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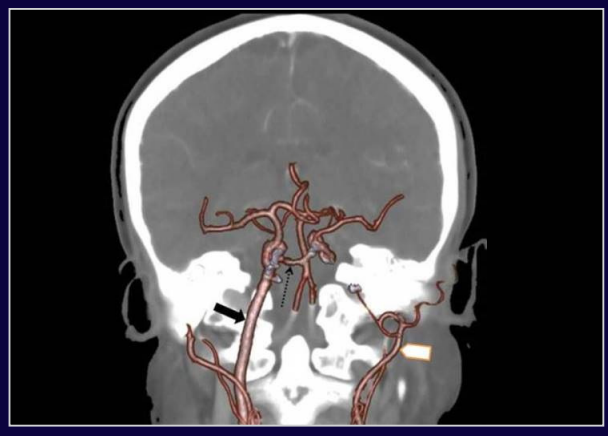

Patulous Eustachian Tube Accompanied by Internal Carotid Artery Anomalies
Page: 38-41

Original Investigations

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Contents

The Effect of Cochlear Implant Stimulation on Postural Control

Original Investigation

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Abstract

Objective: There are contradictory reports on the effect of cochlear implantation on postural control. Associated vestibular loss, electrode insertion trauma, and electrical stimulus of a cochlear implant can influence postural control. This study focused on the electrical stimulation of the cochlea. We aimed to examine whether a cochlear implant's electrical stimulation affects postural control measured by posturography.

Methods: Thirty-three patients with unilateral cochlear implants were included. We used three preprogrammed main tests and their nine subtests in posturography. Postural stability [general stability index (GSI)], fall risk index (FRI), and sensory integration [modified clinical test of sensory integration of balance (m-CTSIB)] were calculated. All tests were performed under three conditions: implant off (1), implant on (2), and implant on music (3).

Results: The mean age was 46.29±16.09 years. GSI was above normal limits in 78% of adult cochlear implant users. We found that FRI was high in 30% of patients, and m-CTSIB was defective in 42%. There were no statistically significant differences in GSI, FRI, and m-CTSIB. Cochlear implant stimulation was found to have positively affected postural control when the subject's data were visualized individually. GSI, FRI, and m-CTSIB dropped to 39%, 24%, and 24%, respectively, when music was on. There was a significant correlation between age and fall index. But this correlation disappeared when music was playing.

Conclusion: Cochlear implant stimulation affected the vestibular system in almost all patients. The effect was positive in most patients.

Keywords: Cochlear implant, postural control, posturography, fall risk, hearing implant, postural balance

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Introduction

Cochlear implants (CIs) have become the commonly chosen option to rehabilitate profound or severe sensorineural hearing loss at any age. Although its effects on the hearing system are thoroughly examined, its effects on the vestibular system are still a topic of discussion.

When investigating the interaction between the vestibular system and CIs, various factors must be considered. First, people with severe and profound hearing loss can also have sensory loss in the vestibular end organs. 2.7% of the patients with CIs have been reported to have preoperative dizziness (1).

Furthermore, the risk of falling in older adults with hearing loss was 2.39 times higher than in those without (2). Second, the CI electrode placement is a physical intervention within the sense organ. In addition to the cochlear part, significant damage was observed in the vestibular part in 54% of the samples (3). Vestibular fibrosis, saccular membrane degradation, reactive neuroma, and new bone formation were the most common injuries (4). Third, CIs send continuous electrical signals to the cochlear nerve near the vestibular nerves. Interference with the vestibular system is possible (5).

Vestibular damage has been reported numerous times with organ-specific tests after cochlear implantation surgery. However, the results of the functional tests were inconsistent with the injury. A recent meta-analysis showed that CI surgery had a significant negative effect on caloric test and vestibular evoked myogenic potentials but had no impact on posturography, head impulse test and dizziness handicap inventory (6). Louza et al. (7) measured the risk with portable posturography. They reported that patients with CIs already had a higher risk than usual before surgery, but there was no significant change in fall risk after the surgery.

This study focused on the effect of CIs on functional balance. We aimed to examine whether postural tests are affected by the implant-turn-on/-off conditions. We also aimed to determine whether continuous background sound (continuous electrical stimulation of the cochlear nerve) affected postural balance in patients.

Methods

Participants

Thirty-three patients aged between 16 and 80 years who underwent CI surgery were included in the study. The patients were retrospectively selected from the list and prospectively tested with a posturography. All patients aged over 16 years in our retrospective list were invited to the study. There was no time limit for the duration after surgery. Those with an additional disability, communication problems, bilateral CIs, neurological or psychiatric disease, visual impairment, or orthopedic problems in the lower extremities were not included. None of them were wearing any additional devices like hearing aids during tests. All participants were informed and gave their written informed consent. Permission was obtained from the Pamukkale University Non-invasive Clinical Research Ethics Committee (no: 60116787-020/20941, date: 23.03.2018). The study is registered with clinicaltrials.gov (NCT04404205).

Outcome Measurements

The Biodex Balance System SD (BBS) (Biodex Medical Systems Inc., New York) was used for posturography. The BBS was a valid device for dynamic and static balance assessment (8). The platform was designed to measure postural stability. The reliability was tested in different age groups (9). Three main tests:

Postural stability test: Stable platform with eyes open. The balance of postural stability was measured using three parameters: General stability index (GSI), anterior-to-posterior stability, and median-to-lateral stability. A high score highlights poor balance. When interpreting the results, we used the normal limits mean ±2 standard deviation (SD) (0–1.36) calculated from mean ± SD (0.64±0.36) (10).

Fall risk test (FRI): Unstable platform with eyes open, starting at level 12 and completing at level 1. The device calculates the risk of falling based on the patient's age and GSI. The higher the value, the higher the risk of falling. When interpreting the results, we accepted the normal limits mean ±2 SD (0.39–3.19) calculated from mean ± SD (1.79±0.70) (10).

Modified clinical test of sensory integration of balance (m-CTSIB): Four subtests were included: i) eyes open firm surface (OF), ii) eyes closed firm surface (CF), and iii) eyes open foam surface (OO), iv) eyes closed foam surface (CO). They provide a detailed evaluation of the relationships between sensory integration and visual, somatosensory, and vestibular stimuli. When interpreting the results, we used normal limits mean ±2 SD (0.66–1.7) calculated from mean ± SD (1.18±0.26) (11).

During the test, the patients were asked to stand on the BBS platform with their hands shoulder-width apart and on their sides in the most comfortable position to maintain balance and be upright. The patient's foot coordinates were recorded. The tests were carried out at the same time of day (between 10:00 and 14:00). Each patient was informed about the trials and rules. Patients were subjected to a practice study for each condition to eliminate the possible effects of learning and fatigue. All patients were tested three times; each test took 20 seconds and had 10 seconds of rest between tests. The average of the three trials was automatically calculated and recorded by BBS.

All tests were carried out under three conditions:

1. CI off (baseline),

2. CI on,

3. CI on and music on [non-directional music played by multiple speakers from the different parts of the room at a comfortable level (50 dB)]. We chose music rather than simple sounds to represent daily life.

Factors such as age, sex, and implant duration were also studied.

Statistical Analysis

Statistical analysis was performed using the SPSS 10.0 program (Statistical Package for Social Sciences). Results

were compared with related samples, Friedman's two-way analysis of variance, and the t-test for equality of means. The Pearson correlation coefficient was also calculated between the selected pairs. Statistical significance was established at $p<0.05$ for all analyses.

Results

Thirteen males and 20 females, a total of 33 patients, were tested. The mean age was 46.29±16.09 years at the time of the study. Implantation age was 44.7±16.6 years [minimum (min) 14–maximum (max) 78.5]. The mean duration from implant surgery to test day was 579.12±38.4 days (min 28–max 1463).

All test parameters are summarized in Table 1. No statistically significant differences existed between the three conditions in any of the test parameters. However, when we grouped the patients according to normal and abnormal test results, most patients were seen to be affected to some extent in an increasing or decreasing manner.

GSI was above normal limits in 78% of adult CI users. We found that FRI was high in 30%, and the m-CTSIB composite score was defective in 42% of the patients. CI stimulation was found to have positively affected postural control when the subject's data were visualized individually. The number of patients with normal GSI increased with increasing stimulation (Figure 1). The FRI was better at baseline. There were 23 normal patients at the beginning of the study (Figure 2). The m-CTSIB composite score was normal in 19 patients at baseline (Figure 3). GSI, FRI, and m-CTSIB dropped to 30%, 21%, and 36%, respectively, when the CI was on. When the music was on, m-CTSIB decreased to 24%, while the other parameters increased slightly.

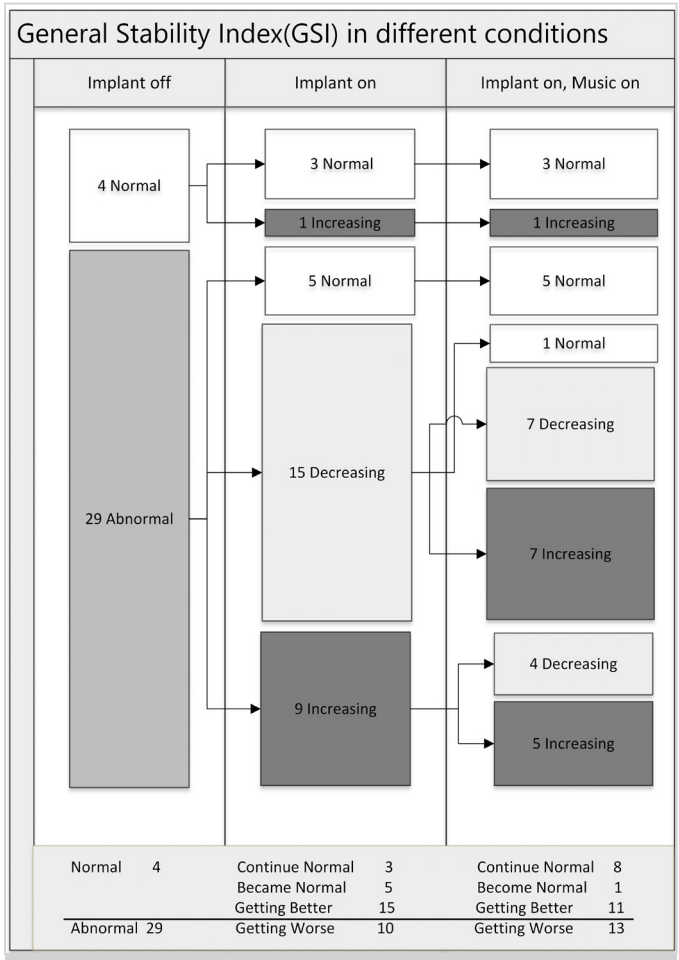

Figure 1. Figure plots the GSI of all patients and their change during the two experimental conditions. At the bottom, the total numbers were included. The postural stability index was above normal limits in 78% of adult cochlear implants

Table 1. Posturographic parameters were obtained in 3 different conditions. They were compared with related samples Friedman's two-way analysis of variance

	Implant off		Implant on		Implant on, music on		
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	p-value
GSI	3.57±2.12	3.4 (0.5–9.8)	3.12±2.04	3.05 (0.5–10.4)	2.94±1.82	2.55 (0.6–7.7)	0.209
APS	2.01±1.53	1.55 (0.3–8)	2.03±1.82	1.6 (0.3–10.1)	1.55±1.05	1.25 (0.4–3.9)	0.754
MLS	2.47±1.73	2.1 (0.4–7)	1.93±1.29	1.6 (0.3–5.7)	2.12±1.63	1.85 (0.4–6.9)	0.1
FRI	2.87±1.72	2.75 (0.7–10)	2.42±1.66	2 (0.3–6.2)	2.9±1.85	2.55 (0.3–8.2)	0.317
m-CTSIB -OF	0.68±0.38	0.57 (0.28–1.95)	0.72±0.45	0.59 (0.25–2.2)	0.65±0.4	0.53 (0.25–2)	0.281
m-CTSIB -CF	1.24±0.48	1.22 (0.58–2.68)	1.19±0.72	1.12 (0.38–4.47)	1.25±0.83	0.97 (0.44–4.31)	0.337
m-CTSIB -OO	1.28±0.45	1.24 (0.51–2.28)	1.29±0.45	1.19 (0.61–2.38)	1.34±0.85	1.08 (0.41–4.12)	0.086
m-CTSIB -CO	3.54±1.53	3.35 (1.12–8)	3.59±1.57	3.06 (1.65–8.55)	3.62±1.68	3.14 (1.19–8.54)	0.703
m-CTSIB	1.68±0.45	1.58 (0.82–2.94)	1.7±0.51	1.67 (0.87–2.76)	1.71±0.68	1.49 (0.78–3.22)	0.476

GSI: General stability index, APS: Anterior-to-posterior stability, MLS: Medial-to-lateral stability, FRI: Fall risk index, m-CTSIB: Modified clinical test of sensory integration of balance, OF: Eyes open/Firm surface, CF: Eyes closed/firm surface, OO: Eyes open/foam surface, CO: Eyes closed/foam surface, SD: Standard deviation, min–max: Minimum–maximum

