkey*

[2]*Kütahya Health Sciences University Faculty of Medicine, Department of Internal Medicine Nursing, Kütahya, Turkey*

[3]*Kütahya Health Sciences University Faculty of Medicine, Department of Hematology, Kütahya, Turkey*

ABSTRACT

Background: This study was conducted retrospectively to examine myalgia and related factors in patients who did not have the symptoms of illness severe enough to be hospitalized in a quarantine center due to Coronavirus disease-2019 (COVID-19). A retrospective evaluation was performed to examine the relationship between myalgia that started after infection and age, gender, chronic disease, presence of lung involvement and other COVID-19 symptoms such as cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, and fatigue.

Materials and Methods: Four hundred-eighty-seven patients hospitalized in the quarantine center between June 2020 and September 2020 were evaluated. Myalgia, age, gender, chronic disease status (diabetes mellitus, hypertension, cardiac and pulmonary diseases and endocrinological diseases), other COVID-19 related symptoms (cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, fatigue), and radiological findings of COVID-19 infected patients were retrospectively examined. Frequency tables and descriptive statistics were used to interpret the findings.

Results: Myalgia was seen at a rate of 33.3% and lung tomography findings were positive at a rate of 39.6% even in patients infected with COVID-19, who did not require hospitalization. Although myalgia did not seem to be associated with age, gender, and chronic diseases, 64% of patients with myalgia had other COVID-19 related symptoms such as cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, and fatigue.

Conclusion: Symptoms most commonly associated with myalgia include cough, weakness and sore throat. It is important to question other symptoms and monitor lung findings, and to closely follow uppatients who are not hospitalized.

Keywords: Quarantine center, myalgia, COVID-19

ÖZ

Amaç: Bu araştırmada Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu nedeniyle karantina merkezinde kalan hastalarda, serviste ya da yoğun bakımda yatacak kadar ağır hastalık semptomları olmayan, enfekte olduktan sonra başlayan miyalji ve yaş, cinsiyet, kronik hastalık, akciğer tutulumu varlığı ve COVID-19 enfeksiyonunda görülen öksürük, boğaz ağrısı, baş ağrısı, bulantı, ishal, tat/koku kaybı, burun tıkanıklığı, nefes darlığı, halsizlik gibi diğer COVID-19 ilişkili semptomlarla ilişkili faktörlerin incelenmesi amacıyla retrospektif değerlendirme yapılmıştır.

Gereç ve Yöntemler: Karantina merkezinde Haziran-Eylül 2020 tarihleri arasında kalan 487 COVID-19 ile enfekte hastaların, enfekte olduktan sonra başlayan miyaljileri olup olmadığı, yaş, cinsiyet, kronik hastalık durumları (diyabet mellitus, hipertansiyon, kardiyak ve pulmoner hastalıklar ve endokrinolojik hastalıklar), diğer COVID-19 semptomları (öksürük, boğaz ağrısı, baş ağrısı, bulantı, ishal, tat/koku kaybı, burun tıkanıklığı, nefes darlığı, halsizlik) ve radyolojik bulguları retrospektif olarak incelenmiştir. Bulguların yorumlanmasında frekans tabloları ve tanımlayıcı istatistikler kullanılmıştır.

Bulgular: COVID-19'la enfekte hastalarda yeni başlayan miyalji görülme oranı %33,3 olup, akciğer tomografisi bulguları %39,6 oranında pozitiftir. Miyaljili hastaların %64'ünde öksürük, boğaz ağrısı, baş ağrısı, bulantı, ishal, tat/koku kaybı, burun tıkanıklığı, nefes darlığı, halsizlik gibi diğer COVID-19 ilişkili semptomlar görülmektedir. Miyalji ile yaş, cinsiyet ve kronik hastalıklar arasında istatistiksel olarak anlamlı bir ilişki yoktur.

Sonuç: En fazla miyalji ile birlikte görülen semptomlar öksürük, halsizlik ve boğaz ağrısıdır. Hastanede yatarak takip olmayan hastaların da yakından takibi, diğer semptomlarının sorgulanması ve akciğer bulgularının izlenmesi önemlidir.

Anahtar Kelimeler: Karantina merkezi, miyalji, COVID-19

Address for Correspondence: Aysun Özlü, Kütahya Health Sciences University Faculty of Medicine, Department of Physıcal Therapy and Rehabilitation, Kütahya, Turkey
Phone: +90 505 398 94 44 E-mail: aysunozlu35@gmail.com **ORCID ID:** orcid.org/0000-0002-1912-6039

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Introduction

Coronavirus disease-2019 (COVID-19) has a fairly wide clinical spectrum, covering severe acute respiratory syndrome, respiratory failure caused by pneumonia, and even death, with a very high pathogenity and contagion, first identified in Wuhan, China (1). Although symptoms at the onset of the disease vary, the predominant symptoms are fever and cough while gastrointestinal symptoms are rarer. In addition, headache, conjunctival hyperemia, nasal congestion, sore throat, increased secretion, sputum, weakness, hemoptysis, nausea-vomiting, diarrhea, abdominal pain, myalgia, rash, impaired taste, and sense of smell may also be observed in patients (2,3,4).

It may not be necessary to treat patients infected with COVID-19 with mild clinical presentation but without viral pneumonia and hypoxia primarily in hospital, and many patients may be monitored at home. The decision to monitor a patient should be made according to the patient's clinical condition. This decision varies depending on the clinical picture of the disease, the need for supportive care, their chronic illness, and the patient's ability to isolate himself/herself at home. Patients with risk factors for severe disease should be closely monitored, taking into account the risk of progression to a serious disease in sometime after symptoms begin (5). For this purpose, quarantine centers have been established in our country and patient monitoring and clinical course of the disease are evaluated.

Musculoskeletal symptoms are also frequently observed during COVID-19 infection. It is known that 50% of infected people have widespread body pain, 37.5% have myalgia, 5.7% have arthralgia, and 6.8% have back pain (6). From the onset of symptoms and during the most severe stages of COVID-19 disease, musculoskeletal symptoms including myalgia, arthralgia and fatigue are very common complaints although the mechanism of COVID-19 on musculoskeletal system is still unclear (7).

Different opinions on the mechanism of myalgia, one of the most common symptoms, are found in the literature. One is about increased lactate levels due to cell damage (8). While high lactate level reduces the oxygen carrying capacity of erythrocytes to the tissues, it causes hypoxia, and muscle pain may be seen due to low pH. The virus may spread through the blood and endothelium, causing infection in the heart and brain tissues, and therefore the musculoskeletal system may be adversely affected by the infection. Increased creatinine kinase (CK) level during the infection process is evidence of muscle involvement (9).

In a study examining the relationship of myalgia with COVID-19 severity and mortality, it was reported that the presence of myalgia was not associated with the prognosis of the infection (10). Kucuk et al. (9) reported that back pain seen during the COVID-19 process might be related to pneumonia, common myalgia might be longer and more severe than other infectious diseases and would not respond to traditional painkillers. In addition, it was pointed out that the severity of myalgia was possible only when the viral load was reduced with treatment (red blood cell oxygenation increases and muscle lactate level decreases). In the study of Batur et al. (11) it was determined that there was a significant increase in CK level and lymphocyte count in people with myalgia symptoms and hemoglobin levels decreased significantly and D-dimer increased significantly in people with chronic diseases. Therefore, it is recommended that patients should be followed up in terms of myopathic process and other related factors (11).

In this study, it was aimed to examine the patients who did not have symptoms of illness severe enough to be hospitalized, staying in quarantine center due to COVID-19 in terms of myalgia symptom and related factors to obtain results that can contribute to the literature and to provide recommendations that can be used in myalgia management.

Material and Methods

Study Design

The population of the research is the past records of 487 patients who stayed in Physical Therapy Hospital Quarantine Center between June 2020 and September 2020. Ethical and scientific approval was obtained with the decision numbered 2021/04-07 at Kütahya Health Sciences University Clinical Research Ethics Committee Meeting dated 10.03.2021. The data of the study were collected by retrospectively examining the past records to investigate the relationship between myalgia that started after infection and age, gender, chronic disease, presence of lung involvement and other COVID-19 symptoms such as cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, and fatigue seen in the quarantine center during the COVID-19 process.

Clinical Data

The data of the study were collected by retrospectively examining the past records of age, gender, chronic disease status (diabetes mellitus, hypertension, cardiac and pulmonary diseases and endocrinological diseases), radiologic findings and other COVID-19 related symptoms (cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, fatigue) of the patients who were hospitalized in the quarantine center between June 2020 and September 2020. The inclusion criteria were having positive COVID-19 test and having myalgia after positive tests. The

exclusion criteria were having moderate or more symptoms that required hospitalization, having O_2 saturation values of 95% and below, having previous myalgia or musculoskeletal disease pain.

Statistical Analysis

Statistical analysis was performed using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used to interpret the findings. Non-parametric methods were used for the measurement values that were not suitable for the normal distribution. In accordance with non-parametric methods, the "Mann-Whitney U" test (Z-table value) was used to compare the measurement values of two independent groups. The expected Pearson-χ^2 cross tabs were employed to examine the relationship between two qualitative variables.

Results

The findings of our retrospective study are given in the tables below, which we conducted to examine myalgia and related factors in patients staying in the quarantine center during the COVID-19 process. Table 1 shows the number and frequencies patients in terms of the presence of myalgia, gender, computed tomography results, chronic disease, and age.

It was determined that 325 patients (66.7%) did not have myalgia, 274 (56.3%) were male, 294 patients (60.4%) had negative computed tomography (CT) results and 307 (63%) patients did not have a chronic disease (Table 1). The ages of the patients ranged from 10 to 89 years, with an average age of 43 years.

The findings in which the presence of myalgia and related factors were evaluated in the patients are presented in Table 2.

There was no statistically significant relationship between myalgia status and gender, CT and chronic disease status ($p>0.05$). A significant relationship was found between myalgia status and other symptoms ($p<0.05$). It was determined that 277 people without myalgia (85.2%) had no other symptoms, and 105 people with myalgia (64.8%) had other symptoms. Although not statistically significant, the most common symptoms with myalgia were cough, weakness and sore throat. The least common symptom was nasal congestion (Table 2).

Table 1. Descriptive characteristics of patients

Variable (n=487)	n	%
Myalgia		
No	325	66.7
Yes	162	33.3
Gender		
Female	213	43.7
Male	274	56.3
CT		
Positive	193	39.6
Negative	294	60.4
Chronic disease		
No	307	63.0
Yes	180	37.0

CT: Computed tomography

Discussion

In this study, according to the retrospective data, it was determined that the average age of the patients staying in the quarantine center was 43 years, 56.3% were male, and 37% had a chronic disease. In a study conducted in Iran, it was concluded that the median age of 595 COVID-19 patients hospitalized was 55 years, and 401 (67.4%) were male (12). As a result of a study conducted in Italy, it was determined that the average age of the patients was 65 years, 72.9% were male and 56.3% had a chronic disease (13). According to the results of the research, it is understood that the cases are mainly male and approximately half of the cases followed by hospitalization have chronic diseases. In our study, it is predicted that the average age of patients with infected COVID-19 who do not require hospitalization is lower than those who require hospitalization in the literature, but

Table 2. Examination of the relationship between myalgia status and other characteristics

Myalgia Status	No N=325		Yes N=162		Statistical analysis*
	n	%	n	%	
Gender					
Female	147	45.2	66	40.7	χ^2=0.886
Male	178	54.8	96	59.3	p=0.347
CT					
Negative	208	64.0	99	61.1	χ^2=0.387
Positive	117	36.0	63	38.9	p=0.534
Chronic disease					
No	208	64.0	99	61.1	χ^2=0.387
Yes	117	36.0	63	38.9	p=0.534
Other symptoms					
Yes	48	14.8	105	64.8	χ^2=125.667
No	277	85.2	57	35.2	**p=0.000**
Other symptoms**					
Cough	19	38.8	34	29.8	
Sore throat	2	4.1	17	14.9	
Headache	3	6.1	12	10.5	
Nausea	3	6.1	2	1.8	χ^2=116.30
Diarrhea	4	8.2	10	8.8	p=0.107
Taste/smell loss	8	16.3	14	12.2	
Nasal congestion	1	2.0	1	0.9	
Dyspnea	5	10.2	5	4.4	
Weakness	4	8.2	19	16.7	

CT: Computed tomography

hospitalization may be required as age increases. In terms of gender, male dominance in infected patients was found to be compatible with the literature.

According to the findings obtained from our study, it was determined that 33.3% of the patients staying in the quarantine center had myalgia. According to the results of all studies in the systemic review of Mesquita et al. (14) the incidence of myalgia is 16.7%. In the study of Flores-Silva et al. (15) it was reported that myalgia symptom was seen at a rate of 38.5% among 1072 hospitalized patients.

Even after excluding initial clinical signs and pre-existing comorbidities, new symptoms and complications may occur in hospitalized COVID-19 patients (15). By the way, our study is important in terms of determining the incidence of myalgia in infected COVID-19 cases that do not require hospitalization. The presence of chronic diseases, hypertension, cardiovascular disease, diabetes mellitus, chronic lung disease, malignancies, especially hematological, immunosuppressive therapy or disease, organ transplantation, chronic kidney failure, obesity, and smoking can be considered risk factors for mortality based on the literature (1,2,3,5). In a meta-analysis by Wang et al. (16) involving 1,558 patients and six studies in China, chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, and hypertension were found to be the most important independent risk factors, respectively (16). In a subgroup study by Onder et al. (17) consisting of 355 patients who died due to COVID-19, the mean number of pre-existing comorbidities was 2.7, and no underlying comorbidity was found in only three (0.3%) patients. In this respect, the presence of chronic disease in patients infected with COVID-19 is very important in terms of the course of the disease and the clinical condition of the patient.

In our study, it was concluded that myalgia symptom was not related to age, gender and chronic disease, but 64.8% of people with myalgia had other symptoms (cough, sore throat, headache, nausea, diarrhea, loss of taste/smell, nasal congestion, dyspnea, weakness). However, it is important to examine whether there are other symptoms in people with myalgia, which is one of the most common symptoms, besides being followed up in the hospital.

