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RESEARCH ARTICLE
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Evaluation of Carhart's Notch in Patients with Serous Otitis Media

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ABSTRACT

Objective: To investigate the changes in bone-conduction and air-bone gap in patients with serous otitis media and to evaluate the presence of Carhart's notch.
Material and Methods: Patients with unilateral serous otitis media were included in the study. Audiometric evaluation comprised air-conduction and bone-conduction hearing thresholds, and air-bone gap values. The preoperative and postoperative pure tone audiometry results of 45 patients were compared in terms of the air-bone gap and bone-conduction thresholds.
Results: Carhart's notch was present in 17 (37.8%) patients preoperatively. For pure tone audiometry, there was a statistically significant decrease in air-bone gap at all frequencies postoperatively. The postoperative decrease in the bone-conduction thresholds was statistically significant only at 2 kHz. In the postoperative period, a 4.7 dB improvement was observed in the bone-conduction threshold at 2 kHz for patients with Carhart's notch.
Conclusion: Carhart's notch may be present in patients with serous otitis media. It is not specific to otosclerosis.

Keywords: Otitis Media with Effusion; Audiometry; Hearing Loss, Conductive; Bone Conduction; Carhart's Notch

INTRODUCTION

Carhart's notch (CN) is an audiogram finding first described by Raymond Carhart in 1950 in otosclerosis patients, which involves the greatest depression in bone conduction (BC) thresholds without any change in air conduction (AC) thresholds at 2 kHz (1). Therefore, BC is very important in the formation of CN. A study published in 2005 reported five different pathways contributing to BC hearing: a) sound transmitted into the external ear canal, b) middle ear ossicle stability, c) stability of the cochlear fluids, d) compression of the cochlear walls, and e) pressure transmission from cerebrospinal fluid (2). Considering these different pathways, it is thought that many different external or middle ear pathologies causing conductive hearing loss (in situations a or b) may contribute to CN formation by deteriorating BC.

Serous otitis media (SOM) is a middle ear pathology characterized by the existence of fluid in the middle ear cavity without signs or symptoms of acute ear infection (3). The existence of fluid in the middle ear cavity affects transmission of sound from the external ear to the inner ear, causing an increase in the stiffness and mass of the middle ear system and conductive hearing loss occurs (4). There are studies in the literature that revealed the relationship between CN and middle ear pathologies (e.g., congenital or acquired ossicular chain anomalies and otitis media with effusion) (5-7). Therefore, CN is not specific to otosclerosis, which is characterized by conductive hearing loss.

The aim of this study was to investigate the changes in BC and air-bone gap (ABG) in SOM patients and to evaluate the presence of CN.

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MATERIAL AND METHODS

The patients operated on between October 2017 and October 2019 with a diagnosis of SOM were included in the study. The ethical committee of the institution approved the study protocol (Zonguldak Bülent Ecevit University, Human Research Ethics Committee, Date: 16/10/2019, Approval Number: 2019-169-16/10), and the study adhered to the Declaration of Helsinki. The study was designed retrospectively, and therefore informed consent was not obtained.

Patients with unilateral SOM were included in the study in accordance with the following inclusion criteria: 1) 6 to 65 years of age; 2) presence of clinical signs of SOM (otoscopy revealing matte appearance, bubbles, amberish or honey-like color, fluid accumulation behind the tympanic membrane, retraction of the tympanic membrane, etc.), normal examination of other ENT areas (especially on nasopharyngeal endoscopy) and absence of systemic signs of infection; 3) conductive hearing loss on pure-tone audiometry (PTA) and type B tympanogram curve of the affected ear; 4) no recovery after three months of medical treatment (antibiotics and/or decongestants and/or nasal steroids); 5) placement of a tympanostomy tube (TT) for SOM treatment (Shepard, Invotec, Jacksonville, USA); 6) diagnosis of SOM confirmed by aspirating serous fluid from myringotomy; 7) undergoing a PTA test before TT placement (preoperative); and 8) undergoing a PTA test after removal of TT from the external ear canal (postoperative, at least six months after surgery).

The exclusion criteria were as follows: 1) bilateral presence of SOM; 2) history of any otologic disease (otosclerosis, cholesteatoma, chronic otitis media, Meniere's disease, barotrauma, etc.); 3) history of any otological surgery (TT placement, tympanoplasty, mastoidectomy, etc.); 4) not attending follow-up after TT placement; 5) developing complications due to TT placement (permanent perforation of the tympanic membrane, inflammation and discharge in the middle ear, etc.); and 6) removal of TT from the tympanic membrane or external ear canal earlier than six months postoperatively.

All patients underwent PTA using the same audiometer (GSI-61 clinical audiometer device [Grason-Stadler, Eden Prairie, Minnesota, USA]), performed by the same audiologist in a soundproof room. Parameters measured during the audiometric evaluation comprised AC hearing thresholds at the frequencies of 0.25, 0.5, 1, 2, 4, and 8 kHz, BC hearing thresholds at 0.5, 1, 2, and 4 kHz, and ABG values at 0.5-4 kHz intervals. The criterion for CN was taken as a minimum depression of 10 dB in BC in comparison with the rest of the thresholds at 2 kHz. The preoperative and postoperative 0.5, 1, 2, and 4 kHz PTA test results for 45 patients were compared in terms of the ABG and BC thresholds.

Data analysis was performed using SPSS v. 24.0. In descriptive analyses, categorical variables are presented as percentages and continuous variables as mean±standard deviation (median, min-max) values. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov-Shapiro-Wilk's test) to determine whether they were normally distributed. Since the PTA measurements were not normally distributed, non-parametric tests were conducted to compare these parameters. The Wilcoxon test was used to compare the changes in the PTA measurements from the preoperative period to the postoperative period. Statistical significance was considered at $p<0.05$.

RESULTS

Forty-five patients with SOM were included in the study. Twenty-eight (62.2%) patients were male and 17 (37.8%) were female. The mean age of the patients was 30.3 ± 22.2 (median:21, min:6-max:65) years.

In the PTA performed in the preoperative and postoperative periods, the mean ABG (at 0.5, 1, 2, and 4 kHz frequencies) for patients with SOM were 21.9±8.7 dB (median:18.8, min:2.5-max:41.3) and 7.1±2.9 dB (median:6.3, min:1.3-max:15), respectively. For patients with SOM and CN positive, the mean ABG in the preoperative and postoperative periods were 23.8±7.7 dB (median:22.5, min:12.5-max:36.3) and 8.1±3.2 dB (median:7.5, min:2.5-max:15), respectively. The postoperative decrease in ABG at all four frequencies (0.5, 1, 2, and 4 kHz) was found to be statistically significant ($p<0.001$) (Table 1). While the differences between the preoperative and postoperative period in terms of the BC thresholds values obtained at 0.5, 1, and 4 kHz were not statistically significant ($p=0.660$, $p=0.219$, and $p=0.417$, respectively), the decrease in the BC thresholds at 2 kHz was statistically significant ($p<0.001$) (Table 2). In other words, improvement in AC affected the BC hearing threshold at 2 kHz.

Table 1. Preoperative and postoperative ABG values at different frequencies.

Frequency (kHz)	Preoperative Median (min-max)	Postoperative Median (min-max)	p[a]
0.5	25.0 dB (0-55)	10.0 dB (0-20)	*<0.001*
1	25.0 dB (0-50)	10.0 dB (0-15)	*<0.001*
2	5.0 dB (0-25)	0.0 dB (0-10)	*<0.001*
4	25.0 dB (0-45)	10.0 dB (0-35)	*<0.001*

ABG: air-bone gap, dB: decibel, $p<0.05$ was accepted as significant,
[a]: p-value for Wilcoxon test

Table 2. Preoperative and postoperative BC values at different frequencies.

Frequency (kHz)	Preoperative Median (min-max)	Postoperative Median (min-max)	p[a]
0.5	10.0 dB (0-65)	5.0 dB (0-65)	0.660
1	5.0 dB (0-65)	5.0 dB (0-65)	0.219
2	25.0 dB (5-75)	20.0 dB (0-75)	*<0.001*
4	15.0 dB (0-85)	10.0 dB (0-85)	0.417

BC: bone conduction, dB: decibel, $p<0.05$ was accepted as significant,
[a]: p-value for Wilcoxon test

Preoperatively, CN was present in 17 (37.8%) of the 45 patients. In the CN group, the ABG decreases at all frequencies (0.5, 1, 2, and 4 kHz) were statistically significant according to postoperative PTA (p<0.001, p<0.001, p=0.005, and p=0.001, respectively) (Table 3). In the postoperative period, PTA revealed a 3.2 dB improvement in the BC threshold at 2 kHz, while the patients with CN showed an improvement of 4.7 dB.

Table 3. ABG change in SOM patients with CN.

Frequency (kHz)	Preoperative Median (min-max)	Postoperative Median (min-max)	p[a]
0.5	30.0 dB (20-45)	10.0 dB (5-15)	*<0.001*
1	35.0 dB (10-50)	10.0 dB (0-15)	*<0.001*
2	5.0 dB (0-25)	0.0 dB (0-10)	*0.005*
4	25.0 dB (0-45)	15.0 dB (0-30)	*0.001*

ABG: air-bone gap, dB: decibel, p<0.05 was accepted as significant,
[a]: p-value for Wilcoxon test

DISCUSSION

The depression in BC at 2 kHz is known as CN and is widely considered to indicate stapes fixation. Conijn et al. showed a good relationship between conductive loss in PTA and conductive loss findings estimated in brain-evoked response audiometry for frequencies other than 2 kHz (8). Although the decrease in BC at 2 kHz is based on stapes fixation in otosclerosis, this condition was also reported in other middle ear pathologies such as primary malleus fixation and SOM (5-10). Kumar et al. reported that the accumulation of glue fluid in the middle ear of SOM patients and edema in the middle ear mucosa may cause impedance in the sound transmission resulting in CN (7).

In a study by Shishegar et al. examining patients with SOM, the CN positivity rate was found to be 44.9%**.** The authors also separately discussed the CN-positive SOM cases based on the presence of dullness, redness, and swelling in the tympanic membrane and reported their rate as 25.3% (11). Kumar et al., evaluating 95 ears with SOM, detected CN in 37 (38.9%) ears (7). In another study, Ahmad and Pahor calculated the rate of CN as 26% in their sample of 50 patients with SOM (9). In a study by Telmesani et al., the ability of CN to predict the presence of effusion was evaluated in patients with SOM and CN positivity was reported in 97 of 148 ears (65.5%). The authors found the sensitivity and specificity of CN in predicting effusion in SOM were 85.2% and 87.5%, respectively (12). In the current study, we found that CN was positive in 17 (37.8%) of the 45 patients with SOM. The CN positivity rate might have been higher in our study considering that we used only 2 kHz frequency for CN positivity. Previous studies used different frequencies like 0.5, 1, 2 or 4 kHz to evaluate CN positivity (9, 11). It may be suggested that the CN definition should be redefined in order to ensure integrity in the literature and for more accurate comparison of studies.