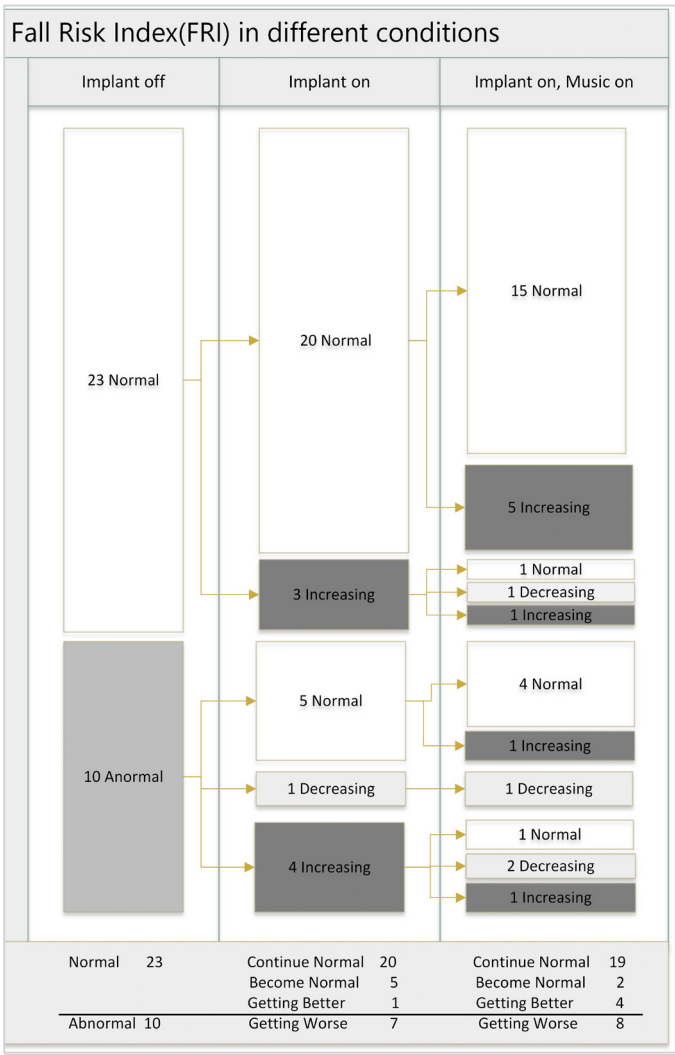

Figure 2. Figure plots the FRIs of all patients and their changes during the two experimental conditions. At the bottom, the total numbers were included. The FRI was initially high in 30% of the patients

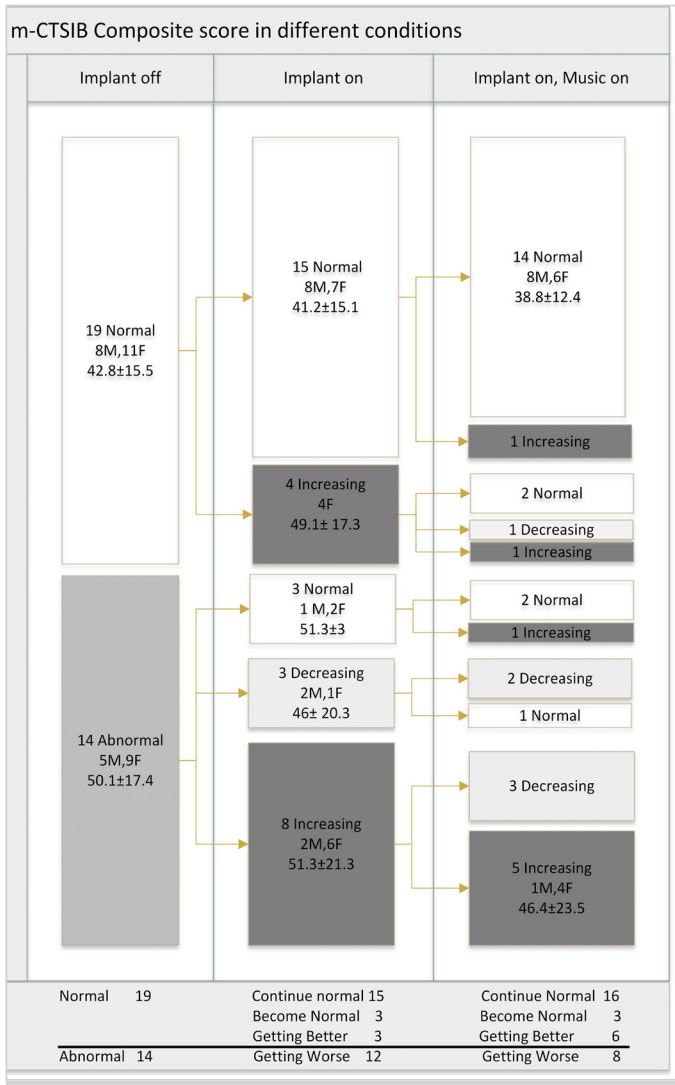

Figure 3. Figure plots the GSI of all patients and their change during the two experimental conditions. Sensorimotor control was defective in 42% of the patients in the baseline. The mean ± SD age and the male/female numbers of the groups were also added to see the relationship between postural control and these factors

GSI: General stability index, SD: Standard deviation

As expected, age and FRI had a moderate correlation (p=0.004). Interestingly, this correlation disappeared when music was on [implant off (r=0.48, p=0.004), implant on (r=0.429, p=0.011), music on (r=0.317, p=0.068)]. When we divided the patients according to age into three groups [group 1:16-40 years (n=13), group 2: 41-59 years (n=13), group 3: 60 years or above (n=7)], statistically significant differences were found in some test conditions like implant off (FRI, p=0.04), implant on (m-CTSIB-OF, p=0.025), music on (m-CTSIB-OF, p=0.023, m-CTSIB-OO, p=0.043). However, no other statistical difference existed in any of the parameters or test conditions.

There was no correlation between postoperative days and balance. When we divided the group into early [shorter than one year (13 patients)] and late [longer than one year (20 patients)] groups, there were no statistically significant relations in any of the parameters or conditions (p>0.05).

Discussion

In this study, we examined the effect of CI stimulation on postural control. We tested patients under different conditions, such as implant on, implant off, and music playing in the room. There were no significant differences between these conditions in any of the parameters; however, the postural control of several subjects improved with CI stimulation. This effect was most prominent in GSI. An interesting finding of the study was the disappearance of the correlation between age and fall risk when music was played in the room.

After placing the CI, an additional factor is added: sound or electrical stimulation of the cochlear nerve. This hypothesis was first studied with hearing aids. The use of hearing aids helps to maintain postural balance in older adults with hearing loss (12). Postural oscillation improved in 41% of healthy people standing in the dark and those with vestibular insufficiency when a sound stimulus was added to the setting (13). In settings where visual warnings were on, the effect of sound stimulation was minimal (13). Adult patients with bilateral CIs or bimodal hearing solutions were tested with the devices on and off. A 45 dB narrowband white noise from the anterior side was used as a structured sound stimulus. They reported that the sound reduced the patient's anteroposterior head tilt in the dark when the devices were on (14). In another study, patients with CIs scored lower in the sensory organization test before surgery but approached the normal score in the first year after surgery. The authors concluded that this improvement could be due to increased auditory signals (15).

The effect is more prominent when electrical pulses stimulate the electrode. Biphasic pulse trains at a rate of 900/s improved tilt perception during the subjective visual vertical test in a group of children with CIs (5). However, the gait test yielded conflicting results. When patients with bilateral CIs or bilateral hearing aids were tested in the on/off condition of the devices during gait, there were no significant differences in the on/off states. There was also considerable variation in gait parameters between patients. In the end, the authors suggested that it worked in some specific groups of patients but could not determine a common specification for these patients (16).

Hallemans et al. (17) conducted a more detailed analysis while the patients were walking. Patients with bilateral areflexia and CIs were tested under implant on/off conditions. They also conducted an additional test by playing music from two speakers located at the end of the walkway at a comfortable level. Although there was little difference between the implant on/off conditions, pelvic motion, knee, ankle, and stride length increased, and stride duration was shortened when music was left on in the test room.

The activation in music-assisted environments has an additional positive effect on postural balance (18). We mostly observed a change in patients' postural conditions when the implant was on.

Interestingly, the positive correlation between age and fall risk index disappeared when music was on. Louza et al. (19) observed comparable results in older adults using music for stimulation. Auditory-motor interactions when playing music have been extensively reviewed extensively (20). Positive effects of music or rhythm were observed in movement disorders. The authors proposed that this effect might be due to the cognitive representation of music and added that further studies were needed to investigate the relationship between music and postural control in vestibular disorders.

Twenty-five children with unilateral implants and bilateral vestibular hypofunction were tested while the implant was turned on and off. The authors used three settings: a double stand with eyes open and closed, a double stand with a dual task, and a transition from a double stand to a single stand. Significant reductions in the anteroposterior and mediolateral displacements were found in the double stance-eyes open condition. They concluded that auditory information positively affected postural balance parameters (21).

There were some limitations in our study. The study group was not evaluated according to the function of the preoperative vestibular system. We used the implant of the condition as a baseline value. The study did not include parameters such as active electrode number, current level, or patient fitness status.

Conclusion

When we looked at individual data, we found that CI stimulation was affecting most patients' vestibular systems. The positive effect was more prominent than the negative effect. The parameters we used could not explain the difference between negatively and positively affected subjects. The age of the subject might be one of these factors. The disappearance of the positive correlation between age and fall risk when the music was on was supporting evidence.

Further studies using different parameters such as active electrode number, current level, patient fitness status, duration of implant use, directional sound stimulation, and proximity of electrodes to the vestibuler nerve will better understand the effect of CI stimulation on balance.

Ethics Committee Approval: This study was carried out in accordance with the principles of the Declaration of Helsinki. The approval was granted by the Pamukkale University Non-invasive Clinical Research Ethics Committee (no: 60116787-020/20941, date: 23.03.2018).

Informed Consent: All participants were informed and gave their written informed consent.

Authorship Contributions

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

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

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Main Points

- The postural stability index was beyond normal limits in 78% of adult cochlear implant (CI) users.
- We found the fall risk index was high in 30%, and sensorimotor control was defective in 42% of patients.
- When the CI was on, the positive effect on postural stability was more prominent than the negative effect.
- Additional music also increased this positive effect in some patients.
- We could not find any specific parameter to explain the difference between patients affected positively and negatively.
- Age might be one of these factors, according to our data.

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The Outcome of Endoscopic Sinus Surgery for Orbital Apex Syndrome Secondary to Sinusitis in a Tertiary Care Center-Our Experience Over 10 Years

Original Investigation

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Abstract

Objective: Orbital apex syndrome (OAS) is a rare condition with multiple cranial nerve involvement caused by varied etiologies. It is not only a threat to the patient's vision but also life-threatening due to the intracranial spread of infection, if not diagnosed early and treated accurately. To study the outcome of endoscopic sinus surgery (ESS) for OAS secondary to sinusitis concerning resolution of ptosis, improvement of ophthalmoplegia, visual prognosis, intracranial spread of infection, and mortality.

Methods: A retrospective review of patients with OAS secondary to sinusitis who underwent ESS from 2011 to 2021 was tabulated and analyzed.

Results: Twenty-seven patients (mean age: 55.11+/-16 years; male 62%) were included in this study. At presentation, blurring of vision (81%), headache (66%), diplopia (63%) ptosis (63%) were the most common symptoms, and ophthalmoplegia (100%) was the most common sign. Five patients had no perception of light and the rest had various degrees of vision impairment. The most common etiopathology of sinusitis was fungal sinusitis (12 mucormycosis and four aspergillus). The final visual prognosis at three months follow-up post-ESS showed vision stabilization (no improvement or worsening) in 13 (48%) patients, improvement in seven (26%) patients, and vision deterioration in two (7%) patients. There was a significant improvement in ptosis (70%) and ophthalmoplegia (85%). There was no intracranial spread of infection or recurrence with a mortality rate of 3.7% (one patient).

Conclusion: ESS coupled with appropriate antimicrobials effectively treats OAS secondary to sinusitis with decreased morbidity and mortality.

Keywords: Orbital apex syndrome, sinusitis, complication, endoscopic sinus surgery, mucormycosis, ocular vision, blepharoptosis, ophthalmoplegia

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Introduction

The pyramid-shaped human orbital apex (OA) has a complex anatomy and is closely related to the superior orbital fissure (SOF), the optic canal (OC), and the cavernous sinus (CS) (1). The orbital apex syndrome (OAS) also called Jacod syndrome is characterized by the involvement of cranial nerves (CN) in the SOF and OC, namely the oculomotor

nerve (III CN), the trochlear nerve (IV CN), the abducens nerve (VI CN), the ophthalmic division of the trigeminal nerve (V CN), and the optic nerve (II CN), respectively. A varied variety of clinical conditions, neoplastic, inflammatory, infectious, iatrogenic, or traumatic can cause this rare syndrome (2). OAS is not only a threat to the patient's vision but also life-threatening if it spreads through the ophthalmic vessels and bony fissures into intracranial structures (3).

OAS secondary to sinusitis is mostly due to infections and accounts for only 15% of the heterogeneous etiologies (4). Fungal and bacterial infections from the adjacent paranasal sinuses, namely the ethmoid and sphenoid sinuses, spread to the OA. This can be treated by endoscopic sinus surgery (ESS) and culture-specific antimicrobials if diagnosed early, and hence morbidity and mortality due to this syndrome can be reduced. Radiological imaging, computerized tomography (CT), and magnetic resonance imaging (MRI) help locate the lesion, some etiologies, and clinical features for differential diagnosis (2).

The literature available on OAS secondary to sinusitis is limited only to case reports in our country. Our study is one of the first retrospective decadal reviews done with the primary objective of studying the outcome of ESS for OAS secondary to sinusitis due to infection and to study etiopathology and varied clinical presentations.

Methods

We reviewed the medical records at Ramaiah Medical College Hospital, a tertiary care center, kept between January 1st, 2011, and December 31st, 2021, and identified the patients who have undergone ESS for OAS secondary to sinusitis due to infection and included those that satisfy the criteria (Table 1).

A tabulation of the patient's demographics (gender and age), comorbidities, clinical manifestations (rhino orbital symptoms and signs), the eye involved, radiological imaging findings (CT/MRI), diagnostic nasal endoscopic findings, microbiology and histopathology findings, initial and final vision at three-month follow-up post-ESS (Snellen's visual acuity chart), etiology, intraoperative findings, prognosis at three-month follow-up post-ESS in terms of resolution of ptosis, improvement of ophthalmoplegia, vision improvement, the intracranial spread of infection, and mortality.

Table 1. Inclusion and exclusion criteria for patient enrollment in the study

Inclusion criteria
• Aged 18 years or more.
• Diagnosed case of orbital apex syndrome secondary to sinusitis due to infection.
• Radiological imaging either computerized tomography or magnetic resonance imaging.
• Undergone endoscopic sinus surgery.
• Three-month follow-up period post-endoscopic sinus surgery.
Exclusion criteria
• Orbital apex syndrome secondary to other etiology.

OAS secondary to sinusitis was diagnosed based on clinical manifestations, radiological imaging, microbiology, and histopathology findings. Treatment included medical and surgical measures. Medical treatment was initiated with empirical intravenous (IV) antibiotics on admission and changed later according to the culture sensitivity and histopathology results. Saline irrigation, topical and systemic decongestants, and anti-inflammatory agents were started. The diabetic patients underwent initial evaluation by an endocrinologist and the glycemic control during the hospital stay was achieved by a combination of short and long-acting insulin. The patients were followed up daily by the endocrinologist with blood sugar readings.