Chest CT plays an important role in the recognition of highly suspicious findings of COVID-19, both typical and atypical (18). The hallmarks of COVID-19 infection on imaging are being bilateral, peripheral ground glass and consolidative pulmonary opacities. It is known that especially 56% of early patients have normal computed tomography findings (19). According to the results of a study conducted in four centers in China, chest CT scans of 121 infected symptomatic patients were reviewed for common CT findings in relation to the time between symptoms, and initial and first CT scan was performed in 36 patients (0-2 days- in early), 33 patients, (3-5 days -in the middle period) and 25 patients (6-12 days- in the late period) (19). In this study, COVID-19 symptoms in the computed tomography results were positive in 39.6% of the cases. In the literature, it has been reported that there is a significant correlation between the degree of pulmonary inflammation determined by CT and the main clinical symptoms and laboratory results (20). In our study, similar to the literature, it was determined that 68.2% of people with COVID-19 symptoms on CT had myalgia and 29.8% of people with myalgia had cough. CT is an important method in the follow-up of the infection process and in determining which phase it is, but it is important not only to depend on the CT results but also to monitor other symptoms in order to prevent possible complications. In a recent article, it is suggested that CT results of patients should be considered for patient-specific comorbidities and other medical conditions (added pneumonia, underlying heart failure or fluid overload, and rheumatologic diseases) (21). It is important to detect the lung involvement of the patients who survive by staying at home during the disease process, without hospitalization. There is a need for more studies that include more patient groups, especially those with moderate pulmonary involvement and who do not require hospitalization, and which can correlate with factors that decrease or increase disease activity.

Study Limitations

In this study, there were patients infected with COVID-19 who stayed in the quarantine center and did not require hospitalization. The presence of myalgia was questioned but the localization of myalgia was not questioned.

In addition, advanced blood tests such as inflammation markers, creatine kinase values, and lactate values that might be associated with myalgia were not evaluated.

Conclusion

According to our retrospective data examined and the findings obtained from the literature, it has been concluded that myalgia is a frequently seen symptom and can be seen together with other symptoms. Myalgia is not associated with chronic diseases, age, and gender, but is associated with other COVID-19 symptoms. The rate of myalgia was seen at a rate of 33.3% and computed lung tomography findings were positive at a rate of 39.6% even in patients infected with COVID-19, who did not require hospitalization. Symptoms most commonly associated with myalgia are cough, weakness and sore throat. It should be kept in mind that there are additional symptoms and lung involvement in patients who do not require hospitalization, and close follow-up is very important for these patients. By the way, this study is the first quarantine center study to retrospectively examine

myalgia and related symptoms in COVID-19 patients who do not require hospitalization.

Ethics

Ethics Committee Approval: This study was obtained with the decision numbered 2021/04-07 at Kütahya Health Sciences University Clinical Research Ethics Committee meeting dated 10.03.2021.

Informed Consent: The study was designed retrospectively.

Peer Review: Externally and internally peer-reviewed

Authorship Contributions

Surgical and medical practice: A.Ö., G.Ü., H.H.G., C.Ö., Concept: A.Ö., G.Ü., H.H.G., C.Ö., G.B., Data collection or Processing: A.Ö., G.Ü., H.H.G., C.Ö., G.B., Literature Search and Writing: A.Ö., G.Ü., H.H.G., C.Ö., G.B.

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Praat-Assisted Nasalance Meter: A Low-Cost Nasalance Measurement System for Evaluation of Nasal Resonance Disorders

Praat Yardımlı Nazalans Ölçer: Nazal Rezonans Bozuklukların Değerlendirilmesinde Kullanılabilecek Düşük Maliyetli Bir Nazalans Ölçüm Sistemi

Mehmet Akif Kılıç[1], Ozan Tüysüz[2], Fatih Mehmet Hanege[2], Ceki Paltura[3]

[1]*University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital, Clinic of ENT, İstanbul, Turkey*

[2]*Istanbul Medeniyet University Faculty of Medicine, Department of Otorhinolaryngology, İstanbul, Turkey*

[3]*Gaziosmanpaşa Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey*

ABSTRACT

Background: This study aimed to introduce a low-cost system measuring nasalance, which can often be performed with high-cost systems, and to present the normative nasalance values for adults using this system.

Materials and Methods: This study included 96 standard native Turkish-speaking literate volunteers who had no hearing and speech problems or nasal obstruction. Nasalance values were measured using the system developed by the principal author, which is called the praat-assisted nasalance meter, using speech materials and related methods.

Results: The participants were 18-65 (average, 33.7) years old. They were divided into three groups according to their age: 18-25, 26-40, and 41-65. A significant difference was found in the nasalance values between the genders. For nearly all speech materials, higher nasalance values were measured in women than in men.

Conclusion: There is no generally accepted rule to ascertain if a speaker's resonance is abnormal according to nasalance values. Therefore, the proposed threshold values should not be considered absolute values but should be decided with perceptual evaluation.

Keywords: Nasal resonance, hypernasality, hyponasality, nasalance

ÖZ

Amaç: Bu çalışmanın amacı, genellikle yüksek maliyetli sistemlerle gerçekleştirilebilen nazalans parametresi ölçümü için kullanılabilecek kendi geliştirdiğimiz düşük maliyetli bir sistemi tanıtmak ve bu sistem kullanılarak erişkinler için belirlenen normatif nazalans değerlerini sunmaktır.

Gereç ve Yöntemler: Standart Türkiye Türkçesi konuşan ve okuma yazma bilen 96 gönüllü çalışmaya dahil edildi. Deneklerin işitme ve konuşma problemi, burun tıkanıklığı yapan herhangi bir hastalığının olmamasına dikkat edildi. Birinci yazar tarafından geliştirilen ve Praat Yardımlı Nazalans Ölçer (PYNÖ) adı verilen sistem yardımıyla aşağıda belirtilen konuşma malzemesi ve yöntem kullanılarak nazalans ölçümü yapıldı.

Bulgular: Çalışmaya katılan 96 konuşmacının yaşları 18 ile 65 arasında değişiyordu (ortalama 33,7 yıl). Katılımcılar yaşlarına göre 18-25, 26-40 ve 41-65 şeklinde üç gruba ayrılarak incelendi. Elde edilen değerler cinsiyet grubuna göre karşılaştırıldığında aradaki farkların istatistiksel olarak anlamlı olduğu görüldü. Hemen her konuşma malzemesi için kadınlarda erkeklerden daha yüksek nazalans değerleri elde edildi.

Sonuç: Bir konuşmacı üzerinde ölçülen nazalans ölçüm sonuçlarının anormal olduğunu söylemek için genel kabul gören bir kural yoktur. Bu nedenle, bu çalışmada önerilen eşik değerler mutlak değerler olarak düşünülmemeli, algısal değerlendirmeyle birlikte karar verilmelidir.

Anahtar Kelimeler: Nazal rezonans, hipernazalite, hiponazalite, nazalans

Address for Correspondence: Mehmet Akif Kılıç, University of Health Sciences Turkey, İstanbul Ümraniye Training and Research Hospital, Clinic of ENT, İstanbul, Turkey
Phone: +90 532 316 01 84 E-mail: makilic@yahoo.com **ORCID ID:** orcid.org/0000-0003-0706-7032

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Introduction

Resonance is changing the frequency spectrum of the waves (particularly aerodynamic and acoustic ones) applied to an object or space; amplitude increases in some frequency regions and decreases in others.

As regards speech production, resonance is the change in the vocal tract of the source that occurs at the glottic level. In addition to determining the personal characteristics of the voice, resonation has an effect on the articulation of speech sounds, especially vowels. Resonance in the vocal tract is determined by the shape and size of the pharyngeal, oral, and nasal cavities, conditions of the mucous membrane covering the inner surface of these cavities, and tonus of the surrounding muscles. Problems with each of these cavities or changing of oral-nasal balance due to dysfunction or malfunction of the velopharyngeal valve will cause abnormal resonation. Resonance disorders are classified as nasal resonance disorders and oropharyngeal (oral and pharyngeal) resonance disorders (1).

Nasal resonance disorders, such as hypernasality, hyponasality, and mixed nasality, are important clinical conditions because of their potential association with morbidity. Hypernasality may be a consequence of velopharyngeal dysfunction or oronasal fistula, which may be or not accompanied by nasal air emission. Hyponasality is generally caused by nasal cavity obstruction (such as space-occupying lesions of the nasal cavity or nasopharynx, structural stenosis, and mucosal edema), or rarely by velopharyngeal malfunction. By contrast, mixed nasality is usually seen in a narrow but unchanging velopharyngeal port. Hypernasality is perceived during the production of vowels and voiced oral consonants, and hyponasality is perceived during the production of nasal consonants and adjacent vowels.

Evaluation of Nasal Resonance Disorders

Formant frequencies and bandwidths of the vowels, first and second nasal formant amplitudes (P0 and P1), acoustic parameters such as A1-P0, A1-P1, and voice low tone to high tone ratio, and nasalance are used to assess nasality (1,2,3). Nasalance is the most reliable parameter to assess nasality and it is measured by the ratio of nasal-derived energy emerging during speech to oral/laryngeal energy.

$$Nasalance = \frac{Nasal\ acoustic\ energy}{Nasal + Oral\ acoustic\ energy} \times 100$$

For nasalance measurement, energy recording is made in three ways: acoustic, mechanoacoustic, and aerodynamic. In the acoustic method, which is the most widely used one, the nasal and oral sound pressure levels are recorded using a dual-headed stereo microphone. In the mechanoacoustic method, vibrations are recorded with accelerometers placed on the nose wings and larynx. In the aerodynamic method, the volume speed and pressure of air coming out of the nose and mouth are measured using special masks and sensors (4).

Acoustic nasalance measurements can be carried out with the software/hardware systems originally developed by Fletcher and Bishop (5) and currently produced by Pentax Medical (Nasometer), Tiger DRS, Inc. (Nasal View), Glottal Enterprises (NAS System), and Wevosys (lingWAVES Nasality). The hardware of these devices consists of two microphones mounted on a separator plate and head attachments to keep them in a horizontal position on the upper lip, or handle to hold it manually, and an audio interface that allows computer processing by turning sound pressure signals into numeric data.

Sound pressure signals are amplified before being processed on the computer (preamplification), and the band is filtered with a band-pass filter. Then, the nasalance value is derived by calculating the ratio of nasal and oral energy according to the aforementioned formula. Since measurement results can be affected by various factors, it is not possible to provide a universal nasalance value that shows the physiological pathological limit. Measurement results can be affected by the hardware/software features, calibration of the system used, hardware-speaker relationship that changes depending on the anatomical characteristics of the speaker or user, recording environment, physiological characteristics of the speaker, language/dialect spoken, and speech material.

With the background above, this study aimed to introduce a low-cost system measuring nasalance, which can often be performed with high-cost systems, and to present the normative nasalance values determined for adults using this system.

Material and Methods

Subjects

The study included 96 standard native Turkish-speaking literate volunteers aged 18-65 years (38 male, 58 female), who had no hearing and speech problems or nasal obstruction. Nasalance values were measured using the system developed by the principal author, which is called the praat-assisted nasalance meter (PANM), using the speech materials and methods specified below. This study was approved by İstanbul Medeniyet University Hospital, Scientific Research Ethics Committee (2018/0312). An informed consent form was obtained from all patients.

PANM

PANM consists of hardware and software similar to other systems measuring nasalance. The hardware has four parts, namely, (1) separator plate, (2) earbuds functioning as microphones, (3) handle, and (4) audio interface (Figure 1).

1. Separator plate: It functions by separating signals coming out of the nose and mouth. A participant holds a PANM device above the vermillion border (Figure 2). It was made by 3 mm-thick plexiglass sheet, using a computer numerical control cutting machine through the real-sized drawing file found at https://bit.ly/2UWjzwl.

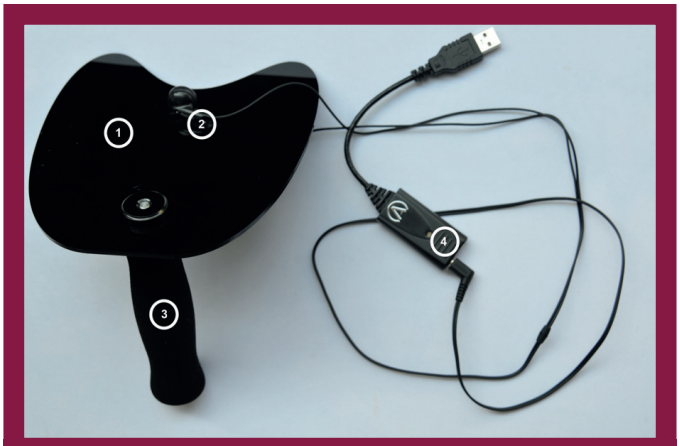

Figure 1. Praat-Assisted Nasalance Meter hardware: (1) Separator plate, (2) Earbuds (left/nasal channel), (3) Handle and thumb nut, (4) Audio interface

Figure 2. A participant holding a Praat-Assisted Nasalance Meter device above the vermillion border. The edge that comes into contact with the upper lip is concave so that there is no gap in between. There is a small line showing the middle line with an oval hole 21 mm away from this edge so that microphones can be easily placed in the appropriate position. The second hole at the other end of the plate with a diameter of 7 mm is for the handle to be mounted.

2. Earbuds: Dynamic headphones function as dynamic microphones when they are connected to the audio interface through the microphone input (6). Philips SHE1350 (Koninklijke Philips Electronics N.V., Netherlands) earbuds were used instead of microphones for audio recording to reduce costs and were glued on to the separator plate placed 20 mm away from the concave edge in a way that the left channel was placed above and right channel was placed below. Instead of the Philips SHE1350, other earbuds with a diaphragm diameter of approximately 15 mm and a resistance of 32 Ω can also be used.

3. Handle and thumb nut: They are mounted on the separator plate by the round hole on it to make it easier to hold the hardware.

4. Audio interface: Andrea USB-SA (Andrea Communications, USA) audio interface was preferred because it allows stereo audio recording, and it can attach to the 3.5 mm TRS microphone input without requiring an adapter.

The software side of PANM consists of the Praat (7) (free software for acoustic analyses) and the script written for it. This script and the customized Praat software, with which it is embedded, can be accessed at https://bit.ly/2Xt6o8x.

Speech Material

The speech material recommended by Oguzhan (8) for Turkish was modified and used in this study. The display of the speech materials in Turkish alphabet was provided in two angle brackets, while the representation in International Phonetic Alphabet was provided in two square brackets.