Kashio et al. divided their patients into three groups as stapes fixation, incudostapedial joint dislocation, and malleus-incus fixation, and determined the CN rates of these groups as 31.4%, 26.3%, and 30%, respectively. In addition, in the presence of CN at a frequency of 2 kHz, they found an improvement in BC hearing thresholds in the postoperative period that was recorded as 4.3 dB, 15 dB, and 19.2 dB, respectively (13). In our study, after TT placement in SOM patients with CN, the hearing threshold in BC improved by an average of 4.7 dB. When BC hearing improvements were compared with Kashio's study, the closest group to the SOM group in our study was the stapes fixation group. The common feature of SOM (via fluid in the middle ear occluding the round window) and stapes fixation (via oval window involvement) is that the windows in the middle ear related with cochlear fluids are affected. In other words, we think that the elimination of the occlusion effect in the oval or round window in the presence of CN is a factor that improves BC hearing together with ABG. As a result, occlusion of the oval or round window for any reason may cause a false depression in BC at 2 kHz on the audiogram.

Kumar et al. detected glue fluid during myringotomy in 36 of 37 ears with SOM and CN, and found the ABG levels of the 47 patients were 10 dB and above (7). Shishegar et al. reported the mean ABG level was 25.9 dB in CN-positive patients with SOM (11). In our study, we determined the preoperative ABG level was 23.8 dB in patients with SOM and CN positive. Kumar et al. also stated that CN was a very important indicator providing an understanding of the presence of glue fluid in myringotomy in patients with SOM and concluded that myringotomy should be performed in cases with CN positivity, type B curve in the tympanogram, and an ABG of ≥30 dB (7). Similarly, in a study by Shishegar et al., a strong correlation was found between the presence of glue fluid in the middle ear and CN positivity, type B tympanogram, and ABG >20 dB (11).

We also recommend myringotomy for SOM patients if the ABG is >20 dB, without CN positivity. In addition, according to the results of our study, in cases with CN positivity, myringotomy should be performed considering the improvement of BC at 2 kHz.

Kashio et al. compared the improvement in BC at 2 kHz with the improvement in ABG and found no relationship in different middle ear pathologies (13). Cook et al., on the other hand, found a weak but significant link between the improvement in AC at 2 kHz and the improvement in BC after stapes surgery (14). However, neither Shishegar et al. nor Kumar et al. compared the improvement between postoperative ABG and postoperative BC at different frequencies (7, 11). When we evaluated the improvement in the mean postoperative ABG and BC threshold values compared to the preoperative period, we found a significant decrease in ABG at the frequencies of 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz (p<0.001). However, only the decrease in the BC threshold at 2 kHz was statistically significant (p<0.001). BC is very important to identify CN in the audiogram. In fact, one point to consider is that CN can be more detectable in middle ear pathologies. In routine PTA, only the main frequencies such as 0.5, 1, 2, and 4 kHz are used. On the other hand, CN may also occur at non-routinely used

intermediate frequencies like 3 kHz. Therefore, we recommend further studies to detect the presence of CN at frequencies that are not routinely tested in middle ear pathologies.

Lastly, Yasan H. reported that while CN at 2 kHz indicates stapes footplate fixation, CN at 1 kHz indicates mobile stapes footplate (15). In our study, 2 kHz was used to determine the CN. After myringotomy was performed in SOM patients with CN, all patients had a remarkable improvement in ABG and an improvement in 2 kHz BC was observed. Therefore, contrary to Yasan H.'s study, CN did not indicate stapes footplate fixation in our study. Most otorhinolaryngologists consider the association of CN - otosclerosis as an inseparable binary and they immediately look for the presence of CN in the audiograms of patients suspected of having otosclerosis. Considering all these studies contributing to the literature, including our study, the tenet of "CN is specific to only otosclerosis" should be abandoned.

The patients' hearing status assessment needs a sustained effort to simultaneously take into consideration many parameters, including patient's cooperation. In the present study, we did not make a standardization on this subject. On the other hand, the retrospective design of the study and the small number of patients included in the study are two other limitations of our study. Prospective studies with larger number of patients are needed on this subject.

CONCLUSION

In the present study we found that CN, which is known to be specific to otosclerosis, could also be positive in SOM. The placement of TT can lead to a significant improvement in ABG and BC level at 2 kHz in patients with SOM.

Ethics Committee Approval: The ethical committee of the institution approved the study protocol (Zonguldak Bülent Ecevit University, Human Research Ethics Committee, Date: 16/10/2019, Approval Number: 2019-169-16/10), and the study adhered to the Declaration of Helsinki.

Informed Consent: The study was designed retrospectively, and therefore informed consent was not obtained.

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RESEARCH ARTICLE
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The Effect of Coenzyme Q10 on Vestibular Compensation Process after Unilateral Labyrinthectomy in Rats Using Behavioral Tests

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ABSTRACT

Objective: To determine the effect of coenzyme Q10 on the vestibular compensation process after unilateral labyrinthectomy.
Material and Methods: Thirty Wistar rats were randomly assigned to 3 equal groups: the negative control group, the experimental group and the control group. Labyrinthectomy surgeries were performed in all 3 groups. After the labyrinthectomy, findings such as nystagmus with its fast phase directed to the undamaged side, deviation of the head to the side operated on, impairment in walking, and decreased tonus of the extensor muscles on the same side were observed.
Results: The values of Group EG and Group CG were somewhat higher than those of Group NCG in terms of the degree of head tilt, but there was no statistically significant difference among the three groups. Although Group EG and Group CG were found to differ statistically significantly from Group NCG on certain days in terms of postural deficit values and nystagmus, this significance remained limited to those particular days.
Conclusion: The effect of CoQ10 on the vestibular compensation process was limited may be due to its limited dose, short duration of administration, and the limited number of rats. We believe that the effects of CoQ10 on the vestibular compensation process after labyrinthectomy should not be neglected. Despite the fact that we administered it at limited doses for a short term on a limited number of rats, CoQ10 should be used in larger samples, in higher doses, and for a longer time because CoQ10 has positive, though limited effects, on the vestibular compensation process.

Keywords: Labyrinthectomy, CoQ10, vestibular compensation

INTRODUCTION

In 1904, Millian and Lake independently identified labyrinthectomy, the last-resort treatment method for controlling vertigo (1, 2). Labyrinthectomy is divided into two categories as chemical and surgical labyrinthectomy. Aminoglycosides are used as vestibulotoxic agents in chemical labyrinthectomy to treat vertigo by performing unilateral vestibular ablation (3). Surgical labyrinthectomy is quite an effective ablative surgical method that can be used for vertigo control in unilateral peripheral vestibular pathologies after medical treatment failure and in the presence of significant hearing loss (1, 2).

Substances that prevent or delay the oxidation of biological molecules such as proteins, lipids, carbohydrates and DNA, which exist in the cellular structure and can be oxidized, are called antioxidants. The prevention of the oxidation of such molecules is called the antioxidant defense system (4, 5). Coenzyme Q10 (CoQ10) is a vitamin-like compound that acts as a coenzyme in key enzymatic reactions in cells during the production of energy. It can be found in every cell and dissolved in fat. Coenzyme Q10 interacts with oxygen-induced radicals and free oxygen, preventing the onset of lipid peroxidation and damage to biomolecules (6-8). In addition to its antioxidant

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effect, it has free radical scavenging and vasodilator effects. It also reduces pro-inflammatory cytokines and blood viscosity. Coenzyme Q10 has been cited in the literature as being used in the field of otolaryngology in patients with vertigo and Meniere's disease, in the treatment of sudden hearing loss, and in the treatment of tinnitus. It has also been used because of its protective effect against ototoxic agents (9-12).

The knowledge on vestibular functions stems from clinical information obtained from unilateral or bilateral labyrinthine lesions and experimental information obtained from animal experiments on this subject. Based on animal experiments, medications, as well as visual and physical exercises, affect the compensation event (13).

This study aimed to assess how parenteral use of CoQ10 affected the vestibular compensation process after labyrinthectomy depending on the degree of head tilt, postural deficit and nystagmus. A review of the literature showed numerous studies involving the treatment of vestibular compensation after labyrinthectomy, but no study involving the use of CoQ10.

MATERIALS AND METHODS

This study involved the use of 30 healthy adult female Wistar albino rats with an average weight of 200–250 grams. The rats were kept in appropriate ventilation conditions and special cages in rooms with sunlight. For seven days before the study began, the rats were housed at room temperature in an environment where they could get 12 hours of light, 12 hours of dark, with free access to food and water. The water they drank was replaced every day, and their cages were cleaned every other day. No dietary restrictions were administered before or during the study. Power analysis was carried out, and the number of rats in the sample for 3 units was determined to be at least 10 for each group based on mean difference, 80% testing power, 95% confidence interval and 2 standard deviations. This study was conducted with 1. Ondokuz Mayıs University Faculty of Medicine ethics committee approval (2016/16).

The 30 Wistar rats were randomly assigned to 3 equal groups: the negative control group (NCG) (n=10), the experimental group (EG) (n=10) and the control group (CG) (n=10). Labyrinthectomy surgeries were performed in all 3 groups.

Surgical intervention: Preoperative ampicillin sodium (20 mg/kg) was injected intra-muscularly for surgical infection prophylaxis. After anesthesia was administered intraperitoneally (IP) as ketamine 10% (50 mg/kg; Richter Pharma AG, Wels, Austria) and xylazine 2% (5 mg/kg; Bayer AG, Leverkusen, Germany), both ears of all rats were examined with the help of an otomicroscope. All rats in all 3 groups underwent surgical labyrinthectomy by the same surgeon on their right ears. Following a post-auricular incision, the submandibular gland and the facial nerve were identified, and the facial nerve was preserved by lateralizing the gland. Tympanic bulla was identified, and the bulla was exposed using a surgical electric drill and a curette. The malleus and the incus were identified. They were removed, and then the oval window and the vestibule were identified and destroyed by using an aspirator and a curette. The neuroepithelium and the membranous labyrinth were ablated using a curette and an aspirator. Finally, alcohol was injected and aspirated 3 times to completely destroy the vestibule. The wound site was stitched using 4.0 prolene sutures, and the sutures were removed 2 weeks later (Figure 1a-f). After the operation, the rats were each taken into a single cage and sheltered under standard conditions, with enough feed and water. The study excluded rats that lost more than 20% weight prior to treatment, developed ulcers in the cornea due to facial nerve damage, lost excessive blood intraoperatively or had symptoms such as convulsions, hemiataxia and paresis. During the study, none of

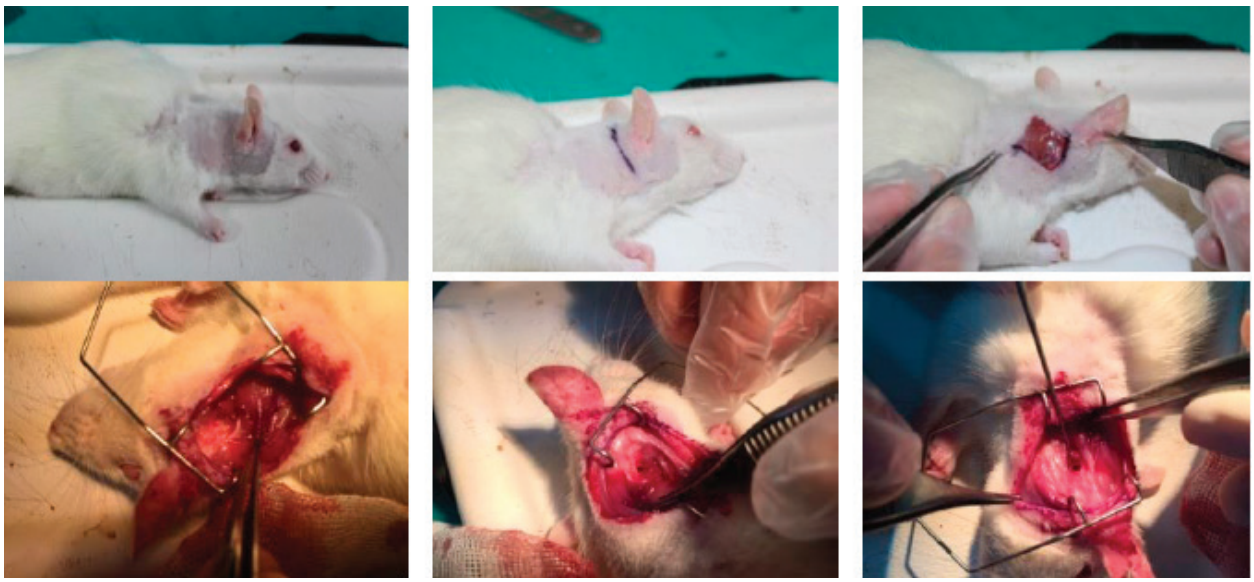

Figure 1a-f. Intraoperative images

the rats were lost. In the postoperative period, none of the rats had dehiscence, and there were no signs of infection.