Surgical intervention was done within 24 hours of the diagnosis and tailored based on radiological imaging and intra-operative findings. All patients underwent ESS with or without orbital decompression, optic nerve decompression, endoscopic medial maxillectomy, and subtotal maxillectomy. ESS began with a repeat diagnostic nasal endoscopy followed by uncinectomy, middle meatal antrostomy, anterior and posterior ethmoidectomy, and sphenoidotomy. The lamina papyracea, the skull base, and the opticocarotid recess were identified. Medial orbitotomy and decompression were done using a blunt elevator to dissect the lamina papyracea in the anteroposterior direction to the medial OA and the periorbita was incised using a sickle knife. Selected patients underwent optic nerve decompression by removing the bone around the OC. Endoscopic medial maxillectomy involved the removal of the uncinate process, the bulla, the inferior and middle turbinate, and the medial wall of the maxilla to clear the disease from the pterygopalatine fossa and pterygoid plates. Patients with palatal involvement underwent subtotal maxillectomy in which the floor of the maxillary sinus (hard palate) was resected in addition to one other wall. The disease was cleared from the SOF. Discharge was sent for culture sensitivity, crusts for potassium hydroxide mount, tissue for histopathology, and necrotic tissue was debrided prudently. Patients diagnosed with mucormycosis underwent repeated debridement as needed.

Treatment outcome was evaluated based on the resolution of ptosis, improvement in ophthalmoplegia, visual prognosis-stabilization of vision (no improvement or worsening), vision improvement, vision deterioration, the intracranial spread of infection, and mortality at three months follow-up post-ESS.

Statistical Analysis

Our study was approved by the Ramaiah Medical College Institutional Ethics Committee (no: MSRMC/EC/AP-04/06-2023, date: 23.06.2023). The study data was analyzed using IBM SPSS Statistics for Windows v29.0.2.0 (IBM Corp: Armonk, NY). Fisher's exact test was used to analyze categorical variables presented as numbers and percentages. Student's t-test was used to analyze continuous variables presented as mean and standard deviation (SD). Descriptive statistics of ptosis, ophthalmoplegia, visual prognosis, intracranial spread of infection, and mortality were analyzed and summarized in terms of percentage. McNemars test was used to compare the resolution of ptosis, improvement in ophthalmoplegia, and visual prognosis pre- and post-intervention, and a p-value of <0.05 was considered statistically significant.

Results

A total of 27 patients were included in our study and their mean age was 55 (SD: +/-16) years. Most patients were male (62%), and 22 (82%) had diabetes mellitus. Among the 22 diabetic patients, four were diagnosed at admission, 13 were on oral hypoglycemics and seven were treated with insulin for an average duration of six years. Five had chronic kidney disease secondary to diabetic nephropathy. Among these five patients, four were in medical management and one was undergoing hemodialysis. At presentation three patients had a history of coronavirus disease-2019 (COVID-19) (11%) and two (7%) were COVID-positive.

All patients had unilateral eye involvement and presented with a variety of rhino-orbital symptoms. The most common symptoms included blurring of vision (81%), headache (66%), diplopia (63%), ptosis (63%), nasal obstruction (48%), and facial pain (48%) (Table 2).

Table 2. Clinical features in patients at presentation

Presenting symptoms	Number of patients	Percent (%)
Blurring of vision	22	81
Headache	18	66.0
Ptosis	17	63.0
Diplopia	17	63.0
Nasal obstruction	13	48.0
Facial pain	13	48.0
Periorbital edema	10	37.0
Facial puffiness	6	22.0
Nasal discharge	6	22.0
Eye pain	6	22.0
Loss of vision	5	18.5
Congestion of eye/chemosis	3	11.0
Watering of eye	1	3.0
Proptosis	1	3.0

On physical examination, there were various degrees of ophthalmoplegia (limitation of extraocular movements) in all patients. Five patients presented with no perception of light and the vision evaluated using a Snellen visual acuity chart ranged from 20/200 to 20/40 (Table 3). Sixty-three percent of patients had a positive relative afferent pupillary defect.

All patients underwent a thorough ear, nose, and throat examination with a diagnostic nasal endoscopy on presentation. Ten patients demonstrated necrotic tissue, blackish crusts, and discoloration of the nasal mucosa. Radiological imaging was done in all patients, 19 patients with CT only, three patients with MRI only, and five patients with both CT and MRI. Ipsilateral sphenoid and ethmoidal involvement were seen in 24 patients, two patients had infiltrative lesions, and 13 patients had bony erosion with calcifications on imaging (Figure 1).

All patients underwent ESS with or without modifications with tissue biopsy for definitive diagnosis (Table 4). Twenty patients had disease extending medial to the medial wall of the orbit and underwent orbital decompression. One patient with OC erosion underwent optic nerve decompression. Endoscopic medial maxillectomy helped clear the disease in three patients. One patient with palatal involvement underwent subtotal maxillectomy. The duration from symptom onset to surgery ranged between 10 to 42 days.

Histopathology and microbiological results showed fungal sinusitis to be the leading cause in 16 patients with aseptate fungal elements–mucormycosis in 12 and septate fungal elements–aspergillus in four patients. The remaining 11 patients had bacterial sinusitis with *Staphylococcus aureus* as the most common isolate (10 patients) and only one

Table 3. Patient vision (Snellen visual acuity chart) at presentation

Vision (feet)	Number of patients	Percentage (%)
No perception of light	5	18.5
Perception of light	5	18.5
20/200	3	11.1
20/70	4	14.8
20/50	3	11.1
20/40	7	25.9

Table 4. Type of surgery

Surgery	Number of patients	Percentage (%)
Endoscopic sinus surgery	27	100.0
Orbital decompression	20	74.0
Optic nerve decompression	1	3.7
Medial maxillectomy	3	11.1
Subtotal maxillectomy	1	3.7

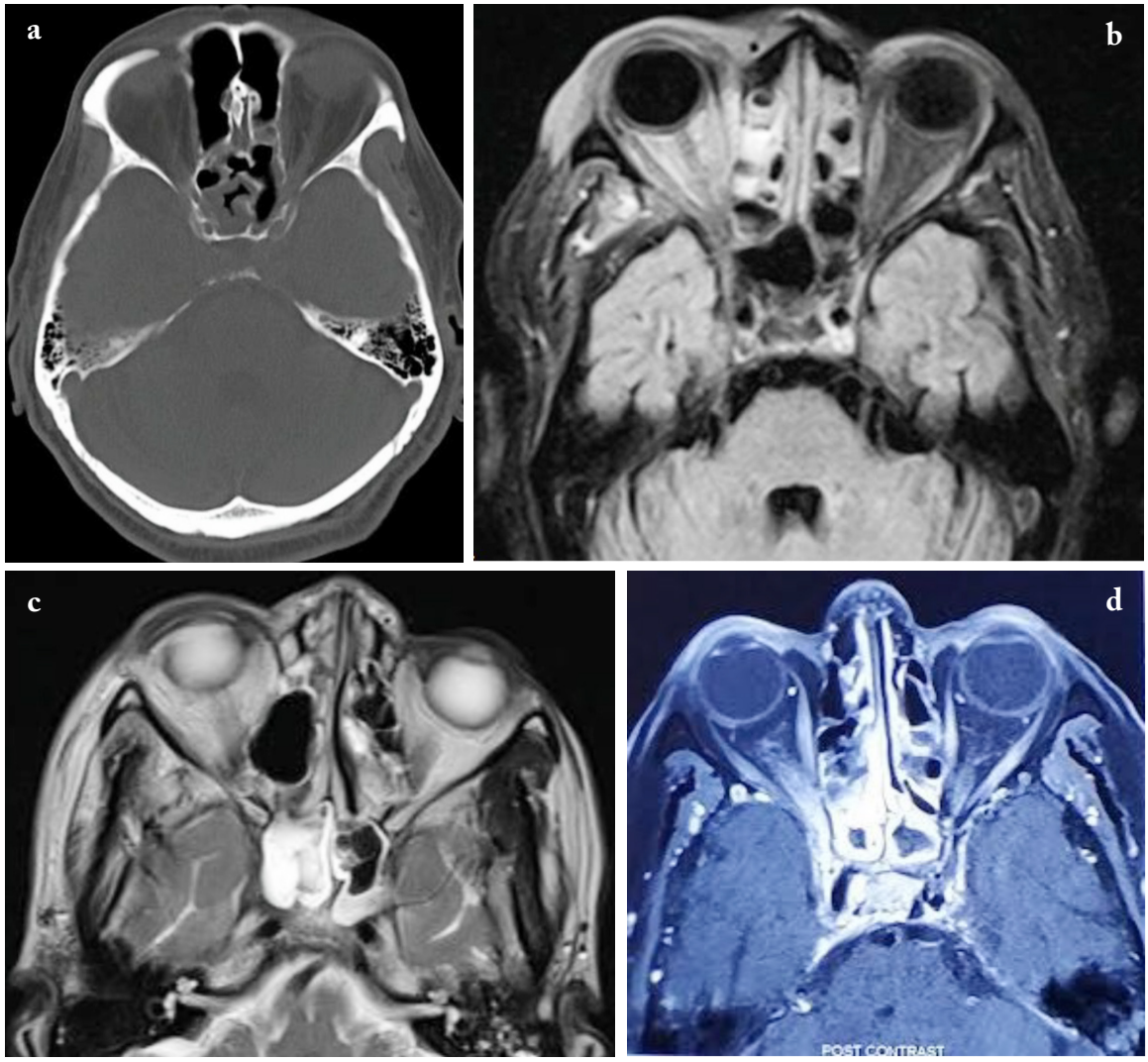

Figure 1. Radiological imaging (CT/MRI) presentations of orbital apex syndrome secondary to sinusitis (a-d)
a) Axial non-contrast CT scan of orbit showing right sphenoid sinus mucosal thickening with involvement of right orbital apex. b) Axial T2 Flair of MRI orbit showing high signal changes in bilateral ethmoid air cells with involvement of right orbital apex. c) Axial T2-weighted MRI scan of orbit showing right eye proptosis with circumferential mucosal thickening of right sphenoid sinus and extension to the right orbital apex. d) Axial T1-weighted post-contrast scan of MRI orbit showing enhancement of right orbital apex, optic nerve, posterior ethmoidal, and sphenoid sinus
CT: Computerized tomography, MRI: Magnetic resonance imaging

patient had *Staphylococcus epidermidis*. Antimicrobial therapy was revised based on the etiology to culture-sensitive IV antibiotics or antifungal agents as per the isolate (IV amphotericin B, voriconazole, itraconazole). Intranasal amphotericin wash was done, and a check endoscopy was performed every third day for two weeks followed by weekly for four weeks for crust removal and planning debridement in patients diagnosed with fungal sinusitis. At the time of discharge, these patients were on prophylactic antimicrobials and hypoglycemic medication to maintain strict glycemic control. They were also on regular follow-up with the endocrinologist with blood sugar readings.

All patients at their follow-up visit after three months post-ESS were evaluated and among the 17 patients who presented with ptosis, 12 (70%) exhibited complete recovery which was statistically significant ($p<0.001$). All 27 patients included in our study had various degrees of ophthalmoplegia at presentation and 23 (85%) showed improvement post-ESS which was statistically significant ($p<0.001$).

The final visual acuity (VA) at three-month follow-ups post-ESS showed vision stabilization (no improvement or worsening) in 13 patients (48%), vision improved in seven patients (26%), and vision deteriorated in two patients (7%). Statistical analysis showed no significant difference between initial and post-intervention VA ($p=0.05$), however, there was no intracranial spread of infection or recurrence in any of the patients. Though not statistically significant, patients with bacterial sinusitis had better improvement in VA when compared to patients with fungal etiology. Worsening of vision post-surgical intervention was seen in two patients

who had not undergone orbital decompression. The patient who underwent optic nerve decompression had no perception of light at presentation and had no improvement in vision postoperatively. However, there was no further spread of infection intracranially or recurrence during the follow-up period in this patient. The patients who underwent endoscopic medial maxillectomy and subtotal maxillectomy had a diagnosis of mucormycosis and did not have any intracranial spread of infection or mortality. The patient who underwent sub-total maxillectomy received an obturator three months after surgery. One patient who was diagnosed with mucormycosis and was receiving medical treatment post-ESS and debridement expired on postoperative day four due to an acute cerebrovascular accident thus resulting in a mortality rate of 3.7% in our study (Table 5).

Discussion

Our study analyzed the presenting rhino-orbital symptoms and outcome in terms of prognosis in ptosis, ophthalmoplegia, vision, intracranial spread of infection, and mortality due to OAS secondary to sinusitis by ESS that could aid in early clinical suspicion, diagnosis and decrease the morbidity and mortality due to this rare syndrome. The literature available on this condition is limited and restricted to case studies due to different etiologies causing OAS (5-7). This, we believe, is the first case series of our population.

The most common presenting complaints of OAS are blurring of vision and ophthalmoplegia despite the varied etiologies (1). The most common presenting complaints in our study were blurring of vision (81%), headache (66%), diplopia (63%), ptosis (63%), nasal obstruction (48%), and facial pain (48%). The most common clinical signs were ophthalmoplegia and positive relative afferent pupillary defect. The signs and symptoms indicate the involvement of neural structures which are closely related to this area and consistent with other studies (8-10).

Even though neuro-ophthalmic symptoms develop at an earlier stage, there is a delay in definitive diagnosis of OAS secondary to sinusitis (11, 12). The duration from symptom onset to surgery ranged from 10 to 42 days as most patients ignored the initial sinonasal symptoms. Our study highlights the other accompanying sinonasal symptoms that can aid in the early diagnosis of sinusitis as etiology, such as headache, nasal obstruction, facial pain, and nasal discharge.

Table 5. Patient vision (Snellen visual acuity chart) on follow-up of 3 months

Initial vision (feet)	Number of patients	Improvement	Final vision (feet)
No perception of light	5	0	
Perception of light	5	1	20/40
20/200	3	1	20/30
20/70	4	2	20/40
			20/30
20/50	3	1	20/20
20/40	7	2	20/20
			20/20

Aryasit et al. (12) in their retrospective study on OAS concluded by stating, "Imaging should be performed on all patients to locate the site of lesion and determine the etiology. Imaging is also a tool for surgical planning". All patients in our study had radiological imaging, which aided the accurate diagnosis–the first step towards treatment. The infection spreads from the adjacent paranasal sinuses to the OA. The majority of our patients had ipsilateral involvement of the sphenoid and ethmoidal sinuses with OA involvement on imaging. Bilateral involvement of the OA is possible, although all our patients had unilateral involvement (13).