Isolated Speech Sounds:

1. Prolonged ⟨m⟩ consonant, [mːːː]
2. Prolonged ⟨ɑ⟩ vowel, [aːːː]

Words (in a carrier sentence ⟨Ahmet …. dedi⟩):

1. The bilabial nasal consonant in the [ɑ] vowel context: ⟨ama⟩, [ɑmɑ] (pre- or post-nasal consonantal vowel)
2. The dental nasal consonant in the [ɑ] vowel context: ⟨ana⟩, [ɑnɑ]

Nasalance values were measured over 1/3 mid-region of the pre- (PreV) and post-consonantal vowels in the neighboring of both nasal consonants (PostV). In the text, the abbreviation PV refers to both PreV and PostV.

Sentences:

1. The Oral Plosive Sentence (OPS): ⟨Petek, kırık tahta kapıyı kapattı.⟩, [pɛtɛc kɯɾɯk tahtɑ kɑpɯjɯ kɑpɑtːɯ]
2. The Oral Sibilant Sentence (OSS): ⟨Seçil, sıcak havuzda

sessizce yüzdü.⟩, [sɛʧil swɑʤak havuzda sɛs:izdʒɛ jyzdy]

3. The Nasal Sentence (NS): ⟨Annem, Emine'ye ninni mırıldandı.⟩, [an:ɛm eminɛjɛ nin:i mɯrɯłdandɯ]

4. The Standard Reading Passage (SRP): ⟨Dar kapısından başka aydınlık girecek hiçbir yeri olmayan dükkanında, tek başına, gece gündüz, kıvılcımlar saçarak çalışan Koca Ali, tıpkı kafese konmuş terbiyeli bir aslanı andırıyordu.⟩, [dɑɪ kɑpɯsɯndɑn bɑʃkɑ ɑjdɯnłɯk ʝirɛʤɛc hiʧ bɪɹ jɛɾi ołmɑjɑn dyc:ɑnɯndɑ tɛc bɑʃɯnɑ ʝedʒɛ ʝyndyz kɯvɯłʤɯmłɑɪ sɑʧɑrɑk ʧɑłɯʃɑn kɔʤɑ ali tɯpkɯ kɑfɛsɛ kɔnmuʃ tɛrbijɛli bɪɹ ɑsłɑnɯ ɑndɯrɯjɔɪdu]

Calibration

For accurate measurements with PANM, the recording sensitivity and frequency response of both channels of the microphone must be equal or very close to each other. Therefore, before the microphones (earbuds) are glued to the separator sheet, audio recording is carried out using SRP, while both head of the earbuds are held at an equal distance from the lips (2-3 cm). Nasalance values measured as described below on the recording are expected to be between 45% and 55%. If values exceeding these limits are obtained, microphones should not be used in the PANM assembly.

After the installation of PANM is completed, the following operations are performed respectively.

1. Three recordings are performed on the same speaker using prolonged ⟨m⟩ consonant and OPS by the nose pinched by fingers.

2. Then, the separator plate is reversed, replacing the microphones, and recording is repeated.

3. Nasalance measurement is made on the recordings. When analyzing recordings obtained with the reversed plate, the nose and mouth channels should be interchanged on the form.

4. Nasalance values should be higher than 90% for the prolonged⟨m⟩consonant and lower than 10% for the OPS.

5. The difference between the initial measurement results and measurements made after the microphones are replaced must be lower than 5%.

Measurements

After the PANM was placed horizontally on the upper lip's vermillion border of the speaker sitting upright, the speaker was asked to utter the above-mentioned speech material. Using Audacity (9) software, signals from the nose were recorded in the left channel and signals from the mouth were recorded in the right channel in stereo. During recording, the amplitude of sound waves was not lower than −35 dBFS, and they were not allowed to exceed −3 dBFS, except for oral plosives. Audio files were opened in the Praat software to mark the location of the speech materials; TextGrid files were created and saved. Using the PANM script, nasalance values were measured separately for each material. Isolated speech sounds and sentences were segmented in one piece, and single measurements were made for each piece. Segmentation of the words was performed at the speech sound (vowel before the nasal consonant, vowel after the nasal consonant) level. On the form of the script, the "tpnum" value was selected as 3, and three separate measurements were made for each segment, i.e., initial, middle, and final.

Statistics Analysis

SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine whether data distribution was normal. Gender and age groups were compared using a t-test or Mann-Whitney U test, depending on the data distribution (normal or not normal). A p-value of <0.05 was considered significant.

Results

The average age of the 96 participants (38 male, 58 female) was 33.7 years. The speakers were divided into three age groups: 18-25, 26-40, and 41-65 groups.

A significant difference was found in the nasalance values between the genders. Women had higher nasalance values for almost every speaking material than men had. Although comparisons by age groups showed a difference between some speech materials, it was not included in the evaluation to avoid complexity. Nasalance values measured without gender discrimination are shown in Table 1, and nasalance values measured by gender discrimination are shown in Table 2 and 3.

Determination of Border Values

Normonasality-hypernasality values were determined by adding twice the standard deviation (SD) to mean nasalance values of speech materials used for determining hypernasality, and hyponasality-normonasality border values were determined by subtracting twice the SD from mean nasalance values of speech materials used to determine hyponasality. This method is similar to the Kummer's method but is slightly different. Kummer (10) used standard deviation when determining the threshold value for simplified nasometric evaluation procedure test and accepted 2 SD above the average value for oral speech material and 1 SD below nasal speech material as a threshold value.

According to values obtained without gender

discrimination, nasalance values of >27% for OPS, >46% for OSS, >67% for SRP, and >75% for PV were considered hypernasality. By contrast, values of <64% for NS, <24% for SRP, and <25% for PV were considered hyponasality. To suggest more memorable values, values higher than 25% for OPS and 45% for OSS are considered hypernasality, and values lower than 65% for NS are considered hyponasality (Table 4).

Table 1. Identifying the statistical results of nasalance values measured without gender discrimination

Purpose	Material	M	SD	Min	Max
Calibration	NC- OPS	2.7	1.7	0.7	8.2
	[m:::]	96.6	2.3	90.2	99.7
Hypernasality	OPS	12.8	7.1	3.7	39.1
	OSS	23.4	11.2	6.2	54.7
Hyponasality	NS	76.4	6.4	61.7	89.6
Hypernasality/ hyponasality	SRP	45.5	10.6	23.0	68.3
	PreV	50.1	13.0	14.9	82.8
	PostV	49.3	12.0	23.4	78.8

M: Mean, SD: Standard deviation, Min: Minimum value, Max: Maximum value, (NC-OPS: Nose-closed oral plosive sentence, [m:::]: Prolonged <m> consonant, OPS: Oral plosive sentence, OSS: Oral sibilant sentence, NS: Nasal sentence, SRP: Standard reading passage, PreV: 1/3 mid-region section of the vowel [ɑ] before the consonant in the nasal word, PostV: 1/3 mid-region of the vowel [ɑ] after the consonant in the nasal word

Table 2. Identifying the statistical results of nasalance values measured in women

Purpose	Material	M	SD	Min	Max
Calibration	NC- OPS	2.4	1.7	0.7	8.2
	[m:::]	97.2	1.9	92.3	99.7
Hypernasality	OPS	15.1	7.7	3.7	39.1
	OSS	27.4	11.1	11.6	54.7
Hyponasality	NS	78.7	6.1	63.9	89.6
Hypernasality/ hyponasality	SRP	50.0	10.2	25.2	68.3
	PreV	52.3	13.6	18.6	83.0
	PostV	51.9	12.1	25.4	78.8

M: Mean, SD: Standard deviation, Min: Minimum value, Max: Maximum value. (NC-OPS: Nose-closed oral plosive sentence, [m:::]: Prolonged ⟨m⟩ consonant, OPS: Oral plosive sentence, OSS: Oral sibilant sentence, NS: Nasal sentence, SRP: Standard reading passage, PreV: 1/3 mid-region section of the vowel [ɑ] before the consonant in the nasal word, PostV: 1/3 mid-region of the vowel [ɑ] after the consonant in the nasal word

Table 3. Identifying statistical results of nasalance values measured in men

Purpose	Material	M	SD	Min	Max
Calibration	NC- OPS	3.0	1.7	0.8	6.7
	[m:::]	95.8	2.6	90.2	99.7
Hypernasality	OPS	9.8	4.9	3.7	25.9
	OSS	18.1	8.9	6.2	37.1
Hyponasality	NS	73.3	5.3	61.7	83.6
Hypernasality/ hyponasality	SRP	39.7	8.2	23.0	52.2
	PreV	46.9	11.3	14.9	69.9
	PostV	45.4	10.7	23.4	68.8

M: Mean, SD: Standard deviation, Min: Minimum value, Max: Maximum value. (NC-OPS: Nose-closed oral plosive sentence, [m:::]: Prolonged ⟨m⟩ consonant, OPS: Oral plosive sentence, OSS: Oral sibilant sentence, NS: Nasal sentence, SRP: Standard reading passage, PreV: 1/3 mid-region section of the vowel [ɑ] before the consonant in the nasal word, PostV: 1/3 mid-region of the vowel [ɑ] after the consonant in the nasal word

Table 4. Average, standard deviation and cut-off values of nasalance values measured without gender discrimination

Purpose	Material	M	SD	M - 2×SS	M + 2×SS
Hypernasality	OPS	12.8	7.1	-1.4	27
	OSS	23.4	11.2	1	45.8
Hyponasality	NS	76.4	6.4	63.6	89.2
Hypernasality/ hyponasality	SRP	45.5	10.6	24.3	66.7
	PV	49.7	12.5	24.7	74.7

OPS: Oral plosive sentence: OSS: Oral sibilant sentence: NS: Nasal sentence: SRP: Standard reading passage: PreV and PostV values in the preceding tables are combined because they are close together. Pay attention to the values in the columns of M + 2×SD for the hypernasality group: values in the M - 2×SD columns for the hyponasality group, and the values in both columns for the hypernasality/hyponasality group. PV, PreV and PostV together

Discussion

Subjective (perceptual) and objective (instrumental) evaluation methods are used in the evaluation of nasal resonance disorders, as in voice disorders. Subjective evaluation is very difficult to standardize, while it yields reliable results when performed with well-trained ears.

In practice, although the level of nasal resonance disorder is misinterpreted, situations in which hypernasality is interpreted as hyponasaltity or hyponasality as hypernasality are frequently encountered. Therefore, in the evaluation of patients who are thought to have a nasal resonance disorder, objective methods such as nasalance measurement must be used and a decision should not be made using a single method.

As mentioned in the introduction, nasalance values are affected by various factors. The normative values set for one device do not apply to another device. Therefore,

separate standardization work is required for each device. Awan and Virani (11) noted possible significant differences even between two versions of the system produced by the same company. Changing any component of the PANM used in this study (e.g., the earbuds used as a microphone) will affect nasalance values naturally.

Considering other factors such as recording environment, language, and dialect, a normative assessment work on a small group before using a newly acquired nasalance meter device on patients could be the right approach. In this way, the speech material used in the study with the language/dialect spoken in the hinterland of that clinic should be tested as well. Other factors, such as gender and age, can also affect nasalance. Studies have reported higher values in women than in men besides those reporting no difference between genders (12,13,14). Since this study was carried out to introduce a newly developed device and to determine normative values related to it, the differences were not emphasized.

In this study, the borders between normonasality and hypernasality, and hyponasality and normonasality were determined 2 SD above the mean value for oral speech material and 2 SD below the mean value for nasal speech material. However, a wide gray area exists between normal and abnormal nasal resonance, so it is difficult to determine a clear nasalance threshold value.

Conclusion

There is no generally accepted rule to ascertain that a speaker's resonance is abnormal based on nasalance values. Therefore, the proposed threshold values should not be considered absolute values but should be decided with perceptual evaluation. For every clinician (a physician or speech therapist), acquiring a new nasalance measurement system on a small group of subjects would be of great benefit to determine individual normative values.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Medeniyet University Hospital, Scientific Research Ethics Committee (2018/0312).

Informed Consent: An informed consent form was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Additional Diagnostic Findings in Acute Appendicitis in Children: Splenomegaly and Mesenteric Lymph Node Enlargement

Çocuklarda Akut Apandisitte Yardımcı Tanı Bulguları: Splenomegali ve Mezenterik Lenf Nodu Büyümesi

Saliha Çıracı

Sakarya University Training and Research Hospital, Clinic of Radiology, Sakarya, Turkey

ABSTRACT

Background: Ultrasonography is an effective diagnostic tool for appendicitis in children. Additional findings such as fatty tissue changes and free fluid are particularly relevant in cases with poor visualization of the appendix. We aimed to investigate splenomegaly and the increase in number and size of mesenteric lymph nodes in acute appendicitis.

Materials and Methods: Because ultrasonography is operator-dependent, and subjective since it is performed by different operators under emergency conditions, we designed this study to re-examine computed tomography studies. In this retrospective study, abdominal tomography scans of 150 children, 75 of whom were diagnosed with acute appendicitis and 75 of whom were in the control group, were evaluated. The number of mesenteric lymph nodes with a short-axis diameter measuring 4-8 mm, exceeding 8 mm, splenic long axis and splenic index were recorded.

Results: Splenic long axis, splenic index and the number of lymph nodes measuring 4-8 mm and exceeding 8 mm were greater in the appendicitis-positive group than in the control group (respectively 107±14 vs. 100±13.0 mm, 276±93 vs. 229±78 cm^3, 4±2.6 vs. 2±2.4 and 1±1.1 vs. 0.2±0.6; p<0.01). Lymph node positivity measuring 4-8 mm, exceeding 8 mm and splenomegaly percentages were 85%, 40%, 19% in the appendicitis group and 52%, 16%, 6.7% in the control group, respectively. The sensitivity/specificity of lymph nodes measuring 4-8 mm, lymph nodes >8 mm and splenomegaly for acute appendicitis were 85%/48%, 40%/84% and 21%/93%, respectively.

Conclusion: Splenic enlargement and increased lymph node number/size may help to diagnose acute appendicitis in equivocal cases where the appendix cannot be visualized.

Keywords: Appendicitis, splenomegaly, spleen, lymph node, computed tomography

ÖZ

Amaç: Çocuklarda apandisit tanısında ultrasonografi etkili bir tanı aracıdır. Apendiksin görüntülenemediği olgularda yağlı doku değişiklikleri, sıvı gibi ek bulgular önem kazanmaktadır. Akut apandisitte splenomegali ve mezenterik lenf nodu sayı ve boyut artışını araştırmayı amaçladık.