The rats in the negative control group did not undergo any preoperative or postoperative medication. In the experimental group, 10 mg/kg CoQ10, dissolved in soybean oil, was administered as 1 mL for a single time per day intraperitoneally, for 3 days before the operation and for 3 days after the operation. In the negative control group, a single intraperitoneal dose of 1 mL soybean oil per day was administered, for 3 days before the operation and 3 days after the operation, to mimic the stress of IP injection that could occur in the rats in the experimental group.

Coenzyme Q10 Administration: Coenzyme Q10 powder (Sigma-Aldrich, Germany, Product Number: C9538-1G) was weighed in amounts for daily use, placed in bottles to protect it from light, wrapped with parafilm and stored at –20°C. The amount to be administered, a dose of 10 mg/kg daily, was dissolved in 1 mL soybean oil (Sigma-Aldrich, Germany) for each subject. After it was mixed in vortex for 10 minutes to obtain a homogeneous solution, it was pulled into injectors to be protected from light again and stored at +4°C (Figure 2a and 2b). The solution that was prepared was administered intraperitoneally for 3 days before and after the operation to the rats in EG. Soybean oil was administered to the rats in the control group intraperitoneally in the same dose and for the same duration. All injections were administered at the same time in the morning.

Evaluation of Vestibular Imbalance: After the labyrinthectomy, findings such as nystagmus with its fast phase directed to the undamaged side, deviation of the head to the side operated on, impairment in walking, and decreased tonus of the extensor muscles on the same side were observed, and the findings were recorded using a video camera (Figure 3a-d). Based on the study by Günther et al. (14), nystagmus, degree of head tilt and postural asymmetry were observed to assess behavioral signs of vestibular imbalance after labyrinthectomy on days 1, 2, 3, 7, and 15, and these behaviors were rated to have a score of a maximum of 10 points. The researchers observed the rats, and two researchers who did not know the group allocation of the rats scored the behavioral tests.

Figure 2a and 2b. Preparation of coenzyme Q10 with soybean oil

Nystagmus was observed visually.

- In the presence of spontaneous nystagmus, a score of 6–10 was given corresponding to 1 point per 60 beats per minute.
- If there was not any spontaneous nystagmus during rest, the animal was touched lightly. Such stimulated nystagmus was given a score of 1–5 corresponding to 1 point per 60 beats per minute.

The degree of head tilt was assessed spontaneously based on the angle between the jaw and the horizontal plane.

- If the angle was 90 degrees or if the head fell to the side of the lesion during rest and a barrel rolling, 10 points were given.
- If the angle was 60 degrees, 7 points were given.
- If the angle was 45 degrees, 5 points were given.

Postural asymmetry was scored as follows:

- Spontaneous barrel rolling was given 10 points.
- Barrel rolling that occurred after a light touch or blowing was given 9 points.
- Taking a lying position without any leg support toward the side of the lesion was given 8 points.

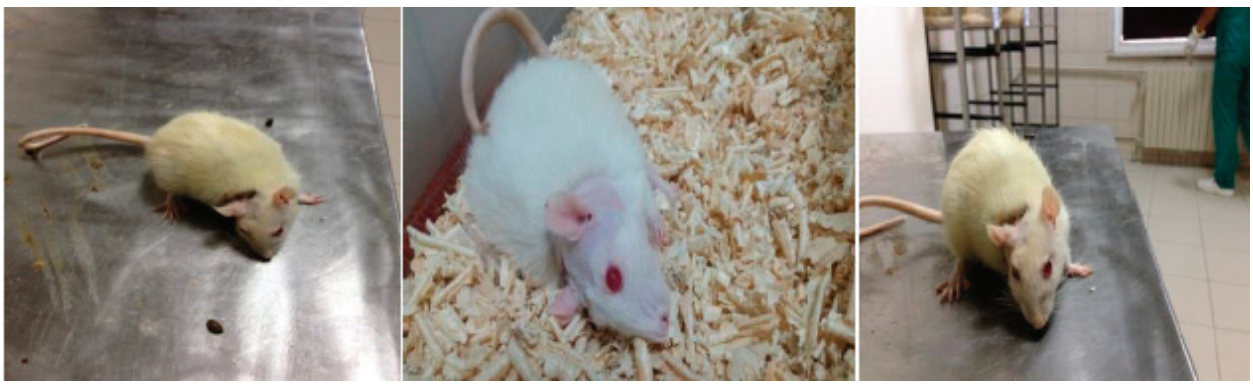

Figure 3a-d. Postoperative views (Behavioral asymmetries after unilateral labyrinthectomy: head tilting toward the operated side and limb extending on the intact side)

- Taking a lying position with leg support toward the side of the lesion was given 7 points.
- Turning in one direction or taking a lying position using the legs on the lesion side were given 6 points.
- Moving by using both legs was given 5 points.
- Wandering around while the head was rarely falling on the lesion side was given 4 points.
- Wandering around while the head was leaning on the lesion side was given 3 points.
- If the asymmetry was difficult to detect, 2 points were given.
- If the postural asymmetry was detectable only when the rat was lifted, 1 point was given.

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Version 23. The normality of the data was examined using the Shapiro Wilk test. Kruskal Wallis, Friedman test and Wilcoxon test were carried out to compare data that did not show normal distribution. The results were presented in the form of medians (minimum–maximum) and frequencies. The statistical significance level was set at $p<0.05$.

RESULTS

Nystagmus Values

Table 1 shows the change of the nystagmus values of the groups as per the day. There was no significant difference between EG and CG on days 1 and 2 in terms of the nystagmus values. However, there were statistically significant differences between EG and NCG and between CG and NCG ($p<0.001$). There was not any statistically significant difference between the groups in terms of the nystagmus values of the rats in each of the 3 groups whose nystagmus persisted on day 3 ($p=0.218$). Nystagmus values in EG and CG decreased over the days. The rate of decrease was statistically significant from day 1 to day 2 ($p<0.05$), but not significant from day 2 to day 3. In NCG, the decrease in nystagmus values was significantly different between all pairs of days ($p<0.05$). Nystagmus was observed in all rats in all 3 groups on days 1 and 2. On day 3, nystagmus persisted in 3 rats in EG, in 5 rats in CG and in 9 rats in NCG. On days 7 and 15, none of the rats were observed to have nystagmus. When the ratios in each time period were compared by carrying out a ratio test, there was a statistically significant difference between EG and NCG in terms of the number of rats whose nystagmus healed on day 3 ($p<0.05$), whereas there was no statistically significant difference between CG and NCG and between EG and CG ($p=0.141$, $p=0.65$, respectively).

Assessment of Degree of Head Tilt

As shown in Table 2, in the first 3 days, no full healing was observed in the degree of head tilt of any rat. There was no statistically significant difference between the groups in terms of the degree of head tilt on these days ($p=0.148$, $p=0.148$, $p=0.060$, respectively). On day 7, there was no statistically significant difference between the groups in terms of the

Table 1: The change of the nystagmus values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	6.5 (4-7)a	3.5(2-5)a	1 (1-2)	---	---
	N	10	10	9	---	---
Group 2	Median (min-max)	4 (3-5)b	1.5(1-2)b	1 (1-1)	---	---
	N	10	10	3	---	---
Group 3	Median (min-max)	4 (3-6)b	1.5(1-3)b	1 (1-1)	---	---
	N	10	10	5	---	---
	χ^2	16.6	16.3	3.0		
	P	<0.001	<0.001	0.218		

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

Table 2: The change of the degrees of head tilt values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	7(5-10)a	7(5-10)a	7 (5-7)a	5(5-7)b	5 (5-5)c
	N	10	10	10	9	6
Group 2	Median (min-max)	7 (5-7)a	7 (5-7)a	5 (5-7)ab	5(5-7)b	5 (5-5)ab
	N	10	10	10	5	3
Group 3	Median (min-max)	7 (5-10)a	7(5-10)a	6 (5-7)a	5(5-7)b	5 (5-5)ab
	N	10	10	10	6	4
	χ^2	3.8	3.8	5.6	1.6	0.0
	P	0.148	0.148	0.060	0.459	1.000

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

Table 3: The change of the postural deficit values of the groups based on the days

		1st Day	2nd Day	3rd Day	7th Day	15th Day
Group 1	Median (min-max)	7.5 (6-9)a	7 (5-9)a	5 (4-7)a	4 (3-5)a	2 (1-3)
	N	10	10	10	10	10
Group 2	Median (min-max)	5 (5-6)b	5 (4-6)b	3.5(3-4)b	2.5 (2-4)b	1 (1-3)
	N	10	10	10	10	10
Group 3	Median (min-max)	6 (5-8)b	5 (4-7)b	4 (3-6)b	3 (2-4)b	2 (1-2)
	N	10	10	10	10	10
	χ^2	14.8	1.9	15.2	12.7	5.9
	P	0.001	0.002	0.001	0.002	0.053

χ^2: Chi-Squared Test Statistics, a-c: no significant difference between groups with the same letter on the day

assessment of the rats whose heads were tilted more than normal (p=0.459). On day 15, there was no statistically significant difference in terms of the values of the rats whose heads were tilted more than normal (p=1). On day 7, the degree of head tilt became normal in 5 rats in EG, in 4 rats in CG, and in 1 rat in NCG. When the ratios in each time period were compared by carrying out a ratio test, there was no statistically significant difference between the groups in terms of degree of head tilt on day 7 (between EG and NCG, CG and NCG, EG and CG; p=0.141, p=0.3, p=1, respectively). On day 15, the degree of head tilt became normal in 7 rats in EG, 6 rats in CG, and 4 rats in NCG. When the ratios in each time period were compared by carrying out a ratio test, there was no statistically significant difference between the groups in terms of degrees of head tilt on day 15 (between EG and NCG, CG and NCG, EG and CG; p=0.37, p=0.65, p=1, respectively).