All our patients underwent ESS with no complications. We were able to reach the narrow OA crevice with the help of endoscopes and achieve disease clearance, acquire tissue for histopathology, and identification of microorganisms which aided in implementing emergent definitive treatment. It also helped in the debridement of the necrotic tissue from the surrounding area, and decompression of the orbit and/or optic nerve which prevented the ascent of infection to the CS (intracranially) and decreased the morbidity and mortality due to this condition. Gu et al. (14) in their report on six cases of OAS caused by sinus disease state that "Endoscopic sinus surgery is a safe and effective method for OAS caused by sinus disease, which is the primary therapy for the disease".

Infectious etiology accounts for only 15% of the cases of OAS and is most commonly due to sinusitis (4). Fungal infection is most commonly due to aspergillus and mucor (15). The most common bacterial isolates belong to staphylococcal species, *Streptococcus pneumoniae*, and Gram-negative bacilli like *Pseudomonas aeruginosa, Klebsiella*, and *proteus* species (16). Diabetics are susceptible to these infections. Most cases in our study were due to fungal sinusitis, mucormycosis (12/16 patients), and four patients due to aspergillus species (4/16 patients). Invasive fungal sinusitis commonly seen in immunocompromised patients often presents as OAS with the presence of necrotic tissue in the OA, which was also a finding of our study (4, 15). The most common bacterial isolate in our study was *Staphylococcus aureus* (10/11 patients) and one patient with *Staphylococcus epidermidis*, a commensal that is recognized as a pathogen in immunocompromised patients (17). Patients with rhino-orbital mucormycosis need extensive surgical and medical treatment to maximize outcomes (18). All our patients underwent ESS with repeated debridement if necessary and received specific antimicrobials. IV liposomal amphotericin B was initiated

for mucormycosis (5–10 mg/day to a final daily dose of 0.5 to 0.7 mg/kg depending on the cardio-renal status, maximum cumulative dose of 2.5 g) followed by posaconazole 300 mg once daily for 4–6 weeks. Voriconazole and itraconazole for aspergillus species 200 mg twice daily for two months and culture-sensitive antibiotics for bacterial sinusitis. Corticosteroids are commonly used in OAS secondary to inflammatory or traumatic etiology or when the definitive etiology is not known. Our patients did not receive systemic corticosteroids.

Lee et al. (4) in their retrospective study on 20 diagnosed cases of OAS have documented that despite aggressive multidisciplinary management, improvement in VA is poor after treatment but there is a relationship between the cause of the disease and visual prognosis. Treatment directed towards underlying etiologies experienced improved VA. Our study showed comparable results concerning VA. We documented a stabilization of vision and prevention of further deterioration of vision in most patients when the treatment was directed at the etiology. Clearance of disease from the narrow crevices by extended surgery helped prevent the spread intracranially but showed no significant improvement in pre- and post-intervention VA.

Yamanoi et al. (19), in their report on three cases of intracranial aspergillosis with OAS, documented an improvement in ophthalmoplegia in two of the cases. In our study, all patients presented with some degree of ophthalmoplegia which is the most common sign of OAS, and 23 patients (85%) had a recovery when the treatment was aimed at the etiology (12). Ptosis improved in 12 (70%) out of the 17 patients who presented with the condition.

All the patients in our study population followed the institutional postoperative anticoagulation protocol. Excluding the two COVID patients, all patients did not receive any anticoagulants given early postoperative mobilization. The COVID patients received antiplatelets i.e., Aspirin 75 mg once daily from 24 hours postoperatively for three weeks and low molecular weight heparin once daily as 1 mg/kg during hospital stay. However, we documented one death on postoperative day four in a COVID positive Mucormycosis patient due to an acute cerebrovascular accident which was attributed to the prothrombotic state created by COVID-19 (20). We did not document any intracranial spread of infection in any of the patients, which is a known complication of OAS, possibly due to the accurate diagnosis and treatment tailored to the etiology. ESS helped in the clearance of the disease, thereby reducing the morbidity and mortality in our study.

The patient data was collected over a decade, but still, a limited number of patients were studied due to the rarity of OAS secondary to sinusitis. We suggest large multicentric studies on OAS secondary to sinusitis due to infection.

Conclusion

Prompt diagnosis and intervention by ESS with appropriate culture-sensitive antimicrobials help reverse some of the CN damage, prevent further deterioration of vision, and primarily prevent the extension of infection intracranially in OAS secondary to sinusitis. There is a decrease in morbidity and mortality when treatment is directed at the etiology of OAS.

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Ethics Committee Approval: Our study was approved by the Ramaiah Medical College Institutional Ethics Committee (no: MSRMC/EC/AP-04/06-2023, date: 23.06.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: C.C., S.B., H.N.R., S.B.P., S.P.D.R., T.U., S.K.R., Concept: C.C., S.B., H.N.R., S.P.D.R., S.K.R., Design: C.C., S.B., S.B.P., S.K.R., Data Collection and/or Processing: C.C., S.B., H.N.R., S.P.D.R., T.U., Analysis and/or Interpretation: C.C., S.B., S.B.P., S.K.R., Literature Search: C.C., S.B., H.N.R., S.P.D.R., T.U., Writing: C.C., S.B., S.B.P., T.U.

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Main Points

- Data emerging from orbital apex syndrome (OAS) secondary to sinusitis due to infectious etiology is largely restricted to isolated case reports and this is the first case series in our population.
- Associated symptoms such as headache, nasal obstruction, facial pain, and nasal discharge are often overlooked as suggestive of OAS secondary to infection-causing sinusitis. However, these can aid in early diagnosis.
- After surgical intervention, an improvement in ptosis and ophthalmoplegia can be seen in most patients.
- Early endoscopic sinus surgery with modifications helps in the clearance of the disease from the narrow crevices and prevents further spread of infection intracranially thereby reducing the morbidity and mortality of this condition.

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The Effect of Rheumatoid Arthritis on Middle and Inner Ear Functions

Original Investigation

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Abstract

Objective: To investigate the middle and inner ear functions, and efferent auditory systems in patients with rheumatoid arthritis (RA).

Methods: Thirty-five RA patients and 40 control subjects participated in the study. Pure-tone audiometry, high-frequency audiometry, multifrequency tympanometry, transient evoked otoacoustic emissions, and contralateral suppression tests were administered to all participants.

Results: Pure-tone hearing thresholds of RA patients were significantly higher at all frequencies except for 2000 Hz, 14,000 Hz, and 16,000 Hz in the right ear and 16,000 Hz in the left ear ($p<0.05$). Resonance frequency values of RA patients were statistically significantly lower than those of the control group ($p<0.001$). Emission amplitudes obtained with contralateral acoustic stimulation were significantly lower at 1400 Hz frequency in both groups than without contralateral acoustic stimulation ($p<0.05$). While contralateral suppression was observed at all frequencies in the control group, no suppression occurred at 2800 Hz and 4000 Hz in RA patients.

Conclusion: The results obtained in this study demonstrated the presence of hearing dysfunction in patients with RA. When a patient is diagnosed with RA, an audiological evaluation should be made, and the patient should be informed about the possibility of audiological involvement.

Keywords: Rheumatoid arthritis, hearing loss, inner ear, middle ear, audiology

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Introduction

Rheumatoid arthritis (RA) is a long-lasting inflammatory autoimmune disease that affects multiple synovial joints. CD4(+) T-cells and monocytes pass from vessels into inflamed synovial tissue and fluid, characterizing the disease. The etiology and pathogenesis, however, remain unknown (1). It is known that diarthrodial synovial joints are more affected by RA. The ossicles malleus, stapes, and incus, which grow together sequentially in the middle ear, are diarthrodial joints and therefore may be affected by RA (2, 3).

Ear disorders are described in up to 85.71% of patients with RA with a higher prevalence of sensorineural hearing loss (SNHL) than conductive hearing loss (CHL) and/or mixed hearing loss (MHL) (4-6). The prevalence of CHL in patients with RA has been reported to range from 0% to 25% (1, 4). It has also been reported that sudden SNHL could occur in RA patients (7-9). Some studies suggest that

there is no association between hearing loss (HL) and RA (10-14).

Auditory efferent function is assessed using contralateral suppression of cochlear responses, and otoacoustic emissions (OAE) (15). Transient evoked otoacoustic emission (TEOAE) can be used to study the function of the medial efferent system by analyzing the levels of responses obtained in the presence of noise and without noise (16). TEOAE suppression is considered an important, rapid, and non-invasive clinical procedure for evaluating cochlear function and the functioning of the efferent medial olivocochlear system (MOC) (17).

Although studies in the literature have shown an association between RA and hearing disorders, there is insufficient data on the location of the pathology causing HL. Studies evaluating middle ear and inner ear functions together are very limited. There is no study examining the olivocochlear efferent neural pathway in patients with RA. In this study, we investigated whether RA affected middle and inner ear functions.

Our study aimed to comprehensively evaluate the middle and inner ear functions and efferent auditory system of RA patients with pure-tone audiometry, high-frequency audiometry, impedancemetry, multifrequency tympanometry (MFT), TEOAEs, and contralateral suppression testing.

Methods

The study was approved by the Clinical Research Ethics Committee of the Medical Faculty of Başkent University (project no: KA15/538, date: 23.12.2015, decision no: 15/111) and all participants signed an informed consent form.

The sample size was calculated by power analysis by adopting a two-tailed type I error of 0.05 and a power of 0.80 as approximately 35 patients in each group. The study group included 35 patients (70 ears) in an age range of 20–60 years, and RA diagnoses were made according to 1987 ACR criteria (18). The control group included 40 healthy age- and sex-matched volunteers (80 ears).

Pure-tone audiometry, high-frequency audiometry (8000–16,000 Hz), immittancemetry, MFT, TEOAEs, and contralateral suppression tests were administered to all participants. Before the audiological examination, all cases underwent a complete ear, nose, and throat examination. Medications taken alone or in combination by the patients with RA consisted of non-steroidal anti-inflammatory drugs, sulfasalazine, methotrexate, and steroids. None of the subjects were undergoing treatment with salicylates, sedatives, tranquilizers, or vestibular suppressants, and none consumed alcohol.

The inclusion criteria for both groups were normal findings in the ear, nose, and throat clinic examination, type A tympanogram in the electroacoustic immittancemetry test, and obtaining ipsilateral and contralateral reflexes. The patients included were those with no history of systemic, chronic, or autoimmune disease other than RA.

The exclusion criteria for both groups were the presence of pathology in the outer ear canal, the tympanic membrane, and/or the middle ear; the use of ototoxic drugs; a history of acoustic and/or physical trauma; having an ear disease that could permanently affect hearing thresholds; or a history of ear surgery.

Audiological Evaluation

We conducted pure-tone audiograms in soundproof cabins using the Clinical Audiometer AC-40 (Interacoustics A/S, Assens, Denmark). Pure-tone absolute thresholds were obtained at pure-tone frequencies between 125 and 8000 Hz. High-frequency hearing thresholds were determined at frequencies between 9000 and 16,000 Hz. Bone conduction thresholds were obtained at 250, 500, 1000, 2000, and 4000 Hz. We calculated pure-tone averages (PTAs) for frequencies of 500, 1000, and 2000 Hz. Northern and Downs' (2002) classification was used to classify HL (19). A PTA of 15 dB or less was considered normal hearing.

Acoustic Impedancemetry

Subjects underwent immittance measurements with a GSI TympStar Version 2 (Grason 05 Stadler Inc., MN, USA) middle ear tympanometer. Ipsilateral and contralateral reflexes were tested at 500, 1000, 2000, and 4000 Hz.

Multifrequency Tympanometry

In this procedure, a probe was inserted into the ear canal and the pressure was maintained at a constant level. Tympanograms were recorded using probe frequencies from 250 Hz to 2000 Hz in 50 Hz intervals.

Measurement of TEOAE with MOC Reflex

TEOAE tests (Titan; Interacoustics A/S Assens, Denmark) were performed in a quiet room. During the measurements, the stimulus severity was 80±3 dB SPL; reproducibility over 65%; frequency bands 1000, 1400, 2000, 2800, 4000 Hz and stimulus stability over 70% in the tested frequency. To investigate TEOAE suppression, a white noise was presented contralateral to the tested ear at 70 dB SPL. The test was applied in two steps. TEOAEs were recorded without and with contralateral noise. The results were recorded to be able to evaluate whether there was contralateral suppression.

Statistical Analysis

SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For continuous variables

with normal distribution, the Student's t-test was conducted, otherwise the Mann–Whitney U test was used. A paired t-test was used to compare TEOAE values before and after contralateral acoustic stimulation (CAS) in each group. Any p-value less than 0.05 was considered statistically significant.

Results

The mean age was calculated as 44.3±10.4 years in the RA patients and 41.4±12.5 years in the healthy control group (p<0.05).

Audiological Results

A total of 150 ears were evaluated, with 70 ears in the patient group and 80 ears in the control group. The hearing thresholds of the patient and control groups were separately compared at 125–16,000 Hz for both ears. The pure-tone hearing thresholds of the right and left ears of the patient and control groups were compared separately at 125–16,000 Hz. When the RA patient group's air and bone conduction hearing thresholds were examined, SNHL was determined at the rate of 15.7% in 11 ears of 7 patients as bilateral in 4 patients and unilateral in 3 patients according to PTAs.

The pure-tone hearing thresholds of the RA patients were significantly higher at all frequencies except for the frequencies of 2000 Hz, 14,000 Hz, and 16,000 Hz in the right ear and 16,000 Hz in the left ear (Figures 1, 2; p<0.05).

Multifrequency Tympanometry Results

Comparisons of the resonance frequency values for both ears in both groups are shown in Table 1. Resonance frequency values obtained in the RA patients were statistically significantly lower than those of the control group (p<0.05). The resonance frequency values of the patient and control groups were 748.8±188.0 Hz and 830.0±122.3 Hz for the right ear and 772.8±157.8 Hz and 847.5±140.9 Hz for the left ear, and the difference was statistically significant (p<0.001).