Gereç ve Yöntemler: Ultrasonografinin operatör bağımlı olması ve incelemelerin acil şartlarda farklı operatörler tarafından yapılması nedeniyle çalışmayı bilgisayarlı tomografi incelemelerini retrospektif değerlendirmek şeklinde planladık. Bu retrospektif çalışmada, 75'i akut apandisit ve 75'i kontrol grubunda olmak üzere 150 çocuğun abdomen tomografileri değerlendirildi. Kısa çapı 4-8 mm ölçülen lenf nodu sayısı, kısa çapı 8 mm'yi geçen lenf nodu sayısı, dalak uzun boyutu ve splenik indeks not edildi.

Bulgular: Apandisit pozitif grubun dalak uzun aksı, splenik indeks, 4-8 mm ölçülen lenf nodu ve >8mm ölçülen lenf nodu sayısı kontrol grubundan yüksekti (sırasıyla 107±14 vs. 100±13,0 mm, 276±93 vs. 229±78 cm^3, 4±2,6 vs. 2±2,4 ve 1±1,1 vs. 0,2±0,6; p<0,01). Çapı 4-8 mm ölçülen lenf nodu >8mm ölçülen lenf nodu ve splenomegali yüzdesi sırasıyla apandisit pozitif grupta 85%, 40%, 19% ve kontrol grubunda 52%, 16%, 6,7% idi. Çapı 4-8 mm ölçülen lenf nodu >8mm ölçülen lenf nodu ve splenomegali pozitifliğinin apandisit için sensitivite/spesifisitesi sırasıyla 85%/48%, 40%/84% ve 21%/93% idi.

Sonuç: Akut apandisit tanısında apendiksin gösterilemediği şüpheli olgularda dalak büyümesi ve lenf nodu sayı/ boyut artışı ek bulgu olarak tanıya yardımcı olabilir.

Anahtar Kelimeler: Apandisit, splenomegali, dalak, lenf nodu, bilgisayarlı tomografi

Address for Correspondence: Saliha Çıracı, Sakarya University Training and Research Hospital, Clinic of Radiology, Sakarya, Turkey
Phone: +90 506 367 24 36 E-mail: atasaliha@hotmail.com **ORCID ID:** orcid.org/0000-0002-3680-9368
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Introduction

Acute appendicitis is the most common surgical emergency in children, which peaks especially in teenagers. Although it may be seen in all age groups, it is rare in infants (1,2). Children present with variable clinical symptoms such as pain, nausea, vomiting, and loss of appetite. History and physical examination are important steps in the diagnosis of acute appendicitis in children (2). Appendicitis scoring systems such as the Alvarado score and pediatric appendicitis score (PAS) can be used to diagnose appendicitis (3,4).

Ultrasonography (US) is an effective diagnostic tool for appendicitis with a sensitivity above 85% and a specificity above 90%. The sonographic criteria include a non-compressed, non-peristaltic appendix with a diameter of 6 mm or greater and an edematous wall. Other ancillary signs include fatty tissue changes around the appendix, mesenteric lymph node enlargement, free fluid, and collection (5). Inability to visualize the appendix and operator dependence are the disadvantages of US (6).

Computed tomography (CT) can also be used to diagnose acute appendicitis. Compared to US, CT is more specific and sensitive for appendicitis. However, due to the radiation exposure risk, it should be performed in equivocal cases (2).

Additional findings such as fatty tissue changes, free fluid, and mesenteric lymph node enlargement are particularly relevant in cases with poor visualization of the appendix. These findings detected on ultrasound may be helpful for decision making on CT scan in equivocal cases. There are few studies showing the relationship between mesenteric lymph node enlargement and appendicitis but they have both enrolled an insufficient number of patients and provided rough data or have not specified the values taken as a basis for evaluating lymph node enlargement (7,8,9,10). In short, there is no comprehensive study evaluating the increase of lymph node number and size in acute appendicitis. We have not come across any study in the literature that has evaluated splenic size or reported splenomegaly in acute appendicitis.

This study aimed to investigate the increase in splenic size, splenomegaly, and the increase in number and size of mesenteric lymph nodes in acute appendicitis.

Material and Methods

This retrospective study was approved by the Ethics committee of Sakarya University (approval date: 01.12.2020, approval number: E.10771). We retrospectively reviewed the CT images of patients presenting with abdominal pain between January 2016 and December 2020, who were evaluated with CT due to vague clinical signs and the inability to visualize the appendix on US, and whose diagnosis of appendicitis was confirmed at surgery. Patients with stable clinical signs who were evaluated with contrast-enhanced CT due to trauma but found to have no parenchymal organ injury or other organ injuries/bleeding during the same period were enrolled as the control group and their CT images were also retrospectively evaluated. The past clinical findings of the patient and control groups were reviewed. The exclusion criteria included infectious-inflammatory diseases, obesity, diabetes, and other acute and chronic disorders that might affect splenic size and size/number of lymph nodes.

The patients' IV contrast-enhanced abdominal CT images scanned with a 16 MDCT device (Toshiba Alexion, Ōtawara, Japan) with a scan thickness of 5 mm were evaluated.

A dilated appendicitis (>6 mm), thickening of the appendiceal wall (>1 mm), and contrast enhancement are diagnostic findings of appendicitis on CT examination (2). Appendix diameter and wall thickness were measured for each group. In our study, mesenteric lymph nodes with a short-axis diameter smaller than 4 mm were not taken into consideration. Lymph nodes were divided into two groups according to short axis diameter of 4-8 mm and ⩾8 mm (8,11). The number of lymph nodes with a short-axis diameter measuring 4-8 mm, the number of lymph nodes with a short-axis diameter exceeding 8 mm, and the total number of lymph nodes were recorded for each patient.

The splenic size was measured in three dimensions (craniocaudal, anteroposterior, and transverse). The splenic index was calculated using the formula: S Vol=30 + 0.58 (W × L × Th) for each patient (12). Splenic long axis dimensions were evaluated for splenomegaly by age group.

Splenic size is correlated to height, weight, and waist circumference (13). The patients' height and weight measurements at the time of imaging could not be accessed. However, each patient's waist circumference was measured and recorded during the time of the CT studies.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 25 IBM Software. Numerical variables were reported as mean and standard deviation and categorical variables as numbers and percentages. The Mann-Whitney U test was used to compare numerical variables between two independent groups, and the chi-square test was used to compare categorical variables. Correlation analyses of parametric and non-parametric variables were performed with the Pearson's correlation analysis and Spearman's correlation analysis, respectively.

Results

Seventy-five patients who were operated on for acute appendicitis were enrolled as the patient group and 75

children who were imaged with CT after trauma as the control group. An analysis of the study groups regarding their waist circumference showed no significant difference between the appendicitis-positive patients and the control group (p>0.05). Similarly, there was no significant difference between the two groups in terms of sex distribution and age (p>0.05) (Table 1).

Appendicitis and control groups were significantly different regarding appendiceal wall diameter, wall thickness, splenic long axis, and splenic index (Table 2). Appendix diameter and wall thickness were significantly greater in the appendicitis-positive group than in the control group (9.6±2.6 vs. 4.5±0.7 mm, respectively and 2.2±0.4 vs. 1.0±0.2 mm, respectively; p<0.0001 for both comparisons) (Figure 1). Splenic long axis and splenic index were significantly greater in the appendicitis-positive group than in the control group (107±14 vs. 100±13.0 mm, respectively and 276±93 vs. 229±78 cm^3, respectively; p=0.0075 and p=0.0016 respectively) (Figure 2). The appendicitis-positive group had a much higher number of mesenteric lymph node measuring 4-8 mm and exceeding 8 mm than the controls (4±2.6 vs. 2±2.4, respectively and 1±1.1 vs. 0.2±0.6, respectively; p=0.0003 and p=0.0049 respectively). Similarly, the total number of lymph nodes of the appendicitis-positive group was significantly higher than that of the control group (4±3.4 vs. 2±2.9; p<0.001) (Figure 3).

Sixty-four (85%) patients in the appendicitis-positive group and 39 (52%) children in the control group had lymph nodes with a diameter exceeding 4 mm. Thirty (40%) patients with acute appendicitis and 12 (16%) control subjects had lymph nodes with a diameter exceeding 8 mm. There was

Table 1. Comparison of the demographic structures of patients with appendicitis and control group

	Patients with appendicitis	Control group	p
Gender, F (%) M (%)	 24 (32) 51 (68)	 24 (32) 51 (68)	1,000
Age, year	14±4.20 16 (3-18)	14±4.16 16 (3-18)	0.757
WC, cm	75.4±14.0 74.3 (44-106)	74.4±13.3 72.2 (51.2-112.6)	0.583

Non-parametric data are given as mean, standard deviation and median (min-max). If p value is less than 0.05, the difference is significant. F: Female, M: Male, WC: Waist circumference

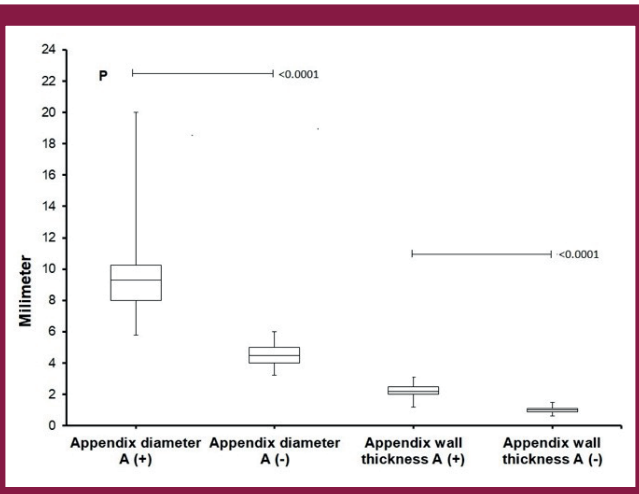

Figure 1. Appendiceal diameter and wall thickness of groups. It can be noted that the appendicitis-positive group (A) has both larger appendiceal diameter and wall thickness

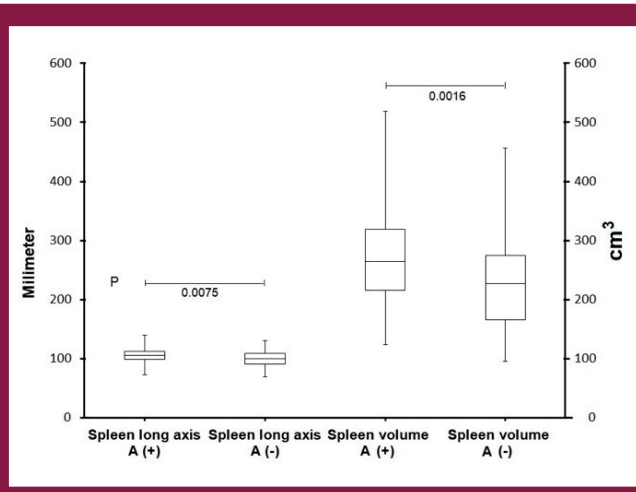

Figure 2. Graphic representation of the comparison of the spleen's long axis and splenic volume (index). It can be noticed that the appendicitis-positive group (A) has both larger spleen long axis and splenic volume

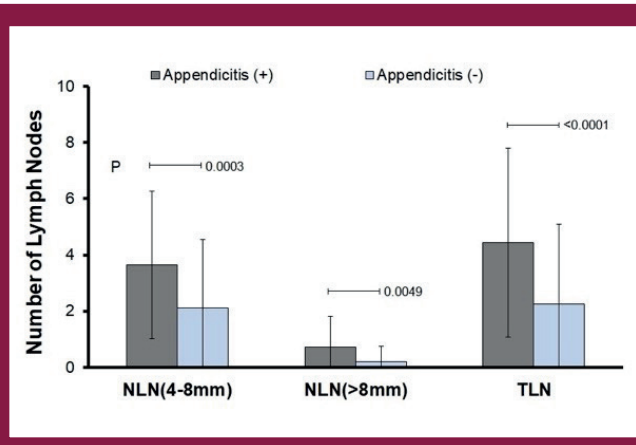

Figure 3. Graphic representation of the evaluation by lymph node size and number. The numbers of lymph nodes with a size of 4-8 mm and >8 mm were significantly greater in the appendicitis-positive group (A) compared to the control group. Similarly, the total number of lymph nodes was also significantly greater

a significant difference between the study groups with respect to the presence of lymph nodes measuring 4-8 mm and exceeding 8 mm. Sixteen (19%) patients in the acute appendicitis group and 5 (6.7%) children in the control group had splenomegaly. The two groups also differed significantly regarding the presence of splenomegaly (Table 3).

Lymph nodes measuring 4-8 mm had a sensitivity of 85% and a specificity of 48%; lymph nodes exceeding 8 mm had a sensitivity of 40% and a specificity of 84% for acute appendicitis. The sensitivity and specificity of splenomegaly for acute appendicitis were 21% and 93%, respectively.

Good positive correlations were found between the status of appendicitis (positive or negative) and appendix diameter, appendiceal wall thickness (Spearman r=0.8652, 95% confidence interval (CI): 0.8168 to 0.9015, p<0.0001 and Spearman r=0.8633, 95% CI: 0.8143 to 0.9001; p<0.0001, respectively). There was a positive correlation close to moderate strength between the presence of appendicitis and the number of lymph nodes (Spearman r=0.3807, 95% CI: 0.2285 to 0.5147, p<0.0001). Similarly, weak, albeit statistically significant, correlations were found between the presence of appendicitis and splenomegaly, splenic index, and splenic long axis size (Spearman r=0.2113, 95% CI: 0.04806 to 0.3636, p=0.0094; Spearman r=0.2582, 95% CI: 0.09740 to 0.4059, p=0.0014 and Spearman r=0.2192, 95% CI: 0.05626 to 0.3707, p=0.0070, respectively).