Postural Deficit Values

As shown in Table 3, there were no rats who fully recovered in terms of postural deficit values during the 5 different days when the measurements were made in any group. There was a statistically significant difference between postural deficit values obtained over time when each group was assessed in itself (p<0.05). The values obtained on each different day in each group were different from each other. Postural deficit values gradually dropped from day 1 to day 15 over time. And these drops were statistically significant (p<0.05). In conclusion, observation of the postural deficit values after labyrinthectomy showed that the rates of healing in EG and CG were similar to each other on days 1, 2, 3, and 7, but were statistically significantly better than those in NCG (p=0.001, p=0.002, p=0.001, p=0.002, respectively). No statistically significant difference was detected between the groups on day 15 (p=0.053).

DISCUSSION

Meniere's disease, trauma, prolonged vestibular neuritis, labyrinthitis, vascular causes, autoimmune inner ear disease and benign paroxysmal vertigo are among the causes of unilateral vestibular dysfunction. Primarily, treatment methods covering all kinds of pharmacological and compensation programs are administered in peripheral vestibular diseases. However, surgical options may be on the agenda for solving the problem in patients for whom these treatment methods are insufficient and who have become unable to do their job due to vertigo attacks and have reached the point of being detached from life (3).

Labyrinthectomy is quite an effective ablative surgical method of intervention that can be administered for vertigo control in unilateral peripheral vestibular pathologies where medical treatment has failed and there is a significant hearing loss (1).

Total hearing loss is an expected result after labyrinthectomy, which limits the scope of application to patients with preoperative severe hearing loss (15).

A significant imbalance develops in firing rates of vestibular nuclei, with a significant portion of ipsilateral second-order neurons going into silence after unilateral vestibular function losses due to causes such as labyrinthectomy, but such an imbalance heals over time (16).

In two different studies, it was observed that static imbalance in guinea pigs healed in the first week and in Rhesus monkeys in the third week (17, 18).

Part of the healing in the rest activity of second-order neurons is intrinsic. On the other hand, other subsequent lesions in other parts of the central nervous system (CNS), such as spinal cord or inferior olive, can cause temporary insufficiencies and a recurrence of static imbalance symptoms. Two important results can be inferred from these observations. The first of them is that a surprising compensation can occur for static vestibular pathologies. However, it might take a few weeks. The second one is that this compensation may be disrupted by other changes in the CNS in subsequent periods and lead to a recurrence of symptoms due to static vestibular imbalance. After permanent unilateral vestibular function losses, asymmetry in dynamic responses to head movements continues for a long time even if the imbalance heals (16).

After a unilateral labyrinthectomy, oculomotor and postural symptoms appear, such as spontaneous nystagmus, the deviation of the head and body toward the side undergoing surgery, and abnormal amplitude and timing in vestibulo-

ocular and vestibulospinal reflexes (19, 20). Most of such symptoms disappear within days or weeks based on vestibular compensation. Certain drugs positively influence the vestibular compensation process that develops after labyrinthectomy, and certain others negatively (21).

N-acetyl-DL-leucine (Tanganil) has long been successfully used in the treatment of acute vertigo (22, 23). Günther et al. used D and L forms of enantiomers of N-acetyl-DL-leucine (Tanganil), which have been used for treating acute vertigo for many years to improve postural compensation after vestibular neurectomy and labyrinthectomy, on rats in their study (14). They rated nystagmus, postural asymmetry and the degree of deviation of the head, which are some of the behavioral tests, before labyrinthectomy and on days 1, 3, 7, and 15 after labyrinthectomy. They observed that nystagmus disappeared on day 3 and that the deviation of the head and postural asymmetry continued until day 15. They did not observe any significant differences between the enantiomers of N-acetyl-DL-leucine (Tanganil) in terms of efficacy.

We also based our study on the study by Günther et al. (14) and chose to observe nystagmus, the degree of head tilt and postural asymmetry on days 1, 2, 3, 7, and 15 as the behavioral signs of vestibular imbalance after labyrinthectomy. In our study, we chose to work on rats as the experimental model because of the facts that rats are easy to look after, they breed fast, they can be obtained in large numbers for acceptable statistical results, experimental procedures with rats are easy, rats and humans have similar overall and ear anatomy, and it is easy to operate on rats.

Park et al. (24) examined the restoration of vestibular functions after a unilateral labyrinthectomy on rats. In their study, nitric oxide, which has antioxidant effects, was used to form two groups: rats that were and that were not given nitric oxide synthase inhibitor. They observed that nystagmus disappeared on day 7 in the group that was given nitric oxide synthase inhibitor, whereas it took 3 days for nystagmus to disappear in the group that was not given any drugs. The study of Park et al. supported our idea of using CoQ10, which is a powerful antioxidant, as an alternative to other treatments because of its antioxidant effect following a labyrinthectomy.

CoQ10 has a lipophilic characteristic, hence is insoluble in water due to its long side ring made up of 10 isoprenoids. For this reason, for the absorption of CoQ10, which is taken exogenously, it is necessary for it to be transported by chylomicrons to lymph and peripheral blood tissue. Because there is no intravenous form of it for humans yet, studies have been conducted for oral forms of it. Substances such as soybean oil, olive oil, and corn oil benefit CoQ10 absorption due to its hydrophobic characteristic (25). Such preparations, of which gastrointestinal absorption is about 4–6%, can be effective if they are taken at high doses and for a long time (26). Studies on volunteering subjects have demonstrated that CoQ10 has no side effects even after its oral intake at high doses (3000 mg/day), revealing that it is an agent that can be used safely (27). The injectable form of CoQ10 has been administered in the form of acute treatment in most of the studies carried out. When CoQ10 is administered parenterally, almost all of it is absorbed, and it reaches stable concentration in serum on the 6th day (26). The amount of CoQ10 detected in serum when it is given orally once a day at a dose of 150 mg/kg is equal to the amount of it measured when given intraperitoneally at a dose of 10 mg/kg. As parenteral CoQ10 absorption is close to 100%, the parenteral route was chosen in our study as the route of injection. CoQ10 was given at a dose of 10 mg/kg once a day, for 3 days before the operation and 3 days after the operation.

Khan et al. (9) examined patients with complaints of tinnitus who were found to have a low level of plasma CoQ10 prior to treatment. They found that 3×100 mg of CoQ10 supplementation per day reduced the patients' tinnitus complaints. Fetoni et al. (10) carried out a study on guinea pigs and observed that CoQ10 treatment inhibited free radicals induced by gentamicin, an ototoxic agent, and that it preserved hair cells against gentamicin ototoxicity and reduced gentamicin-induced hearing loss. In another study, Fetoni et al. (11) investigated the effectiveness of systemic and transtympanic administration of CoQ10 treatment for sudden hearing loss due to noise and assigned some rats into two groups. They systematically administered 100 mg/kg of CoQ10 to a group for 4 days after acoustic trauma and transtympanically administered CoQ10 to another group at 20–40% concentration 1 hour before acoustic trauma. They examined treatment responses through ABR on days 1, 3, 7, and 21. They found that CoQ10 was effective against sudden hearing loss due to noise and that its transtympanic and systemic administrations had similar results. They concluded that in sudden hearing losses, CoQ10 can be administered transtympanically, which is a minimally invasive procedure.

Kumar et al. (12) have found that in vertigo and Meniere-like syndromes, CoQ10 supplementation — which reduces proinflammatory cytokines and blood viscosity, eliminates free radicals and has a vasodilator effect — stimulates the immune system and corrects symptoms in patients with low CoQ10 concentration.

In this study, we assessed the effect of parenteral use of CoQ10 on the vestibular compensation process after labyrinthectomy. A review of the literature showed that there were numerous studies on the treatment of vestibular compensation after labyrinthectomy, but no study involving the use of CoQ10. Based on our study, the analysis of the effects of CoQ10 use after labyrinthectomy on the degree of head tilt revealed that it made positive contributions to the compensation process in EG and CG compared to NCG, but there was no statistically significant difference between the groups. When the postural deficit values were examined, statistically significant differences were found between all pairs of groups on days 1, 2, 3, and 7, but not on day 15. When the nystagmus values were examined, statistically significant differences were found between the pairs of groups on days 1 and 2, but not on day 3. The rate of healing in EG and CG was better than that in NCG on all

three days, and the rates of healing in EG and CG were found to be similar. According to the assessment based on degrees of head tilt, postural deficit values and nystagmus, the results of EG and CG were found to be close to each other. We think this result may have been due to the weak antioxidant effect of soybean oil.

The values of EG and CG were somewhat higher than those of NCG in terms of the degree of head tilt, but there was no statistically significant difference among the three groups. Although EG and CG were found to differ statistically significantly from NCG on certain days in terms of postural deficit values and nystagmus, this significance remained limited to those days. We think that the fact that in our study, the effect of CoQ10 on the vestibular compensation process was limited may be due to its limited dose, short duration of administration, and the limited number of rats. We believe that the effects of CoQ10 on the vestibular compensation process after labyrinthectomy should not be neglected. Despite the fact that we administered it at limited doses for a short term on a limited number of rats, CoQ10 should be used in larger samples, in higher doses, and for a longer time because CoQ10 has positive, though limited effects, on the vestibular compensation process.

Main Points

- Labyrinthectomy is a treatment method of last resort for controlling vertigo.
- After a unilateral labyrinthectomy, oculomotor and postural symptoms appear, such as spontaneous nystagmus, the deviation of the head and body toward the side undergoing surgery, and abnormal amplitude and timing in vestibulo-ocular and vestibulospinal reflexes.
- CoQ10, which is a powerful antioxidant, can be used as an alternative to other treatments because of its antioxidant effect following a labyrinthectomy.
- We assessed the effect of parenteral use of CoQ10 on the vestibular compensation process after labyrinthectomy. We believe that CoQ10 has positive, though limited effects, on the vestibular compensation process.

Ethics Committee Approval: This study was conducted with 1. Ondokuz Mayıs University Faculty of Medicine ethics committee approval (2016/16).

Informed Consent: Written informed consent was obtained.

Peer-Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- F.T., S.G.E., M.E.G.; Data Acquisition- F.T., S.G.E., M.E.G.; Data Analysis/Interpretation- F.T., S.G.E., M.S.Y.; Drafting Manuscript- F.T., S.G.E., M.G.; Critical Revision of Manuscript- F.T., S.G.E., M.G., M.S.Y.; Final Approval and Accountability- F.T., S.G.E., M.S.Y., M.E.G., M.G.

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Is Serum Uric Acid Level a Prognostic Value for Tinnitus Severity?

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ABSTRACT

Objective: Tinnitus is a disease that concerns a large part of society and its pathophysiology and etiology have not been exactly clarified. This study will investigate the association between serum uric acid (SUA) levels and idiopathic subjective tinnitus.
Material and Methods: Ninety-one tinnitus patients and 45 age- and sex-matched healthy volunteers were included in the study. Patients were divided into two groups as mild tinnitus and severe tinnitus according to the Tinnitus Handicap Inventory questionnaire. They underwent otolaryngologic examination, routine hematological and biochemical analyses, pure tone audiometry, doppler ultrasound, and magnetic resonance imaging to exclude possible causes of tinnitus. Patients with abnormalities in any test result were excluded from the study. The blood test results were statistically compared between the groups.
Results: Except for SUA levels, no significant difference was found between groups in any blood test results ($p>0.05$). Significant differences among the groups were determined in SUA levels ($p=0.001$). SUA levels were found to be significantly higher in the severe tinnitus group than in the mild tinnitus or control group ($p=0.002$, $p=0.001$). However, there is no statistically significant difference between the mild tinnitus group and the control group ($p=0.617$).
Conclusion: In this study, it was observed that there was a clear correlation between higher SUA levels and severe tinnitus. But this association did not reveal SUA levels as an accurate biological marker for tinnitus. It could only be utilized as a marker of disease severity. Further studies will help to reveal the exact relation.