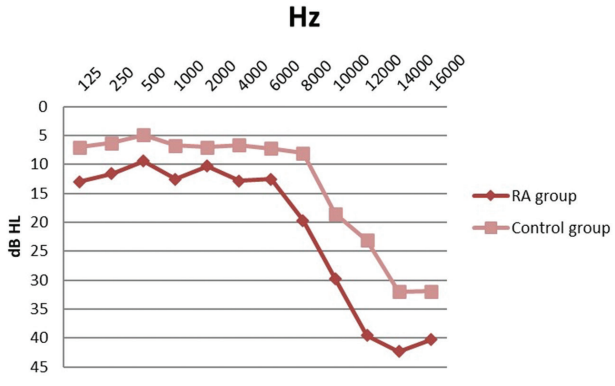

Figure 1. 125–16,000 Hz right ear pure sound hearing threshold averages of the groups

RA: Rheumatoid arthritis, Hz: Hertz, dB: Decibel

OAE and MOC Results

In the comparison of the TEOAE results of the two groups, emission results of RA patients were found statistically significantly lower at 1000 Hz, 2000 Hz, 2800 Hz, and 4000 Hz compared to the control group (p<0.05) (Table 2).

To examine the effects of the disease on the MOC efferent system activity, comparisons of the results of the TEOAE measurement were made before and during CAS application (Table 3). In the measurements taken in the RA patient group while applying CAS, suppression occurred at 1000, 1400, and 2000 Hz but not at 2800 Hz and 4000 Hz, and

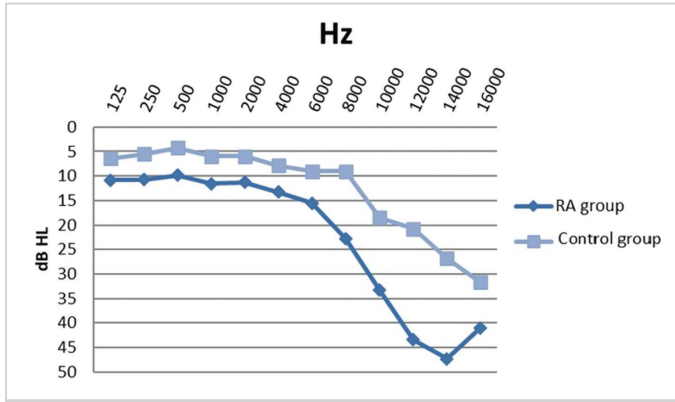

Figure 2. 125–16,000 Hz left ear pure sound hearing threshold averages of the groups

RA: Rheumatoid arthritis, Hz: Hertz, dB: Decibel

Table 1. Comparison of resonance frequency averages of the groups

	Right		Left	
	RA Mean (±SD)	Control Mean (±SD)	RA Mean (±SD)	Control Mean (±SD)
RF	748.8 (188.0)	830.0 (122.3)	772.8 (157.8)	847.5 (140.9)
p-value	<0.001**		0.001*	

RA: Rheumatoid arthritis, RF: Resonance frequency, SD: Standard deviation, *Student t-test, **Mann–Whitney U test were used

Table 2. Comparison of TEOAE results of the groups

Frequency (Hz)	RA Mean (±SD)	Control Mean (±SD)	p-value*
1000 Hz	18.1±6.3	20.8±5.4	0.005
1400 Hz	19.0±6.6	20.9±5.4	0.067
2000 Hz	15.1±4.9	16.7±4.2	0.031
2800 Hz	11.4±4.9	13.5±4.4	0.005
4000 Hz	11.6±4.2	13.4±4.9	0.018

TEOAE: Transient evoked otoacoustic emission, RA: Rheumatoid arthritis, SD: Standard deviation, Student t-test was used, *p<0.05

the difference was determined to be statistically significant (p<0.001).

Suppression was obtained at all frequencies in the control group and the difference was statistically significant (Table 4, p<0.0001).

Discussion

In the presented study, SNHL was found in 15.7% of the RA patients. The pure-tone hearing thresholds of RA patients were higher than those of the control group at all frequencies between 125 Hz and 16,000 Hz. The resonance frequency values of the RA patient group were statistically significantly lower than those of the control group. The TEOAE results of both groups were compared, and except for the 1400 Hz frequency, the amplitude values of the emission responses of the RA patients were statistically significantly lower than those of the control group. In the measurements during CAS application, suppression occurred at all frequencies in the control group, whereas in the patient group, suppression occurred only at the 2800 Hz and 4000 Hz frequencies.

RA may affect the temporomandibular joint, the larynx, the cervical spine, and the audiovestibular system in the head and neck region (2). RA can lead to CHL due to pannus formation in the incudostapedial joint and the incudomalleolar joint between the ossicles in the middle ear, which leads to the accumulation of synovial elements on the disc and articular surface (20). Some studies have shown a higher prevalence of HL, especially of the sensorineural type, in RA patients (4-6, 21-29). The exact mechanism linking RA and SNHL is still controversial, but several possible mechanisms have been proposed. Damage to the cochlea is one of the most frequently mentioned mechanisms (3, 13, 23). Some authors have suggested that the involvement of extra-articular disease is caused by vasculitis, neuritis, as well as cochlear and cochlear nerve involvement (10, 21). While most studies have found no evidence of retro-cochlear effects of RA, Magaro et al. (21) reported such findings. Colletti et al. (3) stated that in rheumatic fixation of the ossicular joint, the protective mechanism of the inner ear is impaired, and the hair cells of the inner ear may be damaged because of long-term exposure to intrinsic and extrinsic trauma. A previous study reported that HL was sensorineural at 8000 Hz and the loss of acoustic reflex was associated with the effects on the middle ear (30). The destruction of cochlear cells or the accumulation of immune complex deposits in the inner ear can lead to HL by triggering the autoimmune process (21, 22). There are publications in the literature reporting that drugs used in the treatment of RA could affect the inner ear (10, 20). In another study, Kastanioudakis et al. (22) did not find a correlation between antirheumatic drugs and inner ear disorders. In our study, the time between the diagnosis of the disease and the time the tests were performed, the medications used, and their duration varied. Therefore, no definitive interpretation can be made as to whether the SNHL detected in our patients was due to the disease affecting the inner ear or to the medications they used. Additionally, none of our patients were being treated with salicylates, which can cause cochleovestibular dysfunction (20).

Several studies have reported varying rates of HL in patients with RA. García Callejo et al. (6) found that 42.7% of their participants experienced HL between 500 and 3000 Hz frequency range. The researchers compared patients with RA to healthy controls and found a significant difference. Furthermore, they discovered that 96% of HL cases were sensorineural, while the remaining 4% were conductive (6). A study found that 12.5% of RA patients without HL developed it within a year, with 90% being sensorineural and 10% conductive (26). Accordingly, 12.5% of the patients developed HL within one year, out of which 90% were sensorineural and the remaining 10% conductive. Lobo et al. (12) reported that 46.5% of RA patients and 30.4% of controls had HL. In 80% of the RA patients and 85.7% of the control subjects with HL, the HL can be described as sensorineural (12). Galarza-Delgado et al. (28) reported that SNHL occurred at 500–3000 Hz in 36.8% of the patients with RA, at 4000–8000 Hz in 68.4%, and at 10,000–16,000 Hz in 94.9%. Treviño-González et al. (31) reported that SNHL was observed in 43.5% of patients at a sensitivity to pure-tones of 125 to 8000 Hz, in 94.0% of patients at a tone

Table 3. TEOAE values before contralateral acoustic stimulation and during contralateral acoustic stimulation in RA patients

Frequency (Hz)	TEOAE before CAS Mean (±SD)	TEOAE during CAS Mean (±SD)	p-value*
1000 Hz	18.1 (6.3)	14.7 (6.4)	<0.001
1400 Hz	19.0 (6.6)	18.1 (5.9)	<0.001
2000 Hz	15.1 (4.9)	14.5 (5.3)	<0.001
2800 Hz	11.4 (4.9)	11.7 (5.0)	No suppression
4000 Hz	11.6 (4.2)	12.3 (4.4)	No suppression

CAS: Contralateral acoustic stimulation, TEOAE: Transient evoked otoacoustic emission, RA: Rheumatoid arthritis, SD: Standard deviation, Hz: Hertz, *Paired sample t-test was used

Table 4. For the control group, TEOAE values before contralateral acoustic stimulation and during contralateral acoustic stimulation

Frequency (Hz)	TEOAE before CAS Mean (±SD)	TEOAE during CAS Mean (±SD)	p-value*
1000 Hz	20.8 (5.4)	16.2 (5.3)	<0.001
1400 Hz	20.9 (5.4)	18.8 (5.3)	<0.001
2000 Hz	16.7 (4.2)	16.0 (4.5)	<0.001
2800 Hz	13.5 (4.4)	12.5 (4.5)	<0.001
4000 Hz	13.4 (4.9)	13.2 (4.0)	<0.001

CAS: Contralateral acoustic stimulation, TEOAE: Transient evoked otoacoustic emission: SD: Standard deviation, Hz: Hertz, *Paired sample t-test was used

threshold of 10,000 to 16,000 Hz in the right ear, and in 95.7% in the left ear. Another study found that 69.8% of 53 RA patients had SNHL at high frequencies (10,000–18,000 Hz), while only 43% reported SNHL on standard audiometry at 125–8000 Hz (27). There are also studies looking at MHL in RA patients. Kakani et al. (32) found MHL in 4% of their RA patients. Ozcan et al. (5) reported 35.1% SNHL, 24.3% CHL, and 10.8% MHL. Almasi et al. (29) reported that the frequency rates of CHL in the left and right ears were 2% and 5%, respectively, and the rates for SNHL were 55% and 61%, respectively. In addition, the percentage of HL in low-, mid-, and high-frequency ranges was 18%, 19%, and 57%, respectively. The presence of MHL suggests multifocal involvement of the auditory system in RA (5). Some studies suggest that there is no link between HL and RA disease (10-14). The most common HL reported in the literature is SNHL. Recent studies have reported that sudden SNHL could occur in RA patients (7-9). In addition, Wang et al. (7) reported that HL recovery was difficult in sudden SNHL patients with RA, and its prognosis could worsen as the course of RA lengthened. In our study, we observed SNHL in 15.7% of the RA patients, as consistent with the literature, and the pure-tone hearing thresholds of these patients were higher than those of the control group in the pure-tone and high-tone audiometry measurements at all frequencies between 125 Hz and 16,000 Hz. Except for the 2000 Hz, 14,000 Hz, and 16,000 Hz frequencies in the right ear and 16,000 Hz in the left ear, this difference was statistically significant at all frequencies. From these findings, it can be concluded that the cochlea is a target organ in RA.

In studies of RA patients, lower OAE responses were obtained compared to the control subjects, or in the majority of cases, not at all. Halligan et al. (14) found no differences in TEOAE, whereas Dikici et al. (10) and Salvinelli et al. (4) observed significantly lower TEOAE amplitudes in patients with RA compared with controls. Lobo et al. (12) found that RA patients had reduced response amplitudes to stimulation compared to controls at all frequencies tested, with statistical significance only at 2 kHz in both ears. Murdin et al. (33) found no TEOAE in a vast majority of their RA patients. It was hypothesized that this could be an indication of early symptomatology of HL. When the TEOAE results of both groups were compared in our study, the emission responses of the RA patients were significantly lower at the amplitude levels of 1 kHz, 2 kHz, 2.8 kHz, and 4 kHz compared to those of the control group. From these findings, it can be concluded that the outer hair cells could be affected by the disease process.

In studies using MFT in RA patients, abnormal resonant frequencies were found in RA patients compared to control groups. In a study by Colletti et al. (3) resonance frequency was examined with MFT in 30 RA patients and 48 control subjects. Abnormal resonance frequency values were found in 12 RA patients (40%), while normal resonance frequencies in the range of 900–1250 Hz were found in the control group. Biasi et al. (34) studied 30 RA patients and 48 control subjects and found normal resonance frequencies between 800 and 1250 Hz in the control group and abnormal resonance values in 11 of the RA patients. In these studies, it was reported that the abnormal resonance frequency values in RA patients could be due to an impairment of ossicular mechanics related to the involvement of the incudomalleolar and incudostapedial joints. Pascual-Ramos et al. (26) reported a normal tympanogram in 93 patients (82%), although high-frequency tympanometry was abnormal in 80 patients (71.4%). In our study, the resonance frequency values of the patient group were statistically significantly lower compared with those of the control group. We think that the low-frequency values in the patient group were related to inflammation of the soft tissue and ligamentous structures. However, further studies are needed to investigate the physiology of low resonance frequency in RA patients.

Although there are several studies in the literature on the MOC reflex, there are no studies on RA patients in this regard. However, there are findings indicating that outer hair cell functions are impaired in RA patients. In our study, while contralateral suppression occurred at all frequencies in the control group, no suppression was observed at 2800 Hz and 4000 Hz in the patients with RA. According to these results, the contralateral suppression ability in RA patients associated with the efferent auditory system is impaired at 2800 Hz and 4000 Hz, so it can be said that RA disease has an impact on the function of the efferent auditory system. However, further studies are needed to show the sensitivity of the peripheral auditory system in RA patients.

RA activity and its effects on hearing is a controversial issue. Murdin et al. (33) found no relationship between hearing thresholds and markers of disease activity or other rheumatological parameters. Salvinelli et al. (4) found no differences in hearing thresholds between active and inactive RA patients and between RA patients and controls. Ozcan et al. (5) could not detect a relationship between hearing thresholds and disease activity and other rheumatological parameters. Yilmaz et al. (25) reported that while there was a slight increase in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor values of patients with suspected inner ear pathology, these differences were not found to be statistically significant. There are studies in the literature showing a relationship between disease activity and SNHL (1, 10, 21). Takatsu et al. (1) showed that the frequency of SNHL was associated with ESR and plasma concentrations of IL-6 and matrix metal loproteinase-3. Dikici et al. (10) concluded that higher ESR and CRP levels were associated with HL. The disease activity of the patients participating in the study, diagnosis/symptom duration, laboratory parameters, and the effects of

the treatments they received on hearing were not examined. A meta-analysis is needed to draw definitive conclusions in this area. Another limitation of our study is that we only measured HL at one point in time, without considering its progression over time. Therefore, we were unable to properly analyze the effects of treatment over time.