Table 2. Comparison of the appendix and spleen diameters of patients with appendicitis and control group

	Patients with appendicitis	Control group	p
Appendix diameter, mm	9.6±2.6 9.3 (5.8-20)	4.5±0.7 4.5 (3.2-6)	<0.001
AWT, mm	2.2±0.4 2.2 (1.2-3.1)	1.0±0.2 1 (0.6-1.5)	<0.001
SLA, mm	107±14 106 (73-140)	100±13.0 100 (69-131)	0.007
Splenic index, cm^3	276±93 264 (124-519)	229±78 227 (95-456)	0.002

Non-parametric data are given as mean, standard deviation and median (min-max). If p value is less than 0.05, the difference is significant. AWT: Appendix wall thickness, SLA: Spleen long axis

Table 3. Comparison of the lymph node with a short axis measuring 4-8 mm and exceeding 8 mm, and splenomegaly between appendicitis and control groups

	Patients with appendicitis	Control group	p
Lymph node (4-8 mm), n (%)	64 (85)	39 (52)	<0.001
Lymph node (>8 mm), n (%)	30 (40)	12 (16)	0.001
Splenomegaly, n (%)	16 (21)	5 (6.7)	0.010

Non-parametric data are given as mean, standard deviation. If p value is less than 0.05, the difference is significant

Discussion

History and physical examination are important tools for making the diagnosis of appendicitis in children (2). In 1986, Puylaert defined the staged compression technique (7). Sonographic identification of an edematous, non-compressed appendix is an important clue for the diagnosis. Furthermore, additional findings such as peri-appendiceal fat tissue changes, appendicolitis, mesenteric lymph node enlargement, and free fluid may be found (14). In the present study, we defined splenomegaly as an additional finding. In our study, 16 (19%) patients with acute appendicitis and 4 (6.7%) children in the control group had splenomegaly. There was a significant difference between the two groups in terms of the presence of splenomegaly.

US is operator-dependent and requires experience, which makes sonographic diagnosis difficult, as well as various factors such as retrocecal appendix and obesity (15,16). Nonspecific signs such as peri-appendiceal fatty tissue changes and free fluid may guide the clinician especially in pediatric cases where the appendix cannot be visualized in sonographic imaging. Our study detected a weak but significant correlation between acute appendicitis and splenomegaly.

The spleen is composed of red pulp, a white pulp, and the marginal zone (MZ) that forms an interface between the two. Red pulp filters the blood and recycles the iron. Leukocytes in the spleen consist of various T and B cells, dendritic cells (DCs), and macrophages with different functions. Macrophages found in the MZ eliminate bacteria and viruses originating from blood. In addition to macrophages, the MZ also contains B cells and DCs that present antigens to lymphocytes in the white pulp. White pulp is structurally resembling a lymph node in which it contains T-cell and B-cell zones and allows the formation of antigen-specific immune responses against blood-borne infections (17). Considering all these functions of the spleen, which is an important lymphoid organ, a relationship between appendicitis and splenomegaly can be expected. However, no study has ever been conducted to assess splenic size in acute appendicitis. In our study, the splenic long axis and splenic index were significantly greater in the appendicitis-positive group than the controls. There was a weak, albeit significant, correlation between acute appendicitis and splenic index and splenic long axis.

Our study demonstrated a much higher number of lymph nodes measuring 4-8 mm, lymph nodes exceeding 8 mm, and total lymph nodes in the appendicitis-positive group compared to the control group. Puylaert reported that enlarged mesenteric lymph nodes were present in about

40% of acute appendicitis cases (7). Sivit et al. (8) examined patients with mesenteric lymph node enlargement and acute abdominal pain. They reported that among patients with mesenteric lymph node enlargement, acute appendicitis was the most common specific diagnosis following gastroenteritis and abdominal pain of unknown origin (8). Those studies have both had an insufficient number of patients and/or scant data because they took 4 mm as the limit for the short axis lymph node diameter. In our study, when lymph nodes larger than 4 mm were taken into consideration, lymph node positivity had a sensitivity of 85% and a specificity of 48% for acute appendicitis. When only lymph nodes with a diameter larger than 8 mm were considered, sensitivity and specificity were 40% and 84%, respectively. These results suggest that as lymph nodes enlarge, specificity increases but sensitivity decreases.

In various studies, mesenteric adenitis was a common diagnosis in patients operated for suspected appendicitis (18,19,20). Although mesenteric lymphadenitis has been formerly defined as a cluster of lymph nodes with a number exceeding 3 and a diameter exceeding 5 mm, the current definition involves the detection of at least 1 lymph node with a diameter larger than 8 mm (21). Our study detected lymph nodes having a diameter exceeding 8 mm in 30 (40%) patients with acute appendicitis and 12 (16%) of the control subjects. This suggests that acute appendicitis should be considered in addition to mesenteric adenitis in the differential diagnosis of cases presenting with acute abdominal pain in which the appendix cannot be visualized. Our study enrolled no patient group with mesenteric lymphadenitis, which may be considered a limitation of our study.

Our study aimed to stress the importance of detecting an increased splenic size and lymph node number/size as an additional sign when the appendix cannot be visualized by US. However, as US is operator-dependent, and it may not provide objective information since it is performed by different operators under emergency conditions, we designed this study to re-examine CT studies. Again, this is another limitation of our study.

Conclusion

In conclusion, in equivocal cases where the appendix cannot be visualized with US, additional findings such as splenic enlargement and increased lymph node number/size may guide for the evaluation of the appendix with CT. However, as sonography is an operator-dependent modality and these findings are nonspecific, a well-performed physical examination is the most important stage for the decision of CT scan and for an accurate diagnosis.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee of Sakarya University (approval date: 01.12.2020, approval number: E.10771).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Evaluation of Mandibular Foramen Localization with Three-Dimensional Computed Tomography in Adult Individuals

Erişkin Bireylerde Mandibular Foramen Lokalizasyonunun Üç Boyutlu Bilgisayarlı Tomografi ile Değerlendirilmesi

Abdülkadir Bilir[1], Ozan Turamanlar[1], Hilal Güzel[1], Emre Kaçar[2]

[1]*Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Anatomy, Afyonkarahisar, Turkey*

[2]*Private Doruk Setbaşı Medical Center, Division of Radiology, Bursa, Turkey*

ABSTRACT

Background: Mandibular anesthesia is a frequently preferred anesthesia technique in the restorative, pulpal and surgical treatments of milk molars and permanent molars, as well as in mandible fractures and all surgical interventions that involve the mandible. In this reason, localization differences of mandibular foramen should be taken into consideration while applying mandibular anesthesia technique in patients. The aim of this study is to evaluate the localization of the mandibular foramen in living adults with three-dimensional computed tomography images.

Materials and Methods: The study was carried out retrospectively on the radiologic images of 200 randomly selected adult individuals who had computed tomography examination for paranasal sinus and/or head and neck pathologies. The closest vertical (A) and horizontal (C) distances from mandibular foramen to margins of mandibular ramus and total vertical (B) and horizontal (D) distances of mandibular ramus were measured bilaterally in the edandate and dendate individuals, and the A/B and C/D ratios were evaluated.

Results: When the measurements of dentate and edentate mandibles were compared, a statistically significant difference was found in all parameters (A, B, C, D, A/B, C/D) and it was determined that the measurements of dentate mandibles were larger than those of edentate mandibles. When the mandibular measurements were compared according to the sides (left/right), the A and D measurements and AB ratio in the right dentate mandibles and the B, C, D measurements and AB, CD ratios in the right edentate mandibles were statistically significantly larger than the left side. When the measurements were compared by gender, the B, C, D measurements and AB ratio of male dentate mandibles were statistically significantly higher than females.

Conclusion: It was determined that mandible measurements of dentate cases were larger than edentate mandible. Mandibular ramus can be asymmetrical and ramus morphometers may be affected by gender within the clinical syndromes. This study demonstrates that the anatomical landmarks determined to find the target area for nerve block and to determine the safety zone for the ramus osteotomy lines can vary depending on the presence of the teeth.

Keywords: Adult population, mandibular foramen, three-dimensional computed tomography

ÖZ

Amaç: Mandibular anestezi, süt ve kalıcı azı dişlerinin pulpa, restoratif ve cerrahi tedavilerinde, mandibula kırıklarında ve mandibulayı ilgilendiren tüm cerrahi girişimlerde sıklıkla tercih edilen bir anestezi tekniğidir. Bu nedenle hastalarda mandibular anestezi tekniği uygulanırken foramen mandibulae lokalizasyon farklılıkları dikkate alınmalıdır. Bu çalışmanın amacı, yaşayan erişkinlerde foramen mandibulaenin lokalizasyonunun üç boyutlu bilgisayarlı tomografi görüntüleri ile değerlendirmesidir.

Gereç ve Yöntemler: Çalışma, paranazal sinüs ve/veya baş-boyun patolojileri için bilgisayarlı tomografi incelemesi yapılan rastgele seçilmiş 200 erişkin bireyin radyolojik görüntüleri üzerinde retrospektif olarak gerçekleştirildi. Foramen mandibulaedan ramus mandibulae kenarlarına en yakın dikey (A) ve yatay mesafeler (C) ve ramus mandibulaenın toplam dikey (B) ve yatay mesafeleri (D) dişli ve dişsiz bireylerde bilateral olarak ölçüldü.

Bulgular: Dişli ve dişsiz mandibula ölçümleri karşılaştırıldığında, tüm parametrelerde (A, B, C, D, A/B, C/D) istatistiksel olarak anlamlı bir fark bulundu ve dişli mandibula ölçümlerinin dişsiz mandibulalara göre daha büyük olduğu belirlendi. Mandibular ölçümler laterilizasyona (sol/sağ) göre karşılaştırıldığında, sağ dişli mandibulada A ve D ölçümleri ve AB oranı ile sağ dişsiz mandibulada B, C, D ölçümleri ve AB, CD oranları istatistiksel olarak anlamlı derecede sol taraftan daha büyük bulundu. Ölçümler cinsiyete göre karşılaştırıldığında erkek dişli mandibulanın B, C, D ölçümleri ve AB oranı kadınlara göre istatistiksel olarak anlamlı derecede yüksekti.

Address for Correspondence: Abdülkadir Bilir, Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Anatomy, Afyonkarahisar, Turkey
Phone: +0 272 246 33 01 E-mail: fztabdulkadirbilir@gmail.com **ORCID ID:** orcid.org/0000-0003-0633-9542

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ÖZ

Sonuç: Dişli olguların mandibula ölçümlerinin dişsiz mandibuladan daha büyük olduğu ve klinik sendromlar içerisinde ramus mandibulaenın asimetrik olabileceği ve ramus morfometrelerinin cinsiyetten etkilenebileceği belirlendi. Bu çalışma, sinir bloğu için hedef alanı bulmak ve ramus mandibulaenın osteotomi hatları için güvenlik bölgesini belirlemek için anatomik işaretlerin dişlerin varlığına bağlı olarak değişebileceğini göstermektedir.

Anahtar Kelimeler: Erişkin popülasyon, mandibular foramen, üç boyutlu bilgisayarlı tomografi

Introduction

The mandibular foramen is located on the inner surface of the ramus of mandible and forms the entrance part of the mandibular canal. This canal starts from the ramus of mandible and opens out as mental foramen on the outer face of the body of mandible. The inferior alveolar nerve, inferior alveolar artery and inferior alveolar vein pass through this canal together. The inferior alveolar nerve provides sensory innervation to the lower teeth, as well as the lower lip, gingiva and some skin on the lower face. The inferior alveolar artery and vein supply these regions (1,2).

Mandibular anesthesia is a frequently preferred anesthesia technique in the restorative, pulpal and surgical treatments of milk molars and permanent molars, as well as in mandible fractures and all surgical interventions that involve the mandible. Localization differences of mandibular foramen should be taken into consideration while applying mandibular anesthesia technique in edentulous patients. Wrong anesthesia results in many complications such as trismus and facial paralysis (3).

The current literature on mandibular foramen is mostly based on the anatomic data, surgical landmarks derived from dry human skulls, panoramic and radiologic images (4,5). There are a lot of limitations as shrinkage and fracture of subtle structures or magnification, distortion and reproducibility of radiographic images in measurements of these studies (6,7,8,9). While there are enough research and data sets for the mandible surgery of the healthy population in the clinic, there is a lack of data in the mandible surgery of geriatric patients, especially edentate patients because consequences of tooth loss on the maxillary and mandibular alveolar bone are well known. However, those morphological changes require additional examination. As a solution to the limitations mentioned above, the use of three-dimensional (3D) computed tomography (CT) reconstruction technique in clinical trials has become widespread (5,10,11,12).

The aim of this study is to evaluate the localization of mandibular foramen in living adults with three-dimensional computed tomography.

Material and Methods

The study was carried out on the radiologic images of 200 randomly selected adult individuals (91 female, 109 male) aged 18-65 years, who had CT examination for paranasal sinus and/or head and neck pathologies in the department of radiology. Those with mandibular pathology or malformation, and artifact on CT images were excluded from this study. In retrospective archive search, it is not obligatory to obtain patient consent. The study was carried out as a retrospective archive search in accordance with the Declaration of Helsinki after obtaining approval from the Local Ethics Committee of Afyonkarahisar Health Science University (KAEK/2015/09-240).

Scans were performed with 80-row MDCT scanner (Aquilion Prime, Toshiba Medical Systems, Nasu, Japan). The CT protocol was as follows: Peak kilovoltage 120 kVp, tube current 150-165 minimum (min) and maximum (max) collimation: 2.5 mm, slice thickness: 3 mm and rotation time: 0.75 s. Images that included the mandibular foramen were retrospectively analyzed on a workstation (Aquarius, TeraRecon Inc., San Mateo, CA, USA). Reconstruction images with 0,5 mm slice thickness were created from the server images with 3 mm slice thickness. Multiplanar reconstruction and 3D volume rendering images were obtained from sections with 0.5 mm slice thickness. In 3D images, the distance was measured from the mandibular foramen to the specific points on both sides of mandible. Measurements (Figure 1):

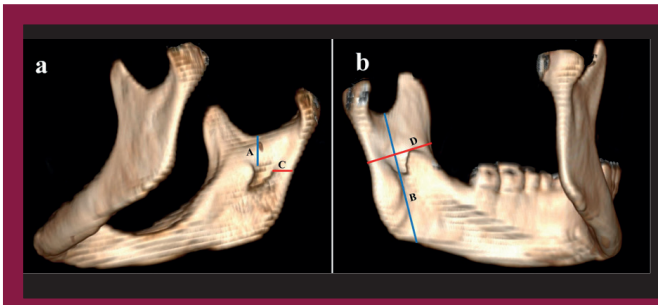

Figure 1. a. The closest vertical and horizontal distances on ramus of edentate mandible from mandibular foramen to margins. b. Total vertical and horizontal distances on ramus of edentate mandible

(A; The closest vertical linear distance from the superior edge of the mandibular foramen (in line with apex of the lingula) to the mandibular notch, B; Vertical linear distance between the mandibular notch and the base of mandible passing on the mandibular foramen, C; The closest horizontal linear distance between the posterior edge of the mandibular foramen and the posterior edge of the mandibular ramus, D; Horizontal linear distance between the anterior and posterior edges of the mandibular ramus passing on the mandibular foramen)

• (A) - The closest vertical linear distance from the superior edge of the mandibular foramen to the mandibular notch.