Keywords: Biologic marker, blood tests, subjective tinnitus, tinnitus, uric acid

INTRODUCTION

Tinnitus is the perception of sound heard spontaneously in one or both ears, in the absence of any external audio stimulus. It is divided into two categories: objective and subjective (1). Objective tinnitus is described as tinnitus perceptible to the clinician as a sound coming out from the external auditory meatus, whereas subjective tinnitus is perceptible solely to the patient and has prevalence ranging from 2-32% (1-3). Although the most common cause of subjective tinnitus is acoustic trauma, conditions such as arterial hypertension, diabetes, cardiovascular diseases (CVD) and hyperlipidemia are also associated with tinnitus (1-4).

Uric acid (UA) is the product of purine metabolism and consists of xanthine through the reaction of xanthine oxidase (5, 6). Serum uric acid (SUA) levels frequently increase when renal excretion is reduced, such as when there is impaired renal function or decreased renal blood flow (6). In addition, some epidemiological studies have implicated a relationship between elevated SUA levels and hypertension, hyperlipidemia, cardiovascular disease, pre-eclampsia, renal failure, cerebrovascular events, and vascular dementia. Many authors have suggested that SUA might be an independent risk factor for all these conditions (1, 7, 8). However, there is no study showing whether SUA levels, which are known to be associated with cardiovascular diseases, can be used as a marker for tinnitus. The aim of the current study was to evaluate the possible relationship between SUA levels and subjective idiopathic tinnitus.

MATERIALS AND METHODS

Erzincan Binali Yıldırım University Clinical Research Local Ethics Committee's approval was obtained on 20.03.2020 with the

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decision numbered 03/24 prior to this prospective clinical trial. The study included patients from the ENT outpatient clinic with the complaint of tinnitus which had been ongoing for at least two weeks. All the patients underwent a detailed otorhinolaryngological examination, pure tone audiometry (PTO), carotid and vertebral artery Doppler ultrasound (US), and magnetic resonance imaging (MRI) of the inner ear to exclude possible causes of tinnitus. Auscultation of the neck was performed on all patients to eliminate objective tinnitus. According to evaluations, patients who were diagnosed with idiopathic subjective tinnitus (IST) were included in the study.

The Tinnitus Handicap Inventory (THI) was used to assess the intensity of the tinnitus. Turkish validity and reliability tests of the THI were conducted by Aksoy et al. (9). The THI consists of 25 questions with each item scored from 0-4 (0=no, 2=sometimes, 4=yes) and the total score ranges from 0 to 100 points. The patients were classified into five intensity grades in respect of the THI scores as slight (0–16 points), mild (18–36 points), moderate (38–56 points), severe (57–76 points), and catastrophic (77–100 points). For analysis in this study, two groups were formed according to the THI scores. Patients with a grade of 1 or 2 were included in the "mild tinnitus group", and those with grade 3, 4, or 5 in the "severe tinnitus group".

The study exclusion criteria was defined as the presence of neuro-otological problems that are known to cause tinnitus (Meniere's disease, asymmetric sensorineural hearing loss, vertigo, chronic otitis media, otosclerosis), chronic disease (diabetes, hyperlipidemia, hypertension, cardiovascular disease, liver, or kidney failure etc.) or medication use for any reason. Complete blood count and full biochemical analysis (glucose and UA levels, liver, renal and thyroid function tests) were performed from venous blood samples taken after 8 hours fasting. Patients with abnormalities in any test result (physical examination, blood tests, PTO, Doppler US, and MRI) were excluded from the study.

The study control group was formed of 45 age and sex-matched volunteers who attended the Outpatient Clinic for a check-up with no complaints. The control group subjects underwent the same physical examination, audiometric and blood tests as the tinnitus patients, but not Doppler US and MRI. Glucose and uric acid levels, liver, renal, and thyroid function tests of the patients and control group were recorded. All the test results were statistically compared between the three groups (mild tinnitus, severe tinnitus, and control).

Informed consent forms were obtained from all the patients and control subjects.

Statistical Analysis

Data obtained in the study was analyzed statistically using SPSS version 22 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Conformity of the data to normal distribution was checked with the Shapiro Wilk test, histograms, and q-q plots (Figure 1). Homogeneity of variance was assessed using the Levene test. Pearson Chi-Square analysis was used to compare the difference between categorical variables (groups and gender). The Kruskal–Wallis test was used to evaluate statistical significance between the groups for non-normal distributed parameters (WBC, hemoglobin, glucose, creatinine, AST, ALT, TSH, FT4). Parameters with normal distribution (age, BUN, platelet, and UA levels) were examined with One-Way ANOVA. The LSD post-hoc test was applied to multiple comparisons of SUA levels between the groups. A value of $p<0.05$ was accepted as statistically significant.

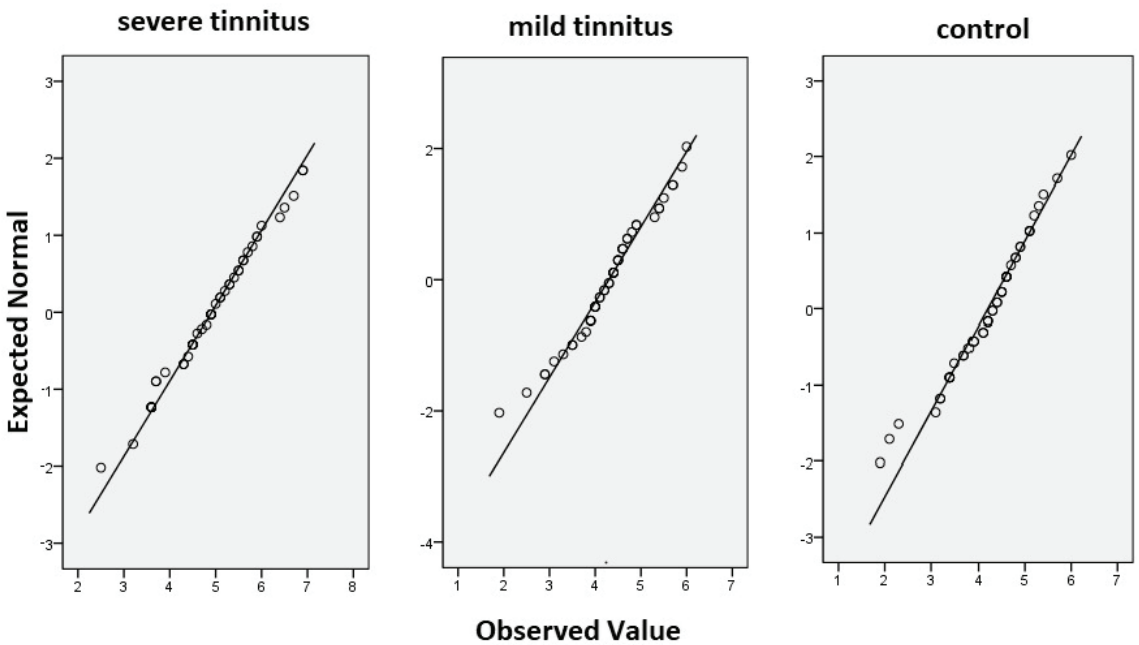

Figure 1. Normal Q-Q plot of serum uric acid levels.

Table 1: Demographic data and laboratory test results according to groups.

Variables	Control	Mild tinnitus	Severe tinnitus	P value
Age (years)	37.2±11.33	36.6±11.72	37.5±12.35	0.937
Gender (female/male)	23 (51.1)/22 (49.9)	24 (52.2)/22 (47.8)	24 (53.3)/21 (46.7)	0.978
WBC (10^3/mm^3)	6.9 (5.77-8.1)	6.7 (5.57-8.15)	6.9 (5.8-8.1)	0.833
Haemoglobin (g/dl)	14 (13.05-14.55)	13.8 (13.2-15.3)	13.8 (13.4-15.65)	0.341
Platelet (10^3/mm^3)	261.6±46.6	255.9±54.2	262.8±46.4	0.772
FG (mg/dl)	92 (87-955)	92 (90-96)	93 (89-97)	0.18
BUN (mg/dl)	14.06±3.58	14.06±3.22	14.15±3.26	0.989
Creatinine (mg/dl)	0.8 (0.7-0.91)	0.81 (0.71-0.92)	0.88 (0.76-0.98)	0.089
AST (IU/l)	22 (18-26)	21 (17-24)	22 (17-25)	0.884
ALT (IU/l)	20 (14-27)	18 (13-28)	21 (16-27)	0.716
TSH (mIU/l)	1.83 (1.42-2.58)	1.74 (1.43-2.73)	2.15 (1.56-2.61)	0.56
FT4 (ng/dl)	1.21 (1.09-1.45)	1.16 (1.04-1.3)	1.17 (1.08-1.3)	0.151
Uric acid (mg/dl)	4.2±0.89	4.29±0.87	4.91±1.02	**0.001**

Values are stated as *n* (%), mean±SD or median (25^{th}-75^{th} percentiles). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FG, fasting blood glucose; FT4, free thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cells. Bold value indicates statistically significance (p<.05).

RESULTS

A total of 134 patients were screened in the study, abnormal complete blood count and biochemical analysis were found in 36 patients, chronic diseases, and regular drug use in 18 patients, abnormal Doppler USG in 7 patients, Meniere's disease in one, and asymmetric hearing loss in two patients. Some of the patients had more than one exclusion criteria at the same time. Forty-three patients were excluded because they did not meet the criteria, and 91 patients were included in the study (48 females, 43 males; mean age, 37.1±12.05 years). According to THI, 46 patients were included in the mild tinnitus group and 45 patients in the severe tinnitus group. The demographic data and blood test results of the patients and control group are listed in Table 1. Age and sex were compared between the groups and no statistically significant difference was observed (p>0.05). Apart from SUA levels, no significant difference was found between the groups in any blood test results (p>0.05). A significant difference was determined between the SUA levels of the groups (p=0.001). According to the paired comparisons of the groups, the SUA levels were found to be significantly higher in the severe tinnitus group than in the mild tinnitus group and the control group (p=0.002, p=0.001). No statistically significant difference was determined between the mild tinnitus group and the control group (p=0.617). A scatter plot graph of the SUA levels of the three groups is shown in Figure 2. Multiple comparisons of serum uric acid levels between the groups are presented in Table 2.

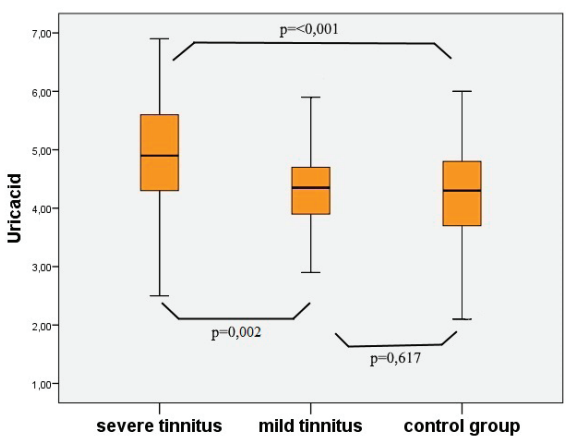

Figure 2. Scatter plot graph of serum uric acid levels

Table 2. Multiple comparisons of serum uric acid levels between the groups (LSD post-hoc test).