Conclusion

The presented study found that RA patients experienced deterioration in pure-tone hearing thresholds, a decrease in resonance frequency values, low amplitude values in emission responses, and high-frequency distortion. These findings demonstrate that middle and inner ear functions are impaired in RA patients. Therefore, patients diagnosed with RA should undergo audiological assessment and be informed of the possibility of otologic involvement.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of the Medical Faculty of Başkent University (project no: KA15/538, date: 23.12.2015, decision no: 15/111).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authorship Contributions

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

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

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Main Points

- Although studies in the literature have shown the presence of a relationship between RA and impaired hearing, there is insufficient data about the location of the pathology that causes hearing loss.
- There are no studies evaluating the olivocochlear efferent neuronal pathway in patients with RA.
- The results of the presented study show that deteriorated middle and inner ear functions could be related to RA, and it is important to evaluate the effect of RA on middle and inner ear functions with a comprehensive test battery.

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Retrospective Analysis of Laryngeal Cancer Patients in a Tertiary Referral Center

Original Investigation

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Abstract

Objective: In this study, we aimed to evaluate the effects of demographic data and comorbid diseases on the prognosis and treatment diagnosed with laryngeal squamous cell cancer (LSCC).

Methods: Medical records of LSCC patients treated and followed up in a single referral center between 2008 and 2019 were retrospectively reviewed. In addition to the demographic data, the results of overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional-free survival (LRFS), and factors affecting recurrence were analyzed.

Results: We included 573 patients with a mean age of 60.1±9.8 years. Of the 573 patients, 94.2% (540) were men, 93.7% (537) were smokers, 40.1% had at least one comorbid disease, and 69.8% (400) presented with glottic LSCC. The five-year OS, DSS, DFS, and LRFS rates for all cases were 65.7%, 79.9%, 67%, and 74.7%, respectively. In early-stage LSCC treatment, the rates of OS (p=0.008), DFS (p=0.024) and LRFS (p=0.01) were statistically significantly higher in the endolaryngeal laser surgery (ELS) group compared with the radiotherapy (RT) group. In advanced-stage LSCC treatment, total laryngectomy had statistically significantly higher five-year DFS (p=0.003) and LRFS (p=0.002) rates compared to chemoradiotherapy.

Conclusion: Our study showed that ELS provided higher rates of OS, DFS, and LRFS compared to RT in the treatment of early-stage LSCC. Recurrence was significantly higher in supraglottic tumors, advanced-stage tumors, and in patients with clinical N positivity.

Keywords: Clinical oncology, laryngeal cancer, squamous cell carcinoma, laryngectomy, organ preservation, survival

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Introduction

Laryngeal squamous cell cancer (LSCC) is the most common head and neck squamous cell carcinoma (HNSCC) in Türkiye, and the second and third most common HNSCC in Europe and the United States, respectively. Every year seven out of 100,000 people, approximately 3,500 new cases, are diagnosed with LSCC in Türkiye (1-3). Globally, nearly 180,000 patients are diagnosed with laryngeal cancer every year, and 95,000 people die with this diagnosis (4). The well-known major etiological factors are smoking and consuming tobacco products. Alcohol, genetic predisposition, gastroesophageal reflux, and viral infections may also play a role. Smoking is thought to be responsible for 30% of cancer-related deaths worldwide, and smokers are ten times more likely to develop laryngeal cancer than non-smokers (5). The combination of alcohol and cigarette abuse synergistically increases the likelihood of cancer development (6).

There are several treatment modalities, both surgical and non-surgical for laryngeal cancer, and the treatment plans are mostly designed based on the stage of the disease. The main purpose is to eradicate cancer as well as to preserve most of the structure and functions of the larynx. Applied treatments to patients are based on patients' choices as well as the physicians' and institutional preferences. Radiotherapy (RT) is used as a non-surgical treatment in the early stages of LSCC, whereas surgical options include transoral endolaryngeal or open partial surgeries, whereas the main treatment modality in advanced-stage disease has been total laryngectomy (TL) for many years. In 1991, the well-known study of Veteran Affairs of Laryngeal Cancer Study Group (VALCSG) (7) reported that survival outcomes were similar for both non-surgical organ preservation treatment and TL plus adjuvant treatments. In the three decades following this study, advances in chemotherapy (CT) and RT regimens have made organ preservation protocols more popular. However, controversies continue in the literature on whether the TL or the organ preservation regimen is best oncologically and functionally in advanced-stage patients, or at least which of the two is the best choice for which patients.

Survival rates in LSCC did not improve in the last four decades despite improved diagnosis and treatment modalities, but apparently, the rate of laryngeal preservation has increased (8).

The purpose of the presented study was to evaluate the prognostic factors along with demographic data, comorbid diseases, and treatment outcomes in LSCC patients who were treated in a single referral head and neck center.

Methods

This retrospective study was conducted following the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 76/10, date: 25.11.2019).

Patients and Treatment Strategy

The charts of the laryngeal cancer patients that were treated in a single referral head and neck center between January 2008 and May 2019 were retrospectively analyzed. Patients with mild to severe dysplasia, non-epithelial cancers, and salivary gland cancers, and those who were lost to follow-up were excluded from the study, and those who were followed-up for at least five years, either alive or dead, were included in the study. Carcinoma *in situ* (Cis), stage 1, and stage 2 were considered early stages, and stages 3 and 4 were considered advanced stages. Data of the patients included in the study were retrieved from the medical records. The pack-year (PY) definition used in the history of smoking was calculated by multiplying the number of packs smoked per day by the number of years of smoking. Details of staging and treatment plans were based on the decisions of the multidisciplinary tumor board. The patients were staged according to the American Joint Committee on Cancer (AJCC) 7th edition (2010).

In general, endolaryngeal laser surgery (ELS), open partial surgery (OPS), or RT options were used as a single treatment modality in patients with Cis, T1, and T2 glottic or supraglottic cancers. Alternatively, chemoradiotherapy (CRT) or TL options were considered in T3 cancers, and the TL option was used in T4-stage tumors.

Follow-up

The patients were followed up and examined twice a month in the first six months, monthly in the second six months, bi-monthly in the second year, quarterly in the third year, and biannually in the fourth and fifth years, and annually after five years. On every visit, a fiberoptic laryngoscope, videolaryngostroboscope, or 70° rigid laryngoscope was used in laryngeal examinations. Microlaryngoscopic examination was done under general anesthesia if a suspicious lesion was defined during the follow-up period. Neck and chest CTs were taken annually for the first five years, and then chest P/A X-ray annually. In our clinical practice, we do not routinely screen patients with a positron emission tomography scan for early laryngeal tumors.

Statistical Analysis

SPSS for Windows version 23.0 software was used for statistical analysis. Numerical variables were expressed as mean ± standard deviation or median along with the attribute variables as numbers and percentages. The Shapiro–Wilk test was used to determine the normality of numerical variables. The chi-square test or Fisher's exact test was used to investigate whether there was an intergroup difference in terms of attribute variables. The Kaplan–Meier product limit

estimation method was used to predict survival probabilities. The Mantel–Cox log-rank test was used to compare the survival curves of different groups. The Cox proportional regression analysis was used to determine the factors that affected survival. The level of significance was determined as $p<0.05$.

Results

Demographic data and tumor characteristics of the 573 patients LSCC are shown in Table 1. Mean patient age was 60.1±9.8 years and 540 (94.2%) of the cases were men. In total, 537 of the patients (93.7%) had a history of smoking with an average rate of 41.5 PY cigarettes, and 83 (14.5%) had a regular alcohol consumption history. At least one comorbid disease was found in 230 (40.1%) of the cases, and the most prevalent one was hypertension (141 cases, 24.6%). The most frequent localization of the tumor was the glottis (400 patients, 69.8%), followed by the supraglottis (169 patients, 29.5%). Four patients (0.69%) had subglottic tumors (one patient stage 2, and three patients stage 4 LSCC). According to TNM staging, 321 (56%) were staged as early, and 252 (44%) were as advanced. Most of the patients (480 cases, 83.76%) had N0 neck at presentation. Overall anterior commissure (AC) involvement was found in 247 cases (43.1%); and in 112 (39.4%) of 284 cases with early-stage glottic LSCC. The most common treatment type was ELS in 182 cases (31.8%). Other treatments used at the early stages were RT in 75 cases (13.1%) and OPS in 69 cases (12%). In the advanced stages, CRT was used as the first treatment option in 166 cases (29%) and TL was used in 81 cases (14.1%) (Table 1).

The five-year overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), locoregional-free survival (LRFS) rates of the 573 cases were 65.7%, 79.9%, 67%, and 74.7%, respectively. The survival rates of the variables are summarized in Table 2.

The OS (p=0.005), DSS (p=0.046), and LRFS (p=0.035) rates of the patients without comorbid diseases were significantly higher than that of the patients with at least one of the comorbid diseases (Table 3). The presence of hypertension did not appear to statistically affect OS (p=0.067), but there was a statistically significant decrease in the rates of DSS (p=0.005), DFS (p=0.02), and LRFS (p=0.001) in patients with HT.

Patients with supraglottic tumors appeared to show a significant decrease in five-year OS ($p<0.001$), DSS ($p<0.001$), and DFS ($p<0.001$) rates, compared to those with glottic tumors, but there was no difference in LFRS rates (p=0.059) (Table 3).

Early-stage patients had significantly better survival rates than the advanced stages in all survival analyses (OS, DSS,

Table 1. Patient demographics and clinical data

Characteristics	**Overall cohort, n=573**
Clinical history	
Age, mean ± SD	60.1±9.8
Gender, male, n (%)	540 (94.2)
Comorbid disease, n (%)	230 (40.1)
Smoking history, n (%)	537 (93.7)
Alcohol use, n (%)	83 (14.5)
Tumor site n (%)	
Glottis	400 (69.8)
Supraglottis	169 (29.5)
AC involvement	247 (43.1)
Stage, n (%)	
Early-stage	**321 (56)**
Carcinoma *in situ*	53 (9.2)
I	166 (29)
II	102 (17.8)
Advanced-stage	**252 (44)**
III	151 (26.4)
IV	101 (17.6)
Clinical T, n (%)	
T *in situ*	53 (9.2)
T1	166 (29)
T2	102 (17.8)
T3	151 (26.4)
T4	101 (17.6)
Clinical N, n (%)	
N0	480 (83.8)
N1	36 (6.3)
N2a	5 (0.9)
N2b	18 (3.1)
N2c	29 (5.1)
N3	5 (0.9)
Histological type, n (%)	
Carcinoma *in situ*	53 (9.2)
Well-differentiated	222 (38.7)
Moderately differentiated	225 (39.2)
Poorly differentiated	73 (12.9)
Type of treatment, n (%)	
ELS	182 (31.8)
RT	75 (13.1)
OPS	69 (12)
TL	81 (14.1)
CRT	166 (29)
Recurrence, n (%)	**176 (30.7)**
Death, n (%)	**182 (31.8)**

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, RT: Radiotherapy, SD: Standard deviation, TL: Total laryngectomy

Table 2. Five-year survival rates in all parameters

Characteristics	OS 5-yr (%)	DSS 5-yr (%)	DFS 5-yr (%)	LRFS 5-yr (%)
Overall	65.7	79.9	67	74.7
Age (yrs)				
<65	69.9	80.9	66.9	74
≥65	54.9	78.3	67.4	76.5
Gender				
Male	64.5	79.2	67	74.8
Female	78	90.9	66	72.2
Smoking				
<30 PY	73	84.3	72.8	76.6
>30 PY	60.3	76.7	64.3	74.5
Comorbid disease				
No	69.6	83.1	69.9	79.1
Yes	58.8	75.1	62.3	68
Localization				
Supraglottic	52.8	69.8	55.5	68.9
Glottic	71.4	84.4	72.2	77.7
Histopathologic type				
Carcinoma *in situ*	85.1	94.5	81	82.2
Well-differentiated	73.2	85.5	73.3	78.1
Moderately differentiated	58	74.9	62.7	71.7
Poorly differentiated	44.4	62.9	44.8	64.6
Stage				
Early	78.9	91.8	77.6	85.5
Advanced	48.3	64.6	52.8	65.1
Stage				
Carcinoma *in situ*	87.1	95.2	79.1	80.6
I	82.6	96	78.4	82.8
II	70.7	84.8	74.6	80.2
III	52.2	71.2	56.1	66.2
IV	42.4	54.2	47	63.2
T stage				
T *in situ*	87.1	95.2	79.1	80.6
T1	82.6	96	78.4	82.2
T2	67.3	82.7	69	77.4
T3	49.4	66.4	54.6	63.6
T4	45.6	59.2	53.8	72.1
N stage				
N0	70.3	85.6	72.1	78.7
N+	38.4	50.2	39.1	51.4
N stage				
N0	70.3	85.6	72.1	78.7
N1+N2a	45.9	57.2	40.3	52.2
N2b and above	31.1	43.3	37.5	51.6
AC involvement				
No	65.6	80.8	70.6	77.4
Yes	64.6	78.8	62	71
Early stage glottic AC involvement				
No	84	97.1	85.8	88.1
Yes	75.2	85.7	65.2	68
Type of treatment				
ELS	85	94.4	78.5	82.5
OPS	74.2	92.7	81.5	89.2
RT	71.5	87.3	67.4	70.8
TL	48.8	69.5	64.4	75.9
CRT	48.1	61.2	47.9	58.9

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, SD: Standard deviation, TL: Total laryngectomy, DSS: Disease-specific survival, DFS: Disease-free survival, LRFS: Locoregional-free survival, OS: Overall survival

LRFS, DFS; p<0.001). N+ patients had significantly worse survival rates in all survival analyses compared to N0 patients (p<0.001). Upon comparison of the N+ cases, when grouped as N1+N2a and N2b+N3, among themselves, no significant difference was observed in any survival analysis (OS p=0.23, DSS p=0.34, DFS p=0.82, LRFS p=0.62). AC involvement did not significantly affect survival (OS p=0.65, DSS p=0.87, DFS p=0.3, LRFS p=0.53). However, when AC involvement was taken into consideration in early-stage glottic cancers, a statistically significant decrease was seen in DSS, LRFS, and DFS (DSS p=0.04, DFS p=0.01, LRFS p=0.01) (Table 3).