• (B) - Vertical linear distance between the mandibular notch and the base of mandible passing on the mandibular foramen.

• (C) - The closest horizontal linear distance between the posterior edge of the mandibular foramen and the posterior edge of the mandibular ramus.

• (D) - Horizontal linear distance between the anterior and posterior edges of the mandibular ramus passing on the mandibular foramen.

• A/B ratio

• C/D ratio

Statistical Analysis

Statistical analysis of the data was done with SPSS version 20.0 package program. Statistical analysis included means and standard deviations. The Kolmogorov-Smirnov test was used to evaluate the suitability of data for normal distribution and it was determined that data were not homogeneous. The Mann-Whitney U test was used to evaluate the significance of the differences by making comparisons between both mandibular foramen measurements of the same person, genders, and dentate/edentate mandibles measurements. The relationship between age groups and evaluation parameters was analyzed with the Pearson's correlation test. The results were evaluated in 95% confidence interval and data with p value less than 0.05 ($p<0.05$) were considered statistically significant.

Results

In our study, CT images of 100 dentate cases (54 male/46 female) and 100 edentate cases (55 male/45 female) randomly selected from the healthy population were evaluated. The mean age of dentate cases was 36.57±13.56 years while the mean age of edentate cases was 65.65±11.14 years. Morphometric measurement data were shown in millimeters as mean and standard deviations.

When the mandibular measurements were compared according to the sides (left/right), the A and D measurements and AB ratio in the right dentate mandibles ($p<0.001$, $p<0.001$, $p<0.001$ respectively) and the B, C, D measurements and AB, CD ratios in the right edentate mandibles were statistically significantly larger than the left side ($p=0.037$, $p=0.057$, $p<0.001$, $p<0.001$, $p=0.033$, respectively) (Table 1). When the measurements were compared by gender, the B, C, D measurements and AB ratio of male dentate mandibles were statistically significantly higher than females ($p<0.001$, $p=0.005$, $p<0.001$, $p=0.012$, respectively) (Table 2). When the measurements of dentate and edentate mandibles were compared, a statistically significant difference was found in all parameters (A, B, C, D measurements and AB, CD ratios) and it was determined that the measurements of dentate mandibles were larger than those of edentate mandibles ($p<0.001$, $p=0.002$, $p<0.001$, $p=0.014$, $p<0.001$, $p<0.001$, respectively) (Table 3).

Discussion

Mandibular anesthesia is a frequently preferred anesthesia technique in the restorative and surgical treatments of the jaw and molars (3). The most common complication in these treatments is nerve injury. This damage is often temporary or permanent. Among nerve injuries, it has been reported that injury to the IAN occurs more frequently due to its anatomical position. It is needed to visualize this area before surgical procedures, as it cannot be easily palpated by hand and can cause severe complications in IAN damage. Therefore, the location of the mandibular foramen should be determined by preoperatively examining the panoramic and radiologic images, and its relationship with the surrounding anatomical structures should be evaluated. Accordingly, the safe zone, which is the area above and behind the mandibular foramen, should be determined in mandibular ramus osteotomies, surgical treatments of the jaw and molars (13,14). In this context, we aimed to evaluate the localization of the mandibular foramen in adult individuals living with or without teeth with three-dimensional computed tomography.

Table 1. Morphometric measurements of dentate and edentate mandibles according to sides

		Left	Right	p
Dentate	A	18.58±3.36	21.09±4.28	p<0.001*
	B	50.76±4.85	51.91±5.17	0.068
	C	12.77±1.77	13.22±1.95	0.159
	D	27.82±3.34	29.76±3.39	p<0.001*
	A/B	0.37±0.06	0.41±0.07	p<0.001*
	C/D	0.46±0.06	0.44±0.05	0.069
Edentate	A	15.81±2.50	15.54±2.58	0.509
	B	49.87±4.72	49.87±4.82	0.954
	C	11.43±2.51	11.51±2.53	0.693
	D	27.66±3.45	28.23±3.64	0.271
	A/B	0.32±0.04	0.31±0.04	0.228
	C/D	0.41±0.07	0.41±0.07	0.614

The mean and standard deviations are shown in millimeters.
The Mann-Whitney U test was used in comparing the statistically significance of the difference between the sides.
*There is a statistically significant difference between the groups

Several studies in the literature have examined the effects of MF with different purposes, methods, and landmarks and on populations with different jaw relationships or age groups (9,13,15,16). In the study of Matundu et al. (15) on dry adult human jaws in the Malawi population, the mean distance of the MF was 11.36 mm from the posterior margin of mandibular ramus and 20.85 mm from the anterior margin. The distance between mandibular notch and MF was 23.7 mm, and the distance between mandibular base and MF was 28.16 mm. They reported that no mandibular asymmetry was observed (15). In Sevmez et al. (13) CT study on 300 adult Turkish individuals, the mean distance of the MF was 14.05 mm from the posterior margin of mandibular ramus and 20.85 mm from the anterior margin. And horizontal and vertical distances of mandibular ramus were 32.99 mm and 23.43 mm, respectively. It was reported that mandibular asymmetry was not observed in their study, but a statistical difference between the genders was determined in all parameters (13). In a study with 224 Jordanian individuals, Al-Shayyab (16) determined that the mean distance of the MF from the posterior margin, anterior margin, mandibular notch and mandibular base were 13.19 mm, 17.53 mm, 19.23 mm, and 25.6 mm, respectively, on CT radiographs. It was suggested by Al-Shayyab (16) that the location of the MF was significantly variable according to age, without divergence according to the side and gender. In Satir's (9) study comparing mandibular morphometry of individuals with Down syndrome and normal individuals in 2019, it was stated that the measurements made in individuals with Down syndrome were shorter than in the normal individuals. In addition, when they evaluated the measurement of mandibles according to gender and sides in both groups, they stated that there was no statistically significant difference. However, it was reported for individuals with Down syndrome that the morphometry of the mandibular foramen was variable, which results from developmental retardation or the characteristic features of the disease (9).

A few studies in the literature, similar to our study, examined the location and course of the mandibular foramen in patients (12,17,18,19,20,21,22). Prado et al. (12) analyzed a total of 159 (80 dentate and 79 edentate) dry adult mandibles. As a result of this analysis, while they did not determine an asymmetry between the sides in both mandible groups, they determined that the horizontal and vertical lengths were higher in the dentate mandibles (12). Captier et al. (21) measured a total of 83 (60 dentate and 23 edentate) dry adult mandibles. They reported that the mean distance between mandibular notch and MF was 29.76 mm, and distance of the

Table 2. Morphometric measurements of dentate and edentate mandibles according to gender

		Female	Male	p
Dentate	A	19.72±3.35	19.93±4.20	**0.976**
	B	49.54±5.20	52.87±4.32	**<0.001***
	C	12.68±1.90	13.27±1.79	**0.005***
	D	27.96±3.08	29.49±3.41	**<0.001***
	A/B	0.40±0.06	0.38±0.07	**0.012***
	C/D	0.45±0.05	0.45±0.06	**0.913**
Edentate	A	16.21±2.38	15.02±2.58	**<0.001***
	B	52.09±4.14	47.16±4.02	**<0.001***
	C	12.15±2.52	10.63±2.24	**<0.001***
	D	29.05±3.33	26.60±3.36	**<0.001***
	A/B	0.31±0.39	0.32±0.43	**0.407**
	C/D	0.42±0.72	0.40±0.06	**0.044***

The mean and standard deviations are shown in millimeters.
The Mann-Whitney U test was used in comparing the statistically significance of the difference between the genders.
*There is a statistically significant difference between the groups

Table 3. Morphometric measurements of dentate and edentate mandibles

	A	B	C	D	A/B	C/D
Dentate	19.83±4.04	51.34±5.02	12.99±1.87	28.79±3.49	0.39±0.07	0.45±0.06
Edentate	15.67±2.54	49.87±4.76	11.47±2.51	27.94±3.55	0.31±0.41	0.41±0.07
p	<0.001*	0.002*	<0.001*	0.014*	<0.001*	<0.001*

The mean and standard deviations are shown in millimeters.
The Mann-Whitney U test was used to compare the statistical significance of the difference between the mandible groups.
*There is a statistically significant difference between the groups

MF from the posterior margin of mandibular ramus was 15.4 mm. They showed that there was no asymmetry between the dentate and edentate mandible groups and between the parties (21). In the radiography study of Merrot et al. (22) on 106 individuals (65 edentate and 41 dentate), it was determined that while the vertical distance was shorter in edentulous mandibles compared to dentate mandibles, there was no statistically significant difference in their study. In the studies of Hayward et al. (17), Doual et al. (18), Raustia and Salonen (19), and Oğuz and Bozkir (20), it was reported that when dentate and edentate cases were compared, the horizontal distance was found to be statistically shorter in edentate mandibles than in dentate mandibles. In our study, the distance between mandibular foramen and mandibular ramus and the distance between the anterior and posterior edge of the mandibular ramus were found to be compatible with the literature. Although Merrot et al. (22) and Captier et al. (21) found the vertical distance to be shorter in edentulous mandibles than in dentate mandibles, Prado et al. (12) did not find a statistically significant difference in their study (21,22). Acoording to our results, it was found to be shorter than the dentate mandibles in the distance from mandibular foramen to the mandibular notch and the distance between the mandibular notch and the base of mandible, and it was compatible with the studies of Merrot et al. (22) and Captier et al. (21). Antero-posterior narrowing can be explained by tooth loss, reduced chewing load transferred to the alveolar portion of the mandible, and bone resorption of the ramus of the mandible (18,19). The distance from mandibular foramen to the mandibular notch in geriatric people decreases due to mandibular ramus resorption as a consequence of decline in muscular activity and remodeling of the condylar and coronoid processes (22). The factors mentioned above can be shown as an explanation of the changes of the mandibular morphometry in edentate cases.

In our study, A and D measurements and AB ratio in dentate mandibles and B, C, D measurements and AB, CD ratios in edentate mandibles were larger on the right side. These results show that asymmetry in mandibular foramen morphology can be seen even in the same individuals. Contrary to our study, no differences were observed between the sides of the mandible in literature studies. It could be said that this asymmetry is due to the force difference between the masticatory muscles or the existing head asymmetry (19).

The changes in morphometers of mandibular foramen were examined in the studies of Merrot et al. (22) and Sevmez et al. (13) and they determined that the length and width of the mandibular ramus were statistically longer in males than in females. In our study, when the measurements were compared by gender, the B, C, D measurements and AB ratio of male dentate mandibles were statistically higher than those of females, no difference was found in edentulous mandible measurements by gender. Most of mandible measurements were found larger in males in healthy people. However, contrary to what is expected in edentate cases, male mandible measurements were determined not to be larger than thoseof females. Considering that, we can declare that the gender factor is ineffective in the change of mandibular morphometry due to tooth loss.

Study Limitations

In our study, we faced limitations due to the low mean age of the control group and the lack of some demographic information. In addition, due to the diversity of the scope of the studies in the literature, a common goal could not be focused on. For this reason, we report that our work can be improved with some modifications and additions.

Conclusion

It was determined that mandible measurements of dentate cases were larger than edentate mandible, and mandibular ramus can be asymmetrical and ramus morphometry may be affected by gender within the clinical syndrome. Our study, which examined the effect of gender, lateralization and tooth loss on mandible morphometry, was a research that contributed to the current literature with its scope and quality. Furthermore, we believe that results of this study will make a great contribution to surgical and clinical branches.

Ethics

Ethics Committee Approval: The study was carried out as a retrospective archive search in accordance with the Declaration of Helsinki after obtaining Approval from the Local Ethics Committee of Afyonkarahisar University (KAEK/2015/09-240).

Informed Consent: In retrospective archive search, it is not obligatory to obtain patient consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.B., O.T., E.K., Design: A.B., O.T., E.K., Data Collection or Processing: A.B., O.T., H.G., E.K., Analysis or Interpretation: A.B., H.G., Literature Search: A.B., Writing: A.B., O.T.

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

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CASE REPORT

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Medication-Induced Lesion in A Young Woman Mimicking Malignancy: Linear-Extended Esophageal Ulcer Due to Tetracycline Usage

Genç Bir Kadında Maligniteyi Taklit Eden İlaç Kaynaklı Lezyon: Tetrasiklin Kullanımına Bağlı Doğrusal Genişlemiş Özofagus Ülseri

İrfan Küçük[1], Yusuf Yazgan[1], Mustafa Kaplan[2], Uğur Demirpek[3], Mehtap Toprak[4], Fatih Özçelik[5]

[1]*University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Internal Medicine İstanbul, Turkey*

[3]*Bursa City Hospital, Clinic of Medical Microbiology, Bursa, Turkey*

[4]*University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Pathology İstanbul, Turkey*

[5]*University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Biochemistry İstanbul, Turkey*

ABSTRACT

Oral tetracycline-induced esophageal injury usually presents with physiological symptoms of esophageal narrowing. The most common location is at the level of the aortic arch, accounting for approximately 76% of all cases.

A 27-year-old woman was admitted to the gastroenterology department of our institute, complaining dysphagia, feeling of food impaction and severe retrosternal chest pain after two weeks treatment of tetracycline for acne vulgaris. She did not have any comorbidity and reported intermittent vomiting sometimes with coffee ground appearance. After excluding possible cardiac conditions as the cause of cardiac chest pain, upper gastrointestinal endoscopy was performed and it revealed hyperemic antral gastropathy. At 30 cm from the incisors, a linear and vertically extended esophageal ulcer resembling a malignant lesion was observed.