Groups	Mean difference	Std. Error	p value
Severe tinnitus - Mild tinnitus	0.613	0.195	**0.002**
Severe tinnitus - Control	0.711	0.196	**<0.001**
Mild tinnitus - Control	0.097	0.195	0.617

Bold values indicate statistically significance (p<.05)

DISCUSSION

Tinnitus is the perception of sound in the absence of any environmental acoustic stimulation. If this sound can be heard by the physician or another person, it is categorized as objective tinnitus, and if heard only by the patient, as subjective tinnitus (1). Causes of subjective tinnitus include presbycusis, noise-induced hearing loss, chronic otitis media, ototoxicity, labyrinthitis, Meniere's disease, otosclerosis, acoustic neuroma, metabolic dysfunction, and neurological diseases such as multiple sclerosis (1, 10). When no cause can be found in patients with subjective tinnitus, it is known as IST (11). It is thought that approximately one third of the population suffers

from tinnitus at least once per lifetime, and approximately 1–5% experience severe psychosocial complications (12).

The pathophysiology of the disease, which is common and impairs quality of life, has not yet been fully clarified. According to one theory, the pathogenesis of tinnitus is the perception of stimulation of the nerve endings with repeated spontaneous discharges as a real sound due to cochlear hair cell damage caused by noise or head trauma (10). Another theory has claimed that tinnitus occurs due to synchronization of the auditory nerve fibers that develops as a result of damage or metabolic abnormality in the central nervous system and auditory pathways (10).

The most common clinical conditions associated with tinnitus are chronic noise exposure, head trauma, and infections (13). In addition, many recent studies have shown a relationship between tinnitus and cardiovascular diseases (14). In a study by Figueiredo et al., a strong relationship was shown between tinnitus and hypertension, especially in elderly patients (15). Huang et al. reported a strong association between ischemic CVD and tinnitus in adults aged <40 years (14). Strikingly, there are also some studies indicating that SUA levels are a strong marker for CVD (6, 16). Therefore, the aim of this study was to reveal the possible association between tinnitus and SUA levels.

SUA level is a rapid and inexpensive test that is obtained from venous blood. In general, the SUA level is increased in kidney-related diseases. However, according to recent research, SUA levels have become a widely used biological marker for many clinical health issues such as systemic inflammatory diseases, hypertension, metabolic syndrome, and CVD (17-20). In addition to systemic diseases, it has been also investigated as a marker for some otological diseases. Ilancioglu et al. researched whether SUA levels are a cue for sudden sensorineural hearing loss (SNHL) and reported no significant difference in SUA levels between SNHL patients and the control group (21). Celikbilek et al. reported a strong positive correlation between SUA levels and benign paroxysmal positional vertigo (BPPV) (5). Yang et al. published a systematic review and meta-analysis, in which it was stated that BPPV is associated with elevated SUA levels but may not be an independent risk factor for the disease (22). To the best of our knowledge, this is the first study to have investigated the relationship between tinnitus and SUA levels.

The tinnitus patients in this study were separated into two groups according to the THI score. The reason for this division was to reveal whether SUA is also a prognostic factor for tinnitus in terms of severity. The statistical analysis results showed that the SUA levels were significantly different between the groups, with higher SUA levels in the severe tinnitus group than in the mild tinnitus group and the control group, but no difference between the mild tinnitus and control groups. The results can be considered reliable due to the normal distribution of SUA data and the application of parametric tests in the statistical analysis. The p value of < 0.001 in the analysis of the SUA levels also indicates a strong relationship. All these results suggest that SUA levels might be a marker only for severe tinnitus.

Severe tinnitus is quite difficult to treat. There is no licensed medication in Europe or North America for treatment of IST, although many have been trialed (11). Standard care is to inform the patient about the disease (including both causation and the progress of related distress), and the use of medication such as betahistine or antidepressants, hyperbaric oxygen therapy, masking devices, and cognitive behavioral therapy (CBT) to reduce the distress (11 ,23, 24). Psychology-based therapies, especially those based on CBT are often cited as the most efficacious of current tinnitus treatments, but nevertheless, there is no definitive cure (25). The presence of an association between high SUA level and severe tinnitus may lead to the consideration of new treatment modalities such as the use of diuretic drugs that reduce SUA or a UA-restricted diet.

There were some limitations to this study. The research was carried out with a small number of subjects because of the limited number of patients matching the inclusion and exclusion criteria during the planned period. Another limitation was that a high frequency audiometry test was not administered to the patients. According to the literature, high frequency hearing loss may cause an inclination to microangiopathic events (26). If patients with hearing loss above 8 kHz had been identified and excluded, the study population would have been more specific.

The results of this study demonstrated that there is a strong association between severe tinnitus and higher SUA levels even if it is within the normal range. However, this relationship has not shown that SUA levels are a definite biological marker for tinnitus. SUA can only be considered as a marker for disease severity. There is a need for further multicenter studies with larger samples to confirm these results. In addition, further investigation of the association between uric acid and tinnitus will shed light on whether diet and/or diuretics might have a place in the treatment of tinnitus.

Ethics Committee Approval: Erzincan Binali Yıldırım University Clinical Research Local Ethics Committee's approval was obtained on 20.03.2020 with the decision numbered 03/24 prior to this prospective clinical trial.

Informed Consent: Written informed consent was obtained.

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CASE REPORT
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Bilateral Parapharyngeal Abscess Complicated with Trismus, Airway Obstruction and Bleeding

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ABSTRACT

Bilateral parapharyngeal abscess is a very rare condition. Placing pressure on the airway on both sides increases the risk of respiratory arrest. Intubation cannot be performed due to the trismus caused by the infection in the mastication muscles, and the need to create an emergency airway can only be provided by invasive means. The adjacency of the region to major vessels and their branches can lead to massive hemorrhages since the infection erodes the vascular wall. In a case of bilateral parapharyngeal abscesses which resulted in respiratory arrest due to the trismus, we were able to ensure airway safety using a coniotomy and subsequent tracheotomy. The presence of massive hemorrhages on both sides in the early postoperative period caused us to remain constantly vigilant until the full recovery of the patient in terms of clinical, laboratory and radiological parameters.

Keywords: Bilateral, parapharyngeal, abscess, airway, bleeding

INTRODUCTION

Because of easy access to antibiotics and physicians, the incidence of parapharyngeal abscesses has been on decrease. However, it is still a condition that should be kept in mind and not be disregarded (1, 2). The most common etiological causes of parapharyngeal abscesses are dental infections and tonsillitis (1, 3, 4). Mediastinitis can cause serious complications such as internal jugular vein thrombosis, carotid artery rupture, cavernous sinus thrombosis, pericarditis, sepsis, epidural abscess and even mortality (1-3, 5).

In our literature review, we found only one case in which a bilateral parapharyngeal abscess was presented (6). In that case report, the bilateral parapharyngeal abscess was complicated with sepsis and pulmonary candidiasis (6). In the present report, we introduce a bilateral parapharyngeal abscess case which was complicated with trismus, upper respiratory obstruction and bleeding.

CASE REPORT

A 28-year-old male patient was admitted to our clinic with the complaints of trismus, difficulty swallowing, neck pain and fever. Our examination showed widespread edema and sensitivity in the neck. An oropharyngeal examination could not be performed since he had trismus. In addition, a laryngeal examination could not be performed due to his inability to tolerate the flexible endoscopic examination. Nasal cavity and nasopharyngeal examinations were normal. The patient's temperature was 38.9°C, leukocytes number was 22830/ml, neutrophil count was 20150/ml, and C-reactive protein level was 287.51 mg/l.

A contrast-enhanced neck CT scan was requested to detect the patient's infection focus. Upon the onset of respiratory distress, which began about one hour after the CT scan, the patient was taken to the operating room for emergency airway intervention. Due to the development of respiratory arrest, an emergency coniotomy was performed. Immediately afterwards, a tracheotomy was carried out and respiratory

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safety was ensured. Bilateral parapharyngeal, sublingual and submandibular abscess foci detected in the CT scan (Figure 1a, b, Figure 2a, b, c) were drained by bilateral submandibular incision. The submandibular gland posterolateral was retracted, dissection was continued upwards, and the parapharyngeal abscess foci were reached. By applying finger dissection, all loculations were combined to completely drain the abscess. After the control of bleeding, Penrose drainage was placed in both parapharyngeal spaces, and the operation was completed. Interventions were performed again under general anesthesia since the patient had bleeding on the left side on the postoperative first day and the right side on the postoperative second day. The patient's hemoglobin value during the admission was 13.76 g/dl. However, after the second bleeding, the hemoglobin level fell to 7.55 g/dl, and therefore, two units of erythrocyte suspension transfusion were applied.

Intravenous antibiotic therapy was applied after his first admission using ceftriaxone 2 x 2 g/100 ml and metronidazole 3 x 500 mg/100 ml. Gram positive cocci were observed in the microscopic examination of the stained abscess fluid taken during surgical drainage. Non-hemolytic streptococcus growth was observed in the culture. The current treatment was continued when it was revealed that the factor was sensitive to the antibiotic therapy which was started empirically.

The patient's oral opening reached a sufficient level on the 18th day of treatment. After the trismus was relaxed and the airway opening was ensured, his tracheotomy was closed, the nasogastric catheter was removed, and oral nutrition was started. The oropharyngeal examination, which could be performed after the oral opening was achieved, showed a caries on the right third molar tooth. Upon consultation with dentistry, the decayed tooth was extracted. After determining that laboratory examinations and contrast-enhanced neck tomography were normal on the 22nd day of the patient's admission (Figure 1c, Figure 2d), the patient was discharged with recovery. No pathology was detected during the patient's six-month follow-ups.

DISCUSSION

The frequency of parapharyngeal abscesses has decreased with the widespread use of antibiotics. However, this decreased frequency brings the danger of neglecting this condition. In addition, unlike other deep neck infections, parapharyngeal abscesses could be difficult to identify by inspection or physical examination. Here, contrast-enhanced tomography comes to the fore. Contrast-enhanced neck tomography is very useful in detecting the infection focus in symptoms such as dysphagia, odynophagia, fever, neck pain, swelling and pain in the neck, and elevated laboratory parameters indicating infection (2, 3, 5).