A comparison of the treatment types in early stages showed five-year OS rates to be 85%, 71.5%, and 74.2% for ELS, RT, and OPS, respectively. ELS had a statistically significant advantage over RT in terms of OS rates in early-stage treatments (p=0.008). However, ELS and OPS (p=0.07), and OPS and RT (p=0.4) were not significantly different in terms of OS. Assessment of DSS in terms of the treatment types -ELS, RT, and OPS-showed no significant superiority to each other in early-stage treatments (RT + ELS p=0.06, APC + RT, p=0.39, APC + ELS p=0.41). It was seen that LRFS rates of RT were significantly lower compared to the other two treatment types (OPS/RT p=0.009, RT/ELS p=0.01) (Table 3).

In the analysis of the survival outcomes according to the type of treatment in the advanced stage, no statistically significant differences were found between CRT and TL in terms of five-year OS and DSS rates (OS p=0.4, DSS 0.12). In the five-year DFS and LRFS rates, TL had a significant advantage over CRT (DFS p=0.003, LRFS p=0.002) (Table 3).

Recurrence was observed in 30.7% of the cases. Analysis of the factors affecting recurrence revealed that recurrence was observed in 39.1% of supraglottic tumors and 26.7% of glottic tumors at all stages (p=0.004). Recurrence was observed in 41.7% of advanced-stage tumors and 22.1% of early-stage tumors (p<0.001). Recurrence was observed in 53.8% of N+ cases and 26.3% of N0 cases (p<0.001). Further, sex, age, the amount of smoking, and AC involvement in all cases did not significantly appear to affect recurrence (gender p=0.52, age p=0.57, smoking p=0.17, AC p=0.34). When considering the type of treatment, the highest recurrence rates were seen in patients who received RT (36%) in early cases and CRT (45.8%) in advanced cases, respectively. The lowest recurrence rate was observed in ELS with 17.6% (Table 4), which was applied in early cases.

Discussion

A well-known etiological factor of LSCC is smoking. Smoking plus alcohol abuse may act synergistically in cancer development (6). In this study, 93.7% of the patients were cigarette addicts, but only 83 cases (14.5%) had both alcohol and smoking history.

Table 3. Univariate cox regression for survival groups

	Overall survival		Disease-specific survival		Disease-free survival		Locoregional-free survival	
Variable	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**
Age >65	**0.001**	1.79 (1.33–2.41)	0.13	1.36 (0.9–2.06)	0.96	1 (0.73–1.39)	0.61	0.9 (0.61–1.33)
Female gender	0.4	0.74 (0.36–1.5)	0.23	0.5 (0.16–1.6)	0.45	0.76 (0.37–1.55)	0.57	0.79 (0.34–1.8)
Smoking (>30 PY vs. <30 PY)	**0.002**	1.66 (1.2–2.29)	**0.039**	1.58(1.02–2.44)	**0.04**	1.39 (1.01–1.92)	0.56	1.11 (0.77–1.6)
Comorbid disease	**0.005**	1.51 (1.13–2.02)	**0.04**	1.49 (1–2.21)	0.31	1.16 (0.86–1.57)	**0.03**	1.45 (1.02–2.05)
Supraglottic localization	**0.001**	2 (1.48–2.69)	**0.001**	2.25 (1.5–3.36)	**0.001**	1.68 (1.24–2.29)	0.059	1.42 (0.98–2.06)
AC involvement	0.65	1.07 (0.79–1.43)	0.87	1.03 (0.69–1.53)	0.3	1.16 (0.86–1.57)	0.53	1.11 (0.78–1.57)
Advanced stage	**0.001**	3.69 (2.69–5.06)	**0.001**	7.4 (4.39–12.5)	**0.001**	2.47 (1.83–3.34)	**0.001**	2.18 (1.54–3.1)
Clinical N+ vs. N0	**0.001**	3.5 (2.55–4.83)	**0.001**	5.3 (3.56–7.97)	**0.001**	3.22 (2.31–4.49)	**0.001**	3.26 (2.21–4.8)
N2b and above vs. N1+N2a	0.23	1.37 (0.8–2.35)	0.34	1.34 (0.72–2.48)	0.82	1.06 (0.61–1.86)	0.62	1.17 (0.61–2.26)
Early stage glottic SCC AC involvement	0.27	1.38 (0.76–2.5)	**0.04**	2.97 (1.01–8.7)	**0.01**	1.82 (1.1–3)	**0.01**	1.93 (1.12–3.32)
Type of treatment (RT vs. ELS)	**0.008**	2.3 (1.24–4.3)	0.068	2.6 (0.92–7.74)	**0.024**	1.81 (1.08–3.03)	**0.01**	2.08 (1.18–3.65)
Type of treatment (OPS vs. RT)	0.4	0.77 (0.42–1.42)	0.39	0.61 (0.2–1.87)	0.066	0.56 (0.3–1.03)	**0.009**	0.36 (0.17–0.77)
Type of treatment (OPS vs. ELS)	0.079	1.79 (0.93–3.43)	0.41	1.64 (0.49–5.41)	0.95	1.01 (0.55–1.86)	0.47	0.75 (0.35–1.61)
Type of treatment (TL vs. CRT)	0.4	0.85 (0.57–1.24)	0.12	0.67 (0.41–1.11)	0.003	0.49 (0.31–0.79)	**0.002**	0.39 (0.21–0.7)

AC: Anterior commissure, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, SCC: Squamous cell carcinoma, TL: Total laryngectomy, CI: Confidence interval, HR: Hazard ratio

The types of treatments for laryngeal cancers evolved in the last three decades and the rate of laryngeal preservation increased, however, the survival rates did not. Transoral laser and robotic surgeries have replaced most of the open partial surgeries with similar oncological but better functional results. Non-surgical treatments have also replaced most of the total laryngectomies with reasonable functional results. In this case series, the leading treatment type was laser surgery (31.8%) and chemoradiation (29%) followed by radiation (13.1%), OPS (12%), and the TL rate was noticeably low (14.1%). A survival analysis of all cases showed five-year DSS and DFS rates to be 79.9% and 67%, respectively. Survival results in our institution are compatible with the current literature along with significantly low rates of TL (14.1%).

Since most of the patients are in their 60s and have a smoking history, one or more comorbid diseases were present at the time of diagnosis in most patients. In their review of the publications, Alho et al. (9) found that the prognosis for laryngeal cancer was the worst in patients with larynx, pharynx, or tongue cancers with the same comorbidity score. These study results revealed that 40% of the cases (230 patients) had at least one of the accompanying diseases, namely, hypertension, diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease. The most common comorbidity was hypertension (n=141, 25%). It was determined that the rates of OS (69.6% vs. 58.8%), DSS (83.1% vs. 75.1%), and LRFS (79.1% vs. 68%) were statistically higher in patients without comorbid diseases. It was also noted that DSS, DFS, and LRFS rates were significantly higher in patients without hypertension than in those diagnosed with hypertension.

Regional lymph node metastases are one of the most important factors affecting the prognosis of laryngeal cancers. It is known that as the tumor stage (T) advances, the clinical and occult lymph node metastasis rate increases (10). Clinically, N+ lymph node reduces the overall survival of patients by 50% (11). Clinical lymph node positivity was found in 93 cases (16.2%) in our study, therefore the number of clinical N0 stages at presentation was predominantly higher than the N+ stages. We do not know the actual rate of occult metastasis as only those undergoing total or open partial laryngectomy had neck dissection. In another study conducted in our institution, patients undergoing total or partial laryngectomy plus elective neck dissection for N0 neck, the occult metastasis rate was found that 17.4% (12). Based on our clinical data, we believe that current high-

resolution imaging techniques reveal neck metastasis more accurately than in previous decades. In the present study, the five-year OS rates in clinical N0 and N+ cases were 70.3% and 38.4%, respectively. It was observed that the LRFS, DSS, and DFS rates in N+ patients decreased significantly. Knowing the fact that neck metastasis is an absolute dismal factor along with our low rates of both clinical (16.2%) and occult neck metastasis (17.4%), correct decisions for the neck treatment should be given in each case. In other words, only necks with clinically positive nodes or N0 necks with a high potential of occult metastasis should be treated. In another study on N+ patients with hypopharynx and larynx cancer, Ho et al. (13) determined that classical N staging had less prognostic value than the number of metastatic lymph nodes, and suggested the limitations of an N classification based only on laterality and lymph node size. In our study, clinical N+ patients were divided into two groups, N1+2a or N2b and above, and in all survival analyses, no significant difference was found between N1+2a or N2b patients, which is also consistent with the findings of Ho et al. (13).

Table 4. Recurrence characteristics and p-values in 176 LSCC patients

Characteristic		Recurrence+, n (%)	p-value
Gender	Male	168 (31.1)	
	Female	8 (24.2)	0.525
Age	<65	123 (31.5)	
	≥65	53 (29.1)	0.572
Smoking	≤30 PY	58 (26.6)	
	>30 PY	105 (33.2)	0.173
Localization	Supraglottic	66 (39.1)	
	Glottic	107 (26.7)	**0.004**
Stage	Early stage	71 (22.1)	
	Advanced stage	105 (41.7)	**<0.001**
Stage	Carcinoma *in situ*	11 (20.8)	
	Stage I	35 (21.1)	
	Stage II	25 (24.5)	
	Stage III	61 (40.4)	
	Stage IV	44 (43.6)	**<0.001**
Clinical T	T *in situ*	11(20.8)	
	T1	35 (21.1)	
	T2	34 (29.6)	
	T3	72 (41.4)	
	T4	24 (36.9)	**<0.001**
Clinical N	N0	126 (26.3)	
	N1+N2a	24 (56.1)	
	N2b and above	26 (51.9)	**<0.001**
N0/N+	N0	126 (26.3)	
	N+	50 (53.8)	**<0.001**
Histopathology	Carcinoma *in situ*	13 (24.5)	
	Well-differentiated	55 (24.7)	
	Moderately differentiated	75 (33.3)	
	Poorly differentiated	33 (45.2)	**<0.001**
Anterior commissure involvement	No	95 (29.1)	
	Yes	81 (32.8)	0.348
Type of treatment	ELS	32 (17.6)	
	OPS	17 (24.6)	
	RT	27 (36)	
	TL	24 (29.6)	
	CRT	76 (45.8)	**<0.001**

LSCC: Laryngeal squamous cell cancer, CRT: Chemoradiotherapy, ELS: Endolaryngeal laser surgery, OPS: Open partial surgery, PY: Package-year, RT: Radiotherapy, TL: Total laryngectomy

The AC is a focal point of anatomical, diagnostic, and therapeutic controversies and challenges in laryngeal oncology. AJCC divided the glottis into three regions as AC, posterior commissure, and vocal cords, but AC involvement was not considered as a separate parameter in the current T staging system (14, 15). Reportedly, 20% of all glottic cancers have AC involvement (16). There are different opinions in the literature regarding the effect of AC involvement on prognosis in patients treated with ELS in early-stage glottic LSCC (17). Carta et al. (18) found that AC involvement shows worse survival outcomes. Hendriksma and Sjögren (19) presented a compilation of 58 publications that examined AC involvement in early-stage glottic SCC in the English literature between 1998 and 2018. The study found that only one of the 14 publications reported that AC involvement in T1b and T2 tumors significantly affected five-year OS, but no difference was observed in T1a. In the other 13 studies, no significant differences were found in Tis-T1-T2 tumors. In the same review, in four out of 13 publications, AC involvement was reported to decrease DSS significantly; and regarding local control rates, it was reported that AC involvement decreased local control rates significantly in about one-third of the studies (19). In our study, no statistically significant differences were observed in OS, DSS, LRFS, and DFS with AC involvement in all tumor stages. However, in early-stage glottic LSCC, though AC involvement did not show a significant difference in OS (p=0.27), it was seen that DSS (p=0.04), DFS (p=0.01) and LRFS (p=0.01) rates decreased significantly with the AC involvement.

Early-stage and locoregionally advanced-stage treatments differ from each other in laryngeal cancer. In the advanced stages, the standard treatment was TL and adjuvant RT until the early 90s, and 1991 VALCSG (8) and Forastiere et al.'s (20) studies pioneered the use of CRT regimens as a standard treatment option.

The advantages of partial surgery and RT over each other in the early stages are still controversial. Upon the review of the publications comparing ELS and RT, Mo et al. (21) in a meta-analysis of 11 studies involving T1 tumors stated that ELS increased OS significantly compared to RT, and no differences were found between local control rates. In the meta-analysis of T1a glottic patients, Abdurehim et al. (22) found no statistically significant differences between the two treatment groups in terms of OS and DSS rates. In the meta-analysis comparing RT and ELS in early-stage glottic tumors (Tis-T1-T2), Higgins et al. (23) found no differences between the two treatment arms in local control and laryngectomy-free survival, whereas OS rates were significantly higher in ELS. In our study, when we compared ELS with RT in early-stage laryngeal cancers (Tis-T1-T2), the five-year OS rate was found significantly lower in RT compared to ELS (71.5% vs. 85%); but in DSS, there were no significant differences between RT and ELS (87.3% vs. 94.4%). Further, the five-year LRFS rate was significantly higher in ELS than in RT (82.5% vs. 70.8%). In summary, when RT and ELS were compared in our study, OS, DFS, and LRFS rates showed a significant difference in favor of ELS, while no significant difference was found between the two groups in terms of DSS. When OPS and RT were compared, no statistically significant differences were found between these two treatment arms regarding OS and DSS. However, it was observed that OPS was statistically superior to RT in local control rates (p=0.009).