Esophageal ulcers, which can show various symptoms and can be confused with cancers, may occur due to the use of oral tetracycline, although rarely. Therefore, patients' use of tetracycline should be questioned in clinical examination. To prevent such complications, patients should be advised to take tetracycline pills in an upright position with enough water.

Keywords: Tetracycline, esophagitis, malignancy

ÖZ

İlaca bağlı özofagus hasarı genellikle fizyolojik daralmalar düzeyinde ortaya çıkar. En yaygın yerleşim yeri, tüm olguların yaklaşık %76'sını oluşturan aortik ark seviyesindedir. Yirmi yedi yaşında kadın hasta, akne vulgaris için tetrasiklin tedavisi sonrasında disfaji, yemek sıkışması hissi ve şiddetli retrosternal göğüs ağrısı şikayetleri ile enstitümüzün gastroenteroloji bölümüne başvurdu. Komorbiditesi yoktu ve bazen kahve telvesi görünümü ile birlikte aralıklı kusma bildirdi. Kardiyak göğüs ağrısının nedeni olası kardiyak durumlar dışlandıktan sonra, hiperemik antral gastropatiyi ortaya çıkaran üst gastrontestinal endoskopi yapıldı. Kesici dişlerden 30 cm uzaklıkta, malign bir lezyonu andıran lineer ve dikey olarak genişletilmiş bir yemek borusu ülseri gözlendi.

Tetrasiklin özofajitte özofagus ülserleri farklı şekillerde ortaya çıkabilir ve bazı nadir durumlarda ülserler yaygın ve şiddetli olabilir. Bazen iyi huylu özelliklerine rağmen karsinom gibi görünebilirler. Maligniteyi dışlamak için ülserlerden ve komşu mukozadan biyopsi alınmalıdır. Bu komplikasyonları önlemek için hastalara yeterli miktarda su ile dik pozisyonda tetrasiklin almaları önerilmelidir.

Anahtar Kelimeler: Tetrasiklin, özofajit, malignite

Address for Correspondence: Mustafa Kaplan, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Internal Medicine İstanbul, Turkey

Phone: +90 533 567 28 71 E-mail: dr_mustafakaplan@yahoo.com **ORCID ID:** orcid.org/0000-0002-0354-4762

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Introduction

Many tetracycline derivatives have been found to date from chlortetracycline discovered by Benjamin M. Duggar in 1948. There are preparations suitable for oral use. Tetracycline group antibiotics (doxycycline, tetracycline, and minocycline) are among the drugs that have important anti-inflammatory properties as well as antibacterial activities. For this reason, it has been preferred by dermatologists in acute exacerbation of acne vulgaris, a chronic inflammatory disease of the pilosebaceous unit. It has also been found that its anti-inflammatory properties provide improvement in non-bacterial acne rosacea (1). However, despite all these features, esophageal ulcers have been reported, albeit rarely, due to tetracyclines, especially in young women. Often there are widespread ulcerations in one, sometimes several, esophageal segments that mimic esophageal cancer (2,3,4). Drug-induced esophageal injury generally occurs at the level of physiologic narrowing. The most common location is at the level of the aortic arch, known as the retro-esophageal aortic segment. Injury here accounts for approximately 76% of all cases. Predominantly, it is encountered in women, due to using culprit medications such as tetracyclines and bisphosphonates. The incidence of pill esophagitis is 3.9/1000000 per year. The mean age of the patients is 41.5 years (2). It generally has a benign prognosis.

Case Report

A 27-year-old woman was admitted to gastroenterology department of our institute, complaining dysphagia, feeling of food impaction and severe retrosternal chest pain after two weeks treatment of tetracycline for acne vulgaris. She did not have any comorbidity and reported intermittent vomiting sometimes with coffee ground appearance. No other abnormal condition was found in radiology, hematology, and biochemical tests. CK-MB and troponin I tests performed due to the patient's retrosternal pain were within normal limits. After excluding possible cardiac conditions as the cause of severe retrosternal chest pain, upper gastrointestinal endoscopy was performed and it revealed hyperemic antral gastropathy. At about 29 cm from the incisors, a linear and vertically extended esophageal ulcer resembling a malignant lesion was observed. It was 1 cm in width and 5 cm in length (Figure 1). Normal esophageal mucosa was observed from the incisors to the ulcer area.

The ulcer was covered with a clean white exudate and included focal hemorrhagic spots explaining the intermittent bloody vomiting. Adjacent mucosa near the ulcer margin was completely normal and the appearance of the rest of the esophagus was unremarkable. Histopathological examination of the endoscopic biopsy from the edges and center of the esophageal ulcer specimen revealed a dense acute inflammatory infiltrate with no evidence of neoplasia or infectious cause. Eosinophilic infiltration was also noteworthy in histopathologic report (Figure 2).

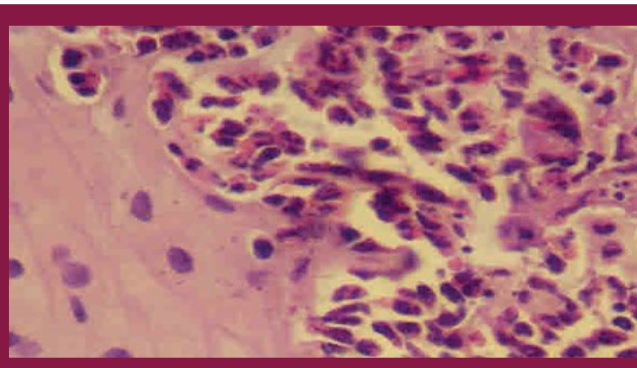

Figure 2. Acute inflammation with eosinophilic infiltration

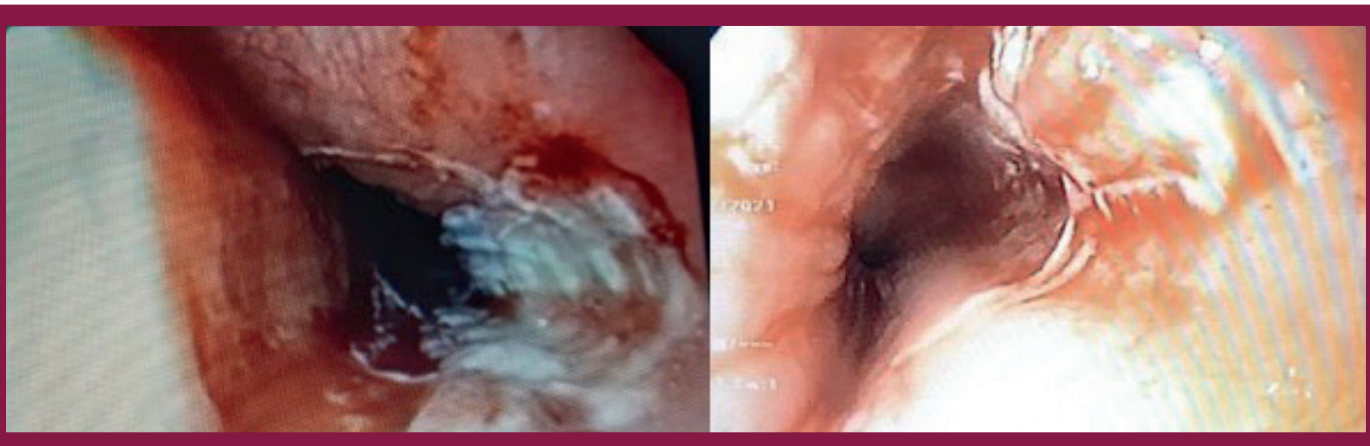

Figure 1. Tetracycline induced esophagitis in distal esophagus

The patient's symptoms improved within 10 days with a liquid diet, sucralfate suspension, and proton pump inhibitor treatment. In addition, written consent was obtained from the patient.

Discussion

Tetracyclines have been used to treat gram-positive and gram-negative bacteria in general, as well as intracellular chlamydia, mycoplasmas, rickettsia, protozoan parasites, and various non-bacterial infections. It is an important option against bacteria that can be used in biological weapons. Because of all these properties, it is one of the most prescribed antibiotics in the world. Doxycycline is one of the most active tetracyclines and is the most preferred one in clinical use (3,5). The clinical area where tetracyclines are most used is acne vulgaris, which is the most common skin disease in adolescence and can have negative emotional consequences. Acne can be acute or chronic. Sometimes dramatically severe inflammation leads to permanent scarring, especially in the face or back area (6). For this reason, it is recommended to start acne treatment with tetracycline derivatives without delay. However, although extremely rare, esophageal lesions induced using tetracyclines have been reported. These lesions are mostly in the form of mild esophagitis and can sometimes be seen as benign ulcers. The reason for this complication has been shown to be taking medications just before bedtime with very little water (3,7). Another clinical pathology in which tetracyclines are frequently used is helicobacter pylori infection. Especially with the spread of clarithromycin resistance all over the world, quadruple therapy regimens containing tetracycline and bismuth citrate have been used extensively as an alternative to the triple standard treatment of H. pylori infection (amoxicillin and clarithromycin and proton pump inhibitor), which has been used for many years (8,9).

Tetracyclines can cause nausea-vomiting, diarrhea, dysphagia, glossitis, enterocolitis, esophagitis, maculopapular rash, urticaria, angioneurotic edema, anaphylaxis, erythema and photosensitivity, and blood urea elevation. Oral tetracycline-induced esophageal ulcer and esophageal injury are rare complications. Esophageal ulcer is not only seen in people taking tetracycline. A similar picture has been reported in drugs with quite different characteristics. When esophageal injuries were first described in 1970, caustic medicinal pills were blamed for the incident. Especially when the passage is delayed, it has been determined that pill esophagitis develops because this pill dissolves in the esophagus and releases its harmful content. When looking at the classes of drugs that cause esophagus damage in general, nonsteroidal anti-inflammatory drugs, tetracyclines, potassium chloride tablets, alendronate and other drugs are listed, respectively. Therefore, quite different drugs have been reported to cause esophageal injury. This type of injury, called pill esophagitis or injury to the esophagus caused by the pill, is common (3,10,11). However, it has not been sufficiently reported. Esophagitis and ulcer frequency due to tetracycline increases by age (12). Comorbidities, esophageal motility disturbances (13) and altered esophageal anatomy also predispose to drug induced esophagitis. However, this patient was younger than usual, and she did not have any chronic diseases. The typical endoscopic appearance of pill-induced esophageal injury is generally a circumferential ulcer (2) but in this case, endoscopy revealed a linear extending ulcer. Although pill esophagitis and ulcers take place in externally compressed and in narrow parts of the esophageal lumen, sometimes they locate in wider parts like the distal third of esophagus as in this case. Another aspect of the ulcer in our case was its resemblance to a malignant lesion as reported previously (3,14).

The incidence of drug-induced esophagitis is affected by the oral forms of the drug. Esophagitis is more common in capsule forms compared to tablets in the form of drugs due to easier adhesion to the esophagus surface. Doxycycline, an acidic drug, accumulates in the epithelium of the esophagus and can cause contact esophagitis due to focal contact. In the advanced stage, it may penetrate deeper with local cytochemical effects and cause ulceration in the esophagus mucosa (2,13).

According to the opinion of Tahan et al. (3) all patients who present with chest pain, odynophagia and dysphagia should be questioned in terms of drug-induced esophagitis. In this way, drug-related morbidity can be reduced with precautions that can be taken beforehand. It was recommended that suspected patients be given information on how and when to take the drugs. In addition, it was recommended to swallow the drug with approximately 100 ml of water and then sit in an upright position for a while.

Esophageal ulcers, which can show various symptoms and can be confused with cancers, may occur due to the use of oral tetracycline, although rarely. Therefore, patients' use of tetracycline should be questioned in clinical examination. To prevent such complications, patients should be advised to take tetracycline pills in an upright position with enough water.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.K., Y.Y., U.D., M.T., Concept: İ.K., Y.Y., U.D., M.T., Design: İ.K., M.K., F.Ö., Data Collection

or Processing: İ.K., Y.Y., Analysis or Interpretation: İ.K., U.D., Literature Search: İ.K., Writing: İ.K., M.K., F.Ö.

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

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

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CASE REPORT

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Acute Thyrotoxicosis Induced Reversible Cardiomyopathy in an Adult Patient

Erişkin Bir Hastada Akut Tirotoksikoza Bağlı Reversibil Kardiyomiyopati

Vedat Çiçek, Tufan Çınar, Murat Selçuk, Ahmet L. Orhan

University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

In most cases, congestive heart failure (CHF) usually develops secondary to coronary artery disease or valvular heart disease. However, acute thyrotoxicosis might be an infrequent cause of CHF in some patients. In this report, we presented a case of adult patient without a previous diagnosis of chronic disorder, who was admitted to the emergency department with CHF and newly developed atrial fibrillation. In addition, in this case, we reported that acute thyrotoxicosis could cause severe but reversible LV dysfunction in relatively young individuals.

Keywords: Thyrotoxicosis, congestive heart failure, reversible

ÖZ

Çoğu olgularda, konjestif kalp yetmezliği (KKY) genellikle koroner arter hastalığına veya kalp kapak hastalığına ikincil olarak gelişir. Bununla birlikte, akut tirotoksikoz, bazı hastalarda KKY'nin seyrek bir nedeni olabilir. Bu olguda, daha önce kronik hastalık tanısı olmayan, KKY ve yeni gelişen atriyal fibrilasyon ile acil servise başvuran erişkin bir hastayı sunduk. Ek olarak, bu olguda, akut tirotoksikozun nispeten genç bireylerde ciddi ancak geri dönüşlü sol ventrikül disfonksiyonuna neden olabileceğini gösterdik.

Anahtar Kelimeler: Tirotoksikoz, konjestif kalp yetmezliği, geri dönüşümlü

Introduction

Congestive heart failure (CHF) is a medical condition that occurs as a result of coronary artery disease or valvular heart disease. On the other hand, a rare cause of CHF might be a thyrotoxicosis disorder, which can be reversible with an appropriate treatment. Initially, patients with thyrotoxicosis develop exercise intolerance due to elevated cardiac output (1). However, if thyrotoxicosis is not diagnosed and treated properly, patients may develop a severe systolic dysfunction in the later stages of the disease. This condition is commonly observed in elderly patients with pre-existing heart disease (2). In this report, we presented a case of an adult patient without a previous diagnosis of chronic disorder, who was admitted to the emergency department (ED) with CHF and newly developed atrial fibrillation (AF). Moreover, this case highlights that systolic heart failure can be reversible in some patients with thyrotoxicosis.