Different clinical treatment modalities are available for the treatment of parapharyngeal abscesses. The approach may vary depending on the general condition of the patient, and the size, location and complications of the abscess. There are studies indicating that localized, small-sized abscesses without complications should be treated only with intravenous antibiotic therapy (2). However, this requires close follow-up of patients (2). In cases where the parapharyngeal abscess is small in size, needle aspiration along with parenteral antibiotic therapy is another treatment alternative (2). Abscess drainage through surgical incision, on the other hand, can be carried out through external skin incision as well as through internal pharyngeal mucosa incision (1, 2, 4). In cases where parapharyngeal abscess originates from peritonsillar abscess, a tonsillectomy could be included in the treatment and the abscess is drained from this space (2). However, in this case, it is important not to ignore the risk of bleeding brought on by hot tonsillectomy. With the advances in the medical technologies, it is possible to reach the uniloculated parapharyngeal abscess and achieve drainage with the help of an endoscope from the nasopharyngeal (7) or oropharyngeal region. However, in

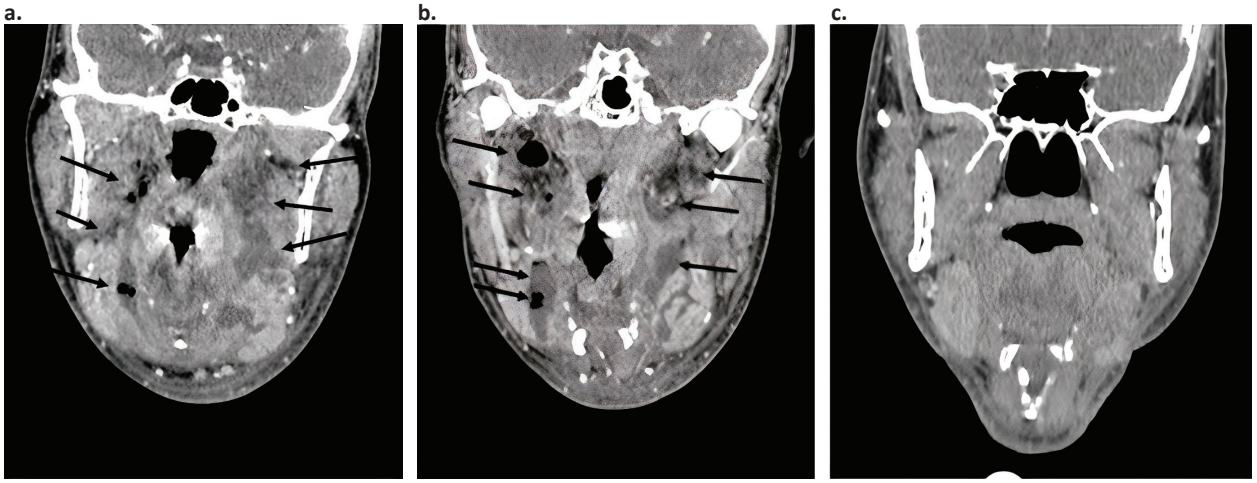

Figure 1: a) and **b)** Air inside the abscess foci (arrows) extending from the bilateral parapharyngeal distances to the submandibular and sublingual distances are shown in the reformatted, contrast-enhanced computed tomography (CT) images on the coronal plane. **c)** Completely regressed abscesses are shown in the reformatted, contrast-enhanced CT images on the coronal plane after the treatment.

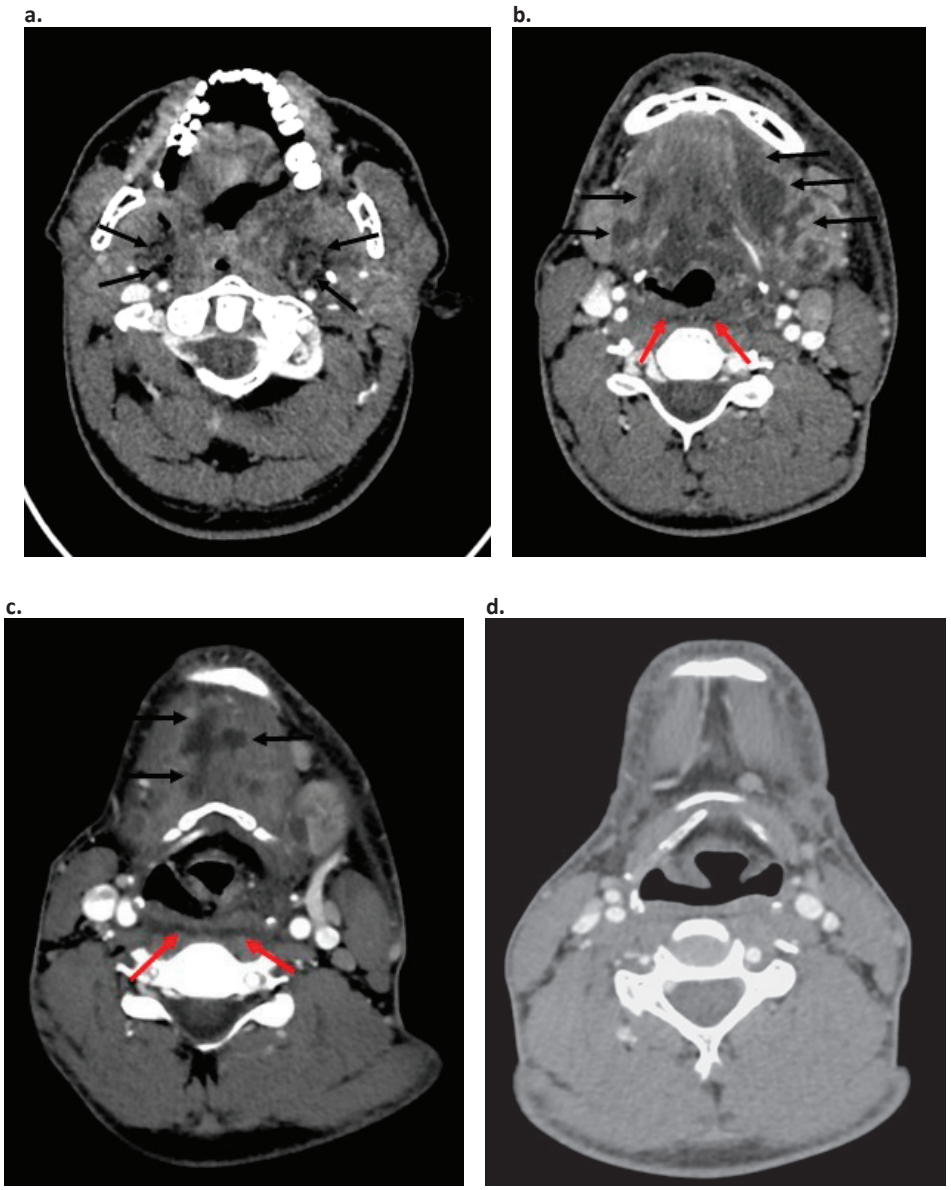

Figure 2: a) Axial CT images show a fluid collection extending from the bilateral submandibular area to the parapharyngeal distance (black arrows) including air densities. **b)** and **c)** Although mild edema is observed in the retropharyngeal space (red arrows), no abscess is evident. Connection of abscess foci between bilateral submandibular and submental area are observed on axial sections. **d)** Completely regressed abscesses are shown in the reformatted, contrast-enhanced CT images on the axial plane after the treatment.

multiloculated, large-sized and extended abscesses like the one in this study, the external approach is preferred (1). In this way, all loculations of the abscess can be drained, and the major vascular structures such as carotid arteries and internal jugular veins can be controlled (1).

In microbiological examination of parapharyngeal abscess material, both polymicrobial growth cases and cases where there is no growth can be observed. The most commonly isolated agents are Streptococcal species, Peptostreptococcus species, Staphylococcus aerius, Bacteroides fragilis, Fusobacterium necrophorum and Pseudomonas aeruginosa, but many other bacterial species can also be encountered (2-4). Therefore, the treatment should be started empirically with aggressive and broad spectrum parenteral antibiotic therapy and should be re-evaluated according to the results of the antibiogram (5, 8). In line with the literature, non-hemolytic streptococcus, a streptococcal type bacterium, was isolated in our case. Treatment was continued since the agent isolated in the culture was sensitive to the empirically started treatment.

A parapharyngeal abscess can cause massive hemorrhages which can lead to carotid pseudoaneurysm or mycotic aneurysm. Cicek et al. managed to treat such a massive bleeding using the endovascular approach (9). In our case, massive bleedings were observed on the right and left side

at one day intervals. However, it was revealed that these hemorrhages did not originate from the internal jugular vein or carotid artery, but from both the branches of the internal maxillary artery and the ascending pharyngeal artery. The occurrence of these hemorrhages despite the good bleeding control during the first surgery confirmed that the infection agents had eroded the vascular wall. We were able to control the bleedingwith the help of bipolar cauterization and surgicel® (Absorbable Hemostat, Ethicon Inc., Johnson & Johnson, NJ 08933, USA).

Providing airway control is crucial in deep neck infections. For this reason, intubation and even tracheotomy can be applied when necessary (2, 4). Since opening the mouth could not be ensured in our case due to trismus, intubation could not be carried out during sudden respiratory distress. Because the neck structures were very rigid and had edema, tracheotomy was tried in the first place. However, due to the need to act quickly, a coniotomy was performed using the same incision. After the coniotomy, a tracheotomy was started in the same session and the abscess was drained on both sides.

In the case of respiratory arrest, asphyxia and death are inevitable unless steps are taken quickly. Indeed, in an autopsy case which was presented by Osculati and Fassina (10) about a 65-year-old woman who died suddenly due to asphyxia, it was revealed that the cause of the mortality was left parapharyngeal abscess and concomitant subtotal closure of aditus laryngis. In our case, the bilateral nature of the parapharyngeal abscess, its extension into the sublingual and submandibular distances and its blocking of the air passage explained why the patient suddenly went into respiratory arrest. Although a caries was detected in the right molar tooth in our case, the question of why the abscess was bilateral needed to be answered. Contrary to what was expected, no spread was observed from the retropharyngeal to the parapharyngeal area in our case (Figure 2b, c). This condition could have been caused by the fact that the infection extended from the submandibular area to the left parapharyngeal distance or could have been a result of a localized infection such as a gingivitis on the left side which regressed with the treatment. Continuation of abscess foci from the two submandibular areas to the submental area in axial CT sections strengthened the argument that bilateral parapharyngeal involvement occurred through the submental and submandibular pathway (Figure 2b, c).

CONCLUSION

Bilateral parapharyngeal abscess is a very rare condition. Placing pressure on the airway on both sides increases the threat to respiratory safety. Moreover, when it is presented with trismus, the patient cannot be intubated. Here, the physician should be prepared for an emergency tracheotomy or coniotomy. In cases where the infection erodes the vascular wall, carotid artery bleeding should be considered in the first place, as typically indicated in the literature. However, it is important to keep in mind that external carotid artery branches such as the internal maxillary artery and ascending pharyngeal artery can also cause serious bleeding.

Informed Consent: Verbal informed consent was obtained from the patient who agreed to take part in the study.

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CASE REPORT
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Bilateral Nasolabial Cyst: A Rare Case Report with Literature Review

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ABSTRACT

A nasolabial cyst (NLC) is a rare, non-odontogenic cyst, usually located unilaterally in the nasolabial fold. The incidence is increasing in women and adult age groups. Bilateral nasolabial cysts are rare and the number of cases reported in the literature is limited. NLC emerges as a slowly growing painless swelling in the nasolabial region and superior gingivolabial sulcus. It is generally asymptomatic. It may cause wiping in the nasolabial folds, facial deformity, and nasal obstruction as a result of elevation on the nasal base. Magnetic resonance imaging and computed tomography can divulge the cystic character of the NLCs in more elaboration and reliability, their relationships with the nasal alas and maxillary bone, and bone involvement that facilitates the diagnosis. The sublabial approach is the most popular and well-appointed operation, in which a larger surgical area and a full resection are secured further. Here, we report a 21-year-old woman who consulted our clinic with nasal obstruction and face swelling, who was later diagnosed with bilateral NLC upon pathological examination. Unlike its precedents seen in the literature with bilateral NLC, the young age of the patient renders this case unique.

Keywords: Bilateral lesions, nasolabial cysts, non-odontogenic, oral surgical procedures

INTRODUCTION

A nasolabial cyst (NLC) is usually unilateral and more common in women (1, 2). There are very few reports of bilateral cases in the English literature. In this article, a 21-year-old Turkish woman with no other medical condition diagnosed with bilateral NLC with histopathological confirmation is presented, accompanied by radiological imaging findings. The etiology, clinical features, and treatment of rare bilateral NLCs are discussed in the literature. This case is of interest both because it is bilateral and the patient is young.

CASE REPORT

A 21-year-old female was admitted to the department of otorhinolaryngology with complaints of a slowly growing swelling on the upper lip for about a year and nasal obstruction on her left side for 3 months.

The patient had no history of surgery, trauma, or congenital anomaly. On examination, there were soft and fluctuant masses causing fullness in the right and left nasolabial regions and upper gingivolabial sulcus. In the anterior rhinoscopy, masses covered with mucosa were observed, and they were narrowing the nasal passage by leading to elevation on the base of the bilateral nasal cavity (Figure 1). On CT, ovoid and well-circumscribed masses with soft tissue density were observed, together with the dimensions of 12 mm on the right side and 17 mm on the left side. Both lesions had similar signal characteristics on MRI. Lesions were found to be isointense in T1-weighted sequences, and hyperintense in T2-weighted sequences (Figure 2). Under general anesthesia, bilateral NLC excision was performed on the patient with the intraoral approach (Figure 3). Histopathological examination was reported as bilateral NLC. There was no recurrence in the 1-year follow-up of the patient who did not develop complications in the postoperative period. Written informed consent was obtained regarding the surgical procedure and the patient's clinical information, examinations, and visual material which could be used in academic publications for educational purposes.

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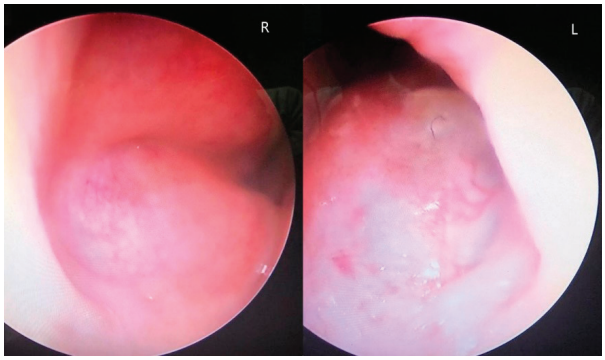

Figure 1: Preoperative endoscopic view of internal nasal valve area; masses covered with mucosa were observed, and they were narrowing the nasal passage by leading to elevation of the base of the bilateral nasal cavity

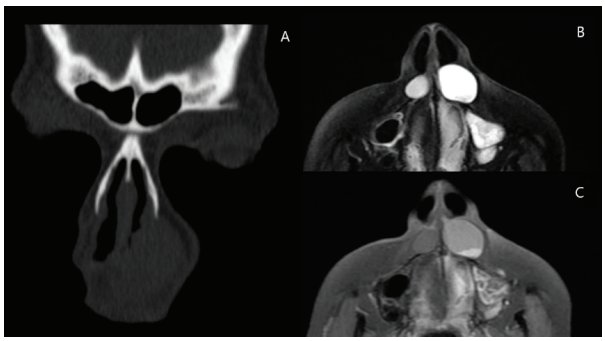

Figure 2: A. Coronal plane of paranasal sinus CT. B. Axial plane of T2-weighted sequences MRI. C. Axial plane of T1-weighted sequences MRI

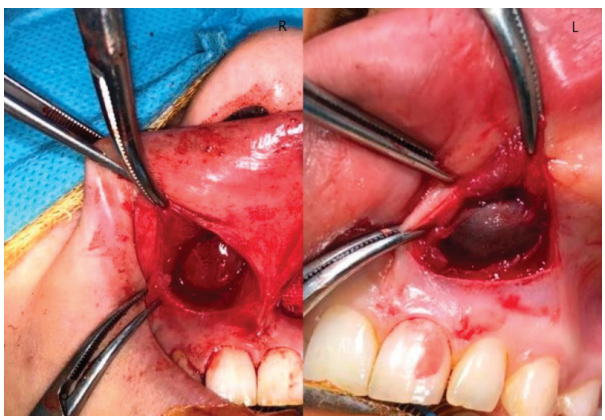

Figure 3: Bilateral NLC can be seen via the sublabial approach

DISCUSSION

NLC is a relatively rare benign, non-odontogenic, and extraosseous soft tissue lesion (3). NLC was first identified by Zuckerkandl in 1882 (1, 4). NLC accounts for less than 1% of jaw cysts and about 2.5% of non-odontogenic cysts (1, 2, 4). It is usually unilateral and more common in women. It is mostly observed in the fourth and fifth decades (1, 2, 4). Although very rare, cases can occur bilaterally. It is predicted that approximately 10-11% of cases are bilateral (1, 2, 4). This lesion is rather encountered in African-Americans (1, 2). There are two main theories related to NLC pathogenesis. The first theory claims that during the development of the facial skeleton, cysts arise from epithelial cells remaining in the mesenchyme after the medial and lateral nasal prominences fuse with the maxillary prominence, and then emerge as an inclusion cyst. The second theory proposes that cysts arise from epithelial remnants of the nasolacrimal duct.

Histopathological similarities between the NLC wall and the nasolacrimal duct epithelium cause the second theory to be more valid today (5). Although pseudostratified columnar epithelium is the most common type of epithelium detected in NLCs, differences can be observed. Goblet cells are seen in the mucosal tissue in approximately half of the cases. (6, 7). Inflammatory cells and collagen-rich fibrovascular tissue form the cyst wall (2, 7). NLC is located in the nasolabial region and superior gingivolabial sulcus. There is usually no pain in the swellings caused by NLCs in these regions. It is generally asymptomatic. It may cause wiping in the nasolabial folds, facial deformity, and nasal obstruction as a result of the elevation of the nasal base (1). If the cyst is infected, pain may occur. In addition, rupture can be seen in infected cysts. In this case, the cyst content may drain into the oral or nasal cavity. (8). In the examination of cysts with the bimanual palpation method, the fingers should be placed on the nasal base and superior labial sulcus. CT and MRI facilitate diagnosis by detecting the cystic structure and its localization. It also reveals the relationship of the lesion with the bone structures in a detailed and reliable way (2). On CT, they are described as well-circumscribed, low-density lesions which are located in the anterolateral side of the pyriform aperture and do not exhibit bone invasion. On MRI, they are seen as medium-intensity in T1-weighted sequences and as hyperintense homogeneous lesions in T2-weighted sequences (8). Differential diagnosis includes other cystic formations such as nasopalatine cysts, periodontal abscesses, benign and malignant soft tissue tumors, and large furuncles at the base of the nose (9). Facial deformity or infection of the cyst constitutes surgical indications. Although many different techniques such as aspiration and drainage are used in the treatment of NLC, surgical excision of the cyst is recommended because of the high recurrence rates in these techniques. (4, 9). For this reason, surgical excision with intraorally performed sublabial incision, which allows complete excision of the cyst, is the most preferred treatment method. After sublabial excision, swelling, pain, hematoma, infection, or oroantral fistula can be observed on the face. Additionally, loss of sensation in the teeth and gingiva and numbness can be counted among the other complications (9).

CONCLUSION

Our patient is unique because it is presented at a younger age than patients seen in the literature with bilateral NLC (Table 1). NLC should be considered in the differential diagnosis of masses that cause facial deformities. In addition, if the cyst is infected,

Table 1: Summary of case reports of bilateral nasolabial cysts

References	Age	Sex	Major Complaint	Size of Right NLC	Size of Left NLC	Surgical Approach
Sato et al., 2016 (2)	67 yo	Female	FS	12 mm	25 mm	Sublabial
Marrcoviceanu et al., 2009 (4)	48 yo	Female	FS	22 mm	22 mm	Sublabial
Dghoughi et al., 2017 (10)	30 yo	Female	FS	19 mm	18 mm	Sublabial
Setukumar et al., 2015 (11)	36 yo	Male	FS	25 mm	23 mm	Sublabial
Parwani et al., 2013 (12)	69 yo	Female	FS	30 mm	15 mm	Sublabial
Our case	21 yo	Female	FS, NO	12 mm	17 mm	Sublabial

NLC: Nasolabial cyst, yo: Years old, FS: Facial swelling, NO: Nasal obstruction, mm: Millimeters

it should be differentiated from inflammatory masses in this region. Today, excision performed with an intraoral approach is a successful and preferred treatment method.

Informed Consent: Written informed consent was obtained regarding the surgical procedure and the patient's clinical information, examinations, and visual material which could be used in academic publications for educational purposes.

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The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW

Peer Review Policies
Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication. He/She must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

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- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/tr/journal/3565/submission/step/manuscript/new Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page**: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: Abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 200-250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings..

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Invited Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over. Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within two days of their receipt of the proof. The latest status of the submitted manuscripts and other information about the journal can be accessed at http://tr-ent.com. The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). An ORCID ID is required for all authors during the submission of the manuscript. The ID is available at http://orcid.org with free of charge.

Reference Style and Examples

Authors are responsible for supply complete and correct references. References should be numbered according to the order used in the text. Numbers should be given in brackets and placed at the end of the sentence. Examples are given below on the use of references. Reference end note style Vancouver

Periodicals: Author(s) Last Name initial(s) name of author(s) (if there are six or fewer authors, all authors should be written; if the number of authors are seven or more, only the first six of the authors should be written and the rest as "et al"). The title of the article, the abbreviated name of the journal according to the Index Medicus, Year; Volume (Issue): The first and last page numbers.

Example: Robson A, Greene J, Ansari N, Kim B. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. The American Journal of Surgical Pathology 2001;25:710-20. Books: Surname of the author(s) initial name(s) of author(s). The name of the book. The edition number. Place of publication: Publisher, Publication year.

Book chapters: The author (s) surname of the chapter initial (s) letter of the name. Section title. In: Surname of editor (s) initial (s) letter of first name (s) ed / eds. The name of the book. Edition number. Place of publication: Publisher, year of publication: The first and last page numbers of the chapter. Web address: If a "web" address is used as the reference address, the web address date should be given in brackets with the address. The DOI (Digital Object Identifier) number must be provided, when a web access article used in the text as a reference.

Example: AB Author, CD Author. Title of document. Retrieved from http://Web address (Accession date: aa/bb/2016).

Congress papers:

Thesis: Maden KL. Experimental investigation of the ..... Master Thesis, Health Science Institute of Ankara University, Ankara, 2005.

SUBMISSION CHECKLIST

- Cover letter to the editor
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  - Confirming that "the paper is not under consideration for publication in another journal".
  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
- Copyright Agreement Form
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- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
- Title page
  - The category of the manuscript
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  - Short title (running head)
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
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- Main Manuscript Document
  - The title of the manuscript
  - Abstract 200-250 words
  - Key words: 3 - 6 words
  - Main article sections
  - References
  - Acknowledgement (if exists)
  - All tables, illustrations (figures) (including title, description, footnotes)

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