Case Report

A 49-year-old male patient presented to our ED with the complaints of palpitation and progressive shortness of breath. Medical records were inconclusive. Upon physical examination, it was noted that the patient was dyspneic and sweaty. The patient's blood pressure was 93/47 mmHg with heart rate of 132 beats/min, and there was 3 (+) bilateral pretibial edema. On lung examination, bilateral diffuse rales were heard. A 12-lead electrocardiography (ECG) obtained in the ED revealed an AF (Figure 1A). A posterior-anterior chest scan was performed, providing an enlargement of the cardio-thoracic ratio and bilateral pleural effusion (Figure 1B). On laboratory analysis, brain natriuretic peptide level was 1373,2 pg/mL. The patient was admitted to cardiac intensive care unit with a pre-diagnosis of acute HF. Bedside transthoracic echocardiography (TTE) was performed, revealing a left ventricle ejection fraction (LVEF) of 23% with mild mitral regurgitation. Low dose inotrope infusion therapy was initiated in addition to the IV diuretic therapy. The patient became hemodynamically stable after the treatment. Thyroid stimulating hormone (TSH) level obtained next day following admission was significantly depressed (<0.0025 uIU/mL). The thyroid ultrasonography findings were compatible with Basedow-Graves' disease. Afterward, propylthiouracil (PTU) treatment was initiated by the endocrinology department. Coronary angiography (CAG) was not planned because the

Address for Correspondence: Tufan Çınar, University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey
Phone: +90 544 230 05 20 E-mail: drtufancinar@gmail.com **ORCID ID:** orcid.org/0000-0001-8188-5020

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patient had recently undergone CAG in another center, which demonstrated normal coronary arteries. The patient's condition was progressively improved following days, and he was discharged with beta-blocker, low-molecular-weight heparin, diuretic, angiotensinogen converting enzyme (ACE) inhibitor, mineralocorticoid-receptor antagonists, and PTU treatment. The patient's TSH level (0.1403 uIU/mL) was within the normal range on one-month outpatient clinic visit. The control TTE showed an improvement of LVEF at a rate of 38% (Figure 2A). Moreover, the patient's ECG was returned to normal sinus rhythm spontaneously and his exercise capacity was significantly improved. Because the patient's CHA_2DS_2-VASc score was "0" and AF was thought to be reversible, anticoagulant treatment was discontinued. On the fifth-month follow-up, the LVEF was 65% on TTE examination (Figure 2B). Moreover, the patient' exercise capacity was over 10 Mets.

Discussion

Thyroid hormone disorders are frequently encountered in clinical practice, and their prevalence increases with age. Thyrotoxicosis is a clinical condition characterized by a suppression of TSH levels and increased peripheral T4 and /or T3 levels. The most common cause is Basedow-Graves' disease that occurs due to thyroid hormone-releasing auto immune antibodies (3). Thyrotoxicosis can affect the cardiovascular system by both decreasing systemic vascular resistance and increasing heart rate, preload, and cardiac output. All of these changes can develop due to vascular smooth muscle relaxation, increase of endothelium-induced nitric oxide release, activation of the renin-angiotensin system, and increased erythropoietin secretion (4). Also, these pathologic mechanisms can lead to HF secondary to elevated cardiac output in patients with thyrotoxicosis. Cardiac output is 50-300% higher in hyperthyroid cases than in individuals with normal thyroid function (5). This causes a high-output HF characterized by blood pumping at a rate above the physiological range at rest or during exertion. Meanwhile, in elderly patients and in those with underlying heart disease, decreased contractile reserve and systemic vascular resistance as well as abnormal high ventricular response can cause low-output HF, where the heart pumps blood at resting rate or at an effort below the physiological range (4,5,6).

In clinical practice, CHF due to thyrotoxicosis is a rare entity. Even though exercise intolerance due to elevated cardiac output is the most common initial symptom in most patients, some patients might present with acute HF signs and symptoms as shown in our case (7). Also, patients may develop severe systolic dysfunction in the later stages of the disease if it is not treated. Although this condition is infrequent and commonly encountered in patients with pre-existing heart disease, our case has showed that it can develop in subjects without pre-existing heart disorder.

Sinus tachycardia and AF are the most common rhythm disorders, and they are usually reversible as a result of the treatment of thyrotoxicosis (8). The mechanism of arrhythmia caused by elevated thyroid hormone levels is multifactorial. Elevated thyroid hormone levels can alter β1-adrenergic and M2-muscarinic receptors of the heart in patients with hyperthyroidism, which can result in an increase in sympathetic function and a decrease in atrial refractory period (8,9). Additionally, high thyroid hormone can play a role in changing ionic channels, which can create a suitable substrate for AF formation (8,9).

In patients with AF who are hyperthyroid at the time of diagnosis, the risks of a failure cardioversion increase

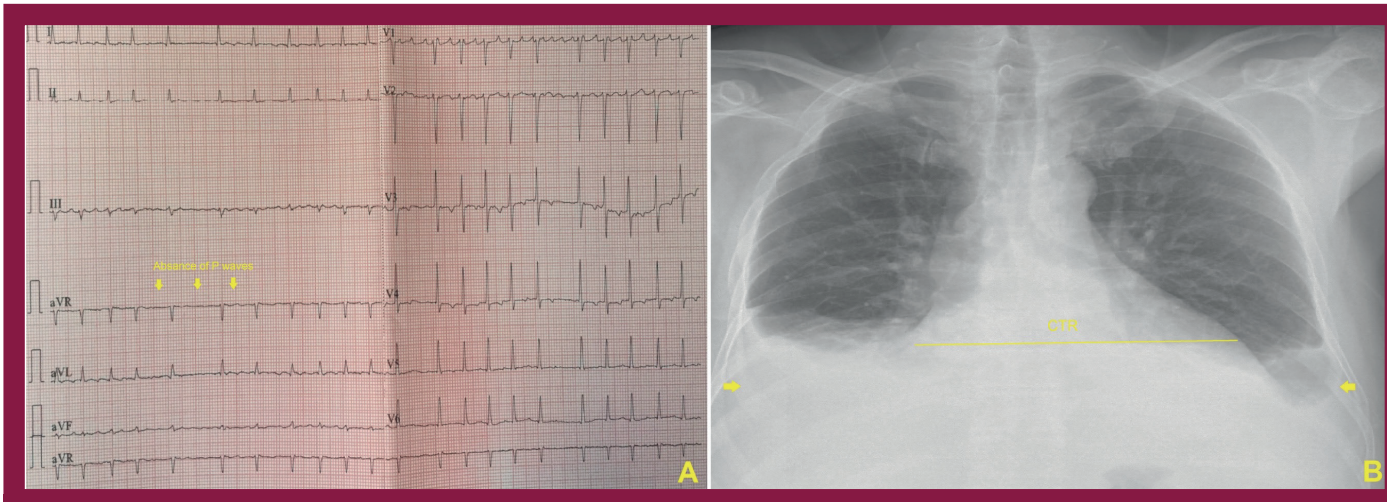

Figure 1. Electrocardiography and posterior-anterior chest scan of the patient. (A) Electrocardiography image showing atrial fibrillation. (B) Posterior-anterior chest scan image showing enlargement of the cardiothoracic ratio and bilateral pleural effusion

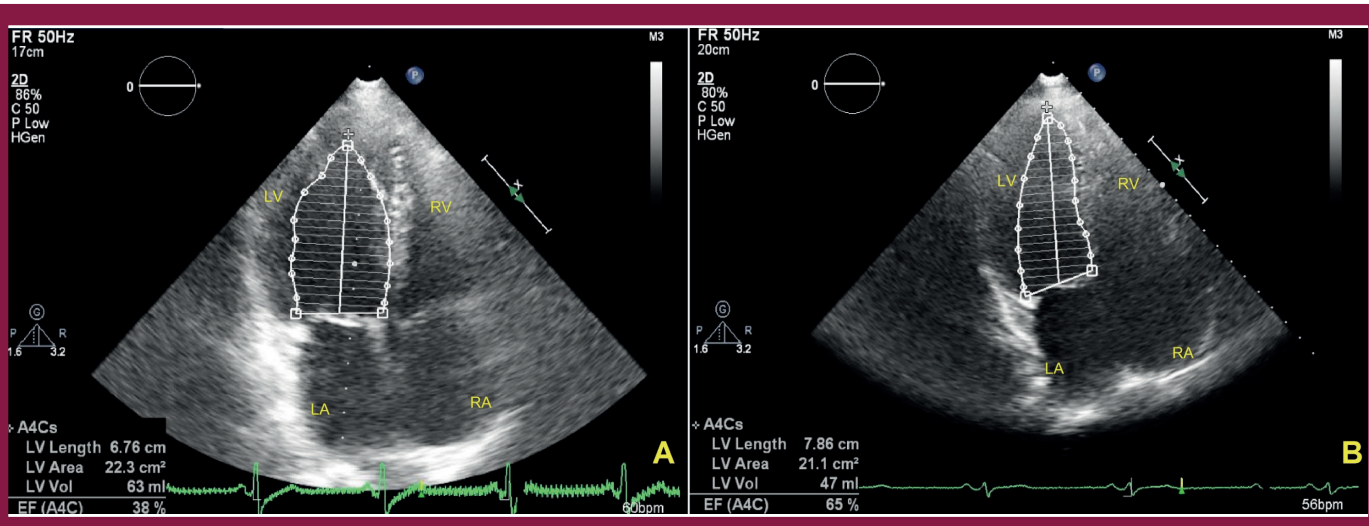

Figure 2. Transthoracic echocardiography of the patient. (A) Left ventricle ejection fraction was found to be 38% on one-month control according to the Simpson method. (B) Left ventricle ejection fraction was found to be 65% on six-month control according to the Simpson method

considerably (9). Thus, cardioversion may be an option for those who remain in AF after 8-10 weeks of remaining in a euthyroid state with anticoagulation for at least three weeks (9).

The mainstay of treatment in patients with HF reduced ejection fraction and AF is a combination of beta-blocker and anti-thyroid agents, such as PTU or methimazole (2,9). Besides that, in the acute setting, amiodarone may be used due to the benefit of restoring normal sinus rhythm when paired with anti-thyroid drugs like PTU to reduce the risk of thyrotoxicosis worsening (2,9). Lastly, patients who have HF findings should also be treated with ACE inhibitors, mineralocorticoid-receptor antagonists, and diuretics in addition to the aforementioned treatments (9).

Conclusion

In conclusion, in this case report, we have demonstrated that thyrotoxicosis can cause severe but reversible LV dysfunction in relatively young individuals without previous chronic disorder. Thus, routine monitoring of TSH levels should be performed in each patient presenting with acute HF to exclude thyrotoxicosis diagnosis.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: V.Ç., T.Ç., Design: M.S., A.L.O., Data Collection or Processing: V.Ç., T.Ç., M.S., Analysis or Interpretation: T.Ç., A.L.O., Literature Search: V.Ç., T.Ç., M.S., Writing: V.Ç., T.Ç.

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

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

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LETTER TO THE EDITOR

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The Utility of Poisoning Severity Score in Emergency Service

Zehirlenme Şiddet Skorunun Acil Serviste Kullanımı

Serdar Özdemir[1], Abdullah Algın[1,2]

[1]*University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Somalia Mogadishu Recep Tayyip Erdogan Faculty of Health Sciences, Mogadishu, Somalia*

Keywords: Poison, Poisoning, toxicology

Anahtar Kelimeler: Zehir, zehirlenme, toksikoloji

Dear editor,

The frequency and characteristics of poisonings vary according to the cultural and socioeconomic structure of the societies. It has been reported that the incidence of intoxication in patients admitted to emergency services worldwide is between 0.5% and 5% (1). In our country, according to the results of a small number of epidemiological studies, the annual poisoning incidence was found between 0.46% and 1.76% (1). It is estimated that this rate is higher in our country due to the fact that some poisoning patients are tried to be treated with traditional methods without applying to hospitals (1).

Poisoning can cause serious consequences depending on the agent and the time of admission to the hospital. Some of these patients are discharged after follow-up and treatment in emergency services. However, it is not enough to observe some patients in the emergency department, and close follow-up and treatment are required by hospitalization. In this case, the clinics, emergency services and intensive care units bring significant burden (2). Determining the severity of poisoning allows better determination of the true risks of these patients and development of treatment protocols (3).

A standard qualitative assessment for staging the severity of poisoning allows the determination of mortality and morbidity caused by poisoning and facilitates data analysis. In clinical toxicology, the glasgow coma score, which focuses on central nervous system toxicity, and Matthew-Lawson Coma scale, which focuses on barbiturate poisoning, have been used for many years (1,4). In addition, the Rumack-Matthew nomogram in paracetamol poisoning and the Done nomogram in salicylate poisoning are used for the clinic decisions. However, the usage area of these systems is limited (4,5).

The poisoning severity score (PSS) was developed by the International Program on Chemical Safety, the Commission of the European Union, the European Association of Poison Centers and Clinical Toxicologists for staging the severity of poisoning (6). The first version of PSS was introduced in 1990. Later, it was tested by the Poison Information Center of many countries and modified in 1994. PSS is used in all types of intoxication for staging adult and child intoxications (6,7). This scale includes both subjective symptoms and objective findings, regardless of the type, amount, serum and plasma concentration of the substance taken. PSS is calculated according to the most serious symptoms and signs of nine different organs or systems in the whole clinical process. Gastrointestinal tract, respiratory system, nervous system, cardiovascular system, metabolic balance, liver, kidney, hemopoietic system, muscular system, local effects on skin, local effects on eye, local effects from bites and stings are evaluated for PSS. PSS is scored from 0 to 4.0 indicates no symptoms and signs, 1 indicates mild grade poisoning, 2 indicates intermediate poisoning, 3 indicates severe symptoms and signs, and 4 indicates death (6,7).

In conclusion, grading the severity of poisoning with PSS as a standard scale will allow qualitative evaluation of the morbidity and mortality caused by poisoning, better determination of actual risks, and standardization of data.

Ethics

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Authorship Contributions

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Address for Correspondence: Serdar Özdemir, University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
Phone: +90 505 267 32 92 E-mail: dr.serdar55@hotmail.com **ORCID ID:** orcid.org/0000-0002-6186-6110

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