Treatment options are TL or CRT in locoregionally advanced LSCC. The social and psychological situation created by TL still prompts clinicians to investigate laryngeal preservation methods that would provide the same survival rates. In a meta-analysis comparing non-surgical organ preservation therapies with TL, Tang et al. (24) reported that there was no statistically significant difference in T3 tumors in OS, but OS was higher in T4 tumors in patients who underwent TL. In addition, this meta-analysis reported that the DSS and local control rates were statistically significantly higher in TL. However, no significant difference was found between the two treatment arms in terms of DFS. Rosenthal et al. (25) compared TL and CRT cases in T4 tumors. While no statistically significant differences were found between OS and DSS, a significant superiority of TL was observed in locoregional control rates. In a 10-year study in which 182 patients were evaluated, Timmermans et al. (26) applied CRT to T3 tumors and adjuvant RT after TL to T4 tumors. They did not detect any significant OS differences between T3 and T4 tumors, between stage 3 and stage 4 tumors, and between CRT and TL, and based on their findings they concluded that the optimal treatment for T3 tumors was CRT. Our current strategy is compatible with the aforementioned metanalysis as we perform CRT in T3 tumors and T1-2-3 tumors with N+ necks. We prefer TL and adjuvant treatments in T4 tumors regardless of neck status. In the present study, when all locally advanced-stage tumors were evaluated together, no statistically significant differences were found between the two treatment arms in OS and DSS, while the rates of DFS (p=0.003) and LRFS (p=0.002) were found to be significantly higher in TL compared to CRT. Getting similar results between TL and CRT and knowing that TL is applied in more advanced T4a tumors and CRT in T3 tumors, suggests that TL is a good option in the treatment of T4a laryngeal cancer. Therefore, our strategy is to give the larynx the chance of preservation and to protect the patients' quality of life. It is important to recommend CRT in the first place for T3 tumors along with close follow-up. The fact that there were no statistically significant differences between the two treatment arms in terms of OS and DSS in our study also supports that approach. In our study, overall TL was applied in 14% of all laryngeal cancer cases.

Recurrence rates vary according to the laryngeal sub-regions and stages, where the tumor originates, although recurrence is observed in 15% to 30% of patients (27, 28). Haapaniemi et al. (29) advocated that World Health Organization performance status, female sex, supraglottic localization, and primary non-surgical treatments were independent predictors of laryngeal cancer recurrence. Brandstorp-Boesen et al. (30) reported that the risk of recurrence was affected by age, location, T stage, and treatment type, and N+ status did not increase the risk of recurrence in supraglottic cancers; but increased in glottic cancer. In their article, salvage surgeries performed in 241 patients with recurrent laryngeal cancer, Mimica et al. (31) used TL in 74% of the patients, OPS in 16%, and transoral laser surgery in 10%, and reported the rate of DSS after salvage surgery to be 57%.

In our study, the recurrence rate was 30.7%. Similar rates have been reported in the literature (28, 29). The factors that affected recurrence were: N positivity, advanced-stage tumors, supraglottic localization, and AC involvement in early stage glottic tumors. Recurrence rates were also higher in non-surgical treatments than in surgical treatments. Salvage laryngectomy should be considered as the first option in case of recurrence.

The limitations include that our study is a retrospective one due to the nature of cancer studies that contain heterogeneous data and do not provide functional results. The high number of cases and the long follow-up period are the strengths of our study.

Conclusion

In patients diagnosed with LSCC, the most appropriate treatment plan can be determined with careful diagnosis and staging, and approximately two out of three patients can be safely cured. The presented study shows that ELS provides higher rates of OS, DFS, and LRFS compared to RT in the

treatment of early-stage LSCC. In early-stage glottic SCC, AC involvement decreases DFS and increases the local recurrence rate. Supraglottic tumors, advanced-stage tumors, and clinical N positivity significantly increase recurrence. In the treatment of advanced LSCC, the CRT option can be considered primarily in T3 tumors and TL should be reserved as salvage therapy.

Ethics Committee Approval: This retrospective study was conducted following the approval of the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 76/10, date: 25.11.2019).

Informed Consent: Informed consent was not obtained from the patients because of the anonymous and retrospective design of the study.

Authorship Contributions

Surgical and Medical Practices: Ö.B., E.Ç.T., G.S., M.H.K., Concept: A.C.S., Ö.B., Design: A.C.S., Ö.B., Data Collection and/or Processing: A.C.S., Ö.B., G.T., Ş.A., S.K., V.Y., Analysis and/or Interpretation: A.C.S., Ö.B., G.T., Ş.A., S.K., V.Y., Literature Search: A.C.S., Ö.B., V.Y., Writing: A.C.S., Ö.B.

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Main Points

- In early-stage glottic tumors, anterior commissure involvement decreases disease-free survival and increases local recurrence.
- Endolaryngeal laser surgery provides higher rates of survival compared to radiotherapy early-stage laryngeal cancer.
- For laryngeal cancer, only necks with clinically positive nodes or high potential of occult metastasis should be treated.
- Recommending chemoradiotherapy in the first place for T3 tumors along with close follow up is important.

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Reconstruction of Anterior Skull Base After Cleaver Trauma: Combined Use of Fascia Lata and Middle Turbinate Flap in a Patient with Concha Bullosa

Video Article

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Abstract

This video article presents a 47-year-old male patient who presented to the emergency department after a cleaver bounced off the grinding wheel and lodged between his eyebrows. The patient complained of clear nasal drainage since the trauma. Computed tomography showed a comminuted displaced fracture starting from the right frontonasal recess and extending along the right ethmoid roof. The patient underwent surgery. The skull base defect was reconstructed with a free fascia lata graft in the first operation. In the second session, the reconstruction of the skull base was reinforced with a flap that was prepared from the middle turbinate with the concha bullosa. The patient was followed for eight months. The patient's symptoms resolved completely and there was no evidence of rhinorrhoea or any other complication at the control examination. No complications were seen on control magnetic resonance imaging.

Keywords: Trauma, skull base, cerebrospinal fluid leak, rhinology, endoscopic surgery, surgical flaps, turbinates

Introduction

Anterior skull base injuries resulting from trauma present a challenging scenario for reconstructive surgeons due to the complexity of the anatomical structures involved and the potential for cerebrospinal fluid (CSF) leakage, encephalocele, or meningocele. Traditional approaches to anterior skull base reconstruction include various techniques such as free tissue transfer, multilayered fascia lata grafts, and middle turbinate flaps. However, selecting the optimal reconstructive strategy requires careful consideration of the patient's specific injury pattern and anatomical variations.

Case Presentation

A male patient in his late forties presented to the emergency department after the cleaver he was sharpening had bounced off the grinding wheel and lodged between his eyebrows. The patient reported a clear discharge from the right nostril that started immediately after the trauma. Computed tomography revealed a comminuted displaced fracture starting from the right frontonasal recess and extending along the right ethmoid roof. Pneumocephalus was evident in the right frontal region and along the midline of the anterior skull base. The patient was then taken to the operating room.

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Endoscopic examination at the beginning of the procedure revealed the entrance point of the cleaver in the axilla of the middle turbinate. The operation started with an uncinectomy. Anterior and posterior ethmoidectomy were then performed. Pulsation of brain parenchyma could be seen through a defect at the time of ethmoidectomy.

Utilizing a 30-degree scope, it was observed that the frontal lobe was protruding from the dura defect. Following the completion of ethmoidectomy, the frontal recess was found. The frontal sinus ostium was enlarged. Bone fragments were removed, and the margins of the skull base defect were identified. A fascia lata graft, measuring approximately 4 cm in width and 5 cm in length, was harvested. At the lateral margin of the defect, the graft was tucked under the remaining bone margin, while at the medial border, the graft was laid in an overlay fashion in order not to damage the olfactory fibers. A second layer of fascia was placed on top of the first layer and the procedure was completed by supporting the reconstruction with nasal dressing.

In order to reinforce the reconstruction of the base of the skull, a second operation was carried out one week after the first one. Superior and inferior horizontal incisions made on the lateral surface of the middle turbinate were combined with the vertical incision on the anterior surface, and the lateral lamella was excised. The mucosa of the concha bullosa cell was meticulously peeled off. The superior attachment of the axilla was partially released so as not to make the middle turbinate completely unstable. The middle turbinate flap was rotated over the reconstruction (Video 1). A nasal dressing was then applied, and the procedure was completed.

The patient was followed for eight months. The patient's nasal drainage symptoms had completely resolved, and endoscopic examination showed that the reconstructed defect was completely lined with nasal mucosa with no evidence of CSF leak, encephalocele, or meningocele. There was also no evidence of CSF rhinorrhoea, meningocele, or encephalocele on postoperative magnetic resonance imaging.

Discussion

The reconstruction of anterior skull base defects poses significant challenges due to the intricate anatomy and risk of CSF leakage. Various techniques have been described in the literature, including free tissue transfer, multilayered fascia lata grafts, and middle turbinate flaps (1). The size and location of the defect are the most important factors in determining the technique to be used for anterior skull base repair (2, 3). Free tissue transfer offers versatility in reconstructing large defects but may be associated with donor site morbidity and prolonged operative times. The use of nasoseptal flaps is associated with very low postoperative CSF rhinorrhoea. However, the length of the flap may not always extend sufficiently anteriorly to the posterior tabula of the frontal sinus. It may also be associated with impaired mucociliary movement, decreased sense of smell, and decreased quality of life (4). Multilayered fascia lata grafts provide a durable option for reconstruction, however, the use of fascia lata alone may not always suffice, particularly in cases with extensive defects or underlying anatomical variations. In cribriform plate defects as in this case, placement of the fascia underlay is not feasible because of the risk of fracturing the intact edges and injuring the olfactory fibers while trying to detach the dura (4).

This operation demonstrated that a secure repair can be achieved for large defects using a free fascia lata graft and middle turbinate flap together. In addition, we believe that the middle turbinate flap technique is still feasible even in the presence of concha bullosa and that our method is innovative in terms of flap preparation technique.

In conclusion, the combined use of a fascia lata graft and a middle turbinate flap represents a valuable strategy for anterior skull base reconstruction in patients with penetrating trauma even in the presence of concha bullosa. This approach offers durable and vascularized coverage of the defect, with favorable outcomes in terms of symptom resolution and prevention of CSF leakage. Long-term follow-up is essential to monitor for complications and ensure optimal patient outcomes.

Video 1. Anterior skull base reconstruction after penetrating cleaver trauma

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Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

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Main Points

- This video article highlights the successful repair of large skull base defects using a combination of free fascia lata graft and middle turbinate flap.
- The innovative technique presented here demonstrates the feasibility of applying a middle turbinate flap in the presence of concha bullosa.
- The favorable outcome and absence of postoperative complications emphasize the effectiveness and safety of this combined approach for securing repairs of extensive skull base defects.

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Case Series of Endoscopic Transoral Excision of Huge Parapharyngeal Tumors: Pushing the Boundaries

Case Report

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Abstract

Endoscopic transoral excision of parapharyngeal space (PPS) tumors is often condemned for its many limitations. We revisit this approach and aim to introduce some updated perspectives following the advancement of endoscopic instrumentation, robotic transoral surgery, and radical tonsillectomy. We illustrate the techniques that were deployed for six patients with huge benign PPS tumors originating from the pre-styloid compartment at our center. Only patients who had a tumor size of five cm or larger were included in this study. We summarized our patients' outcomes, the important considerations, and the advantages and disadvantages of this approach. With accurate selection and surgical strategy, all our patients had good clinical outcomes. We demonstrated that even larger tumors can be safely removed endoscopically. Surely, this approach will gain traction, and better-designed studies should be conducted in the future to assess its credibility.

Keywords: Parapharyngeal space, neoplasm, endoscopy, surgery, case report

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Introduction

Traditionally, transoral surgery has been limited to only small-sized benign pre-styloid parapharyngeal space (PPS) tumors. Many authors have discouraged this approach due to the belief that the risk of damaging the critical neurovascular structures, incompleteness of removal and tumor spillage were higher than external approaches (1). With the expansion of endoscopic technology, powered instruments and transoral robotic surgery in recent years, the transoral approach has regained momentum. We would like to document six cases of huge PPS tumors originating from the pre-styloid compartment that were successfully removed at our center. Concurrently, we summarize the important surgical pearls, the future direction, and their role in the armamentarium of the otorhinolaryngology field.

Case Presentation

A total of six patients who were diagnosed with benign tumors of five cm or larger, originating from the pre-styloid PPS underwent a transoral endoscopic excision at the University of Malaya Medical Centre between January 2014 and February 2019. The diagnosis was concluded after a thorough history review, physical examination, and imaging that included both computed tomography (CT) and magnetic resonance imaging (MRI) scans. Only patients with tumors

anteromedial to the internal carotid artery without any signs of malignancy were included (Table 1).

All surgeries were conducted by a senior surgeon under general anaesthesia via contralateral nasotracheal intubation. Patients were placed in Rose position and a Boyle Davis mouth gag was used to retract the tongue. Throat packing using ribbon gauze was also placed. An assistant held the endoscope and provided necessary retraction or suctioning to aid the primary surgeon (four-handed technique).

A vertical curvilinear mucosal incision from the soft palate to the lower pole of the mass was made with monopolar cautery. The submucosa, loose connective tissue and superior constrictor muscle were then precisely split without violating the tumor capsule. A healthy cuff of tissue on the anterior pillar was conserved to close the defect and lateralize the preserved tonsil. Blunt dissection was then commenced to gently detach the tumor along its capsule using a combination of Yankauer suction, Kittner sponge on tonsil clamp, hurd dissector, long curved bipolar and finger dissection. The dissection was done slowly and meticulously, releasing the tumor from its loose attachments within the PPS. We worked from the area where visualization and tissue mobilization were the easiest to free the tumor before proceeding to the deeper aspects. Small vessels or oozing were secured with bipolar cautery while any feeding vessels found over the lower pole of the tumor were ligated. The wound bed was then inspected under magnification and irrigated with saline thoroughly to eliminate any possible residual tumor cells. Surgicel was inserted into the wound cavity before closing it with interrupted 3–0 absorbable sutures. All the tumors were removed en bloc successfully. Patients were started on nasogastric tube feeding and antibiotics for at least 72 hours after surgery to prevent infection. On the second postoperative day, they were allowed to take fluids and stepped up progressively weaning off the nasogastric tube before discharge.

Despite the tumor sizes being at least five cm, all were completely excised without tumor spillage (Figures 1-3).

Table 1. Summary of patients' clinical outcomes

No.	Demography	Tumor size (cm)	HPE	Days of admission	Adverse effect	Follow up	Blood loss (cc)	Surgery time (min)
1	71 yo, male	6x4	Schwannoma	3	None	6 years	25	35
2	29 yo, female	8x7	Neurofibroma	4	None	5 years	38	40
3	75 yo, female	8x7	Pleomorphic adenoma	4	None	7 years	40	45
4	64 yo, male	5x5	Pleomorphic adenoma	3	None	5 years	30	30
5	55 yo, female	7x7	Schwannoma	3	None	6 years	35	40
6	40 yo, male	7x6	Schwannoma	3	None	5 years	30	35

HPE: Histopathological examination, yo: Years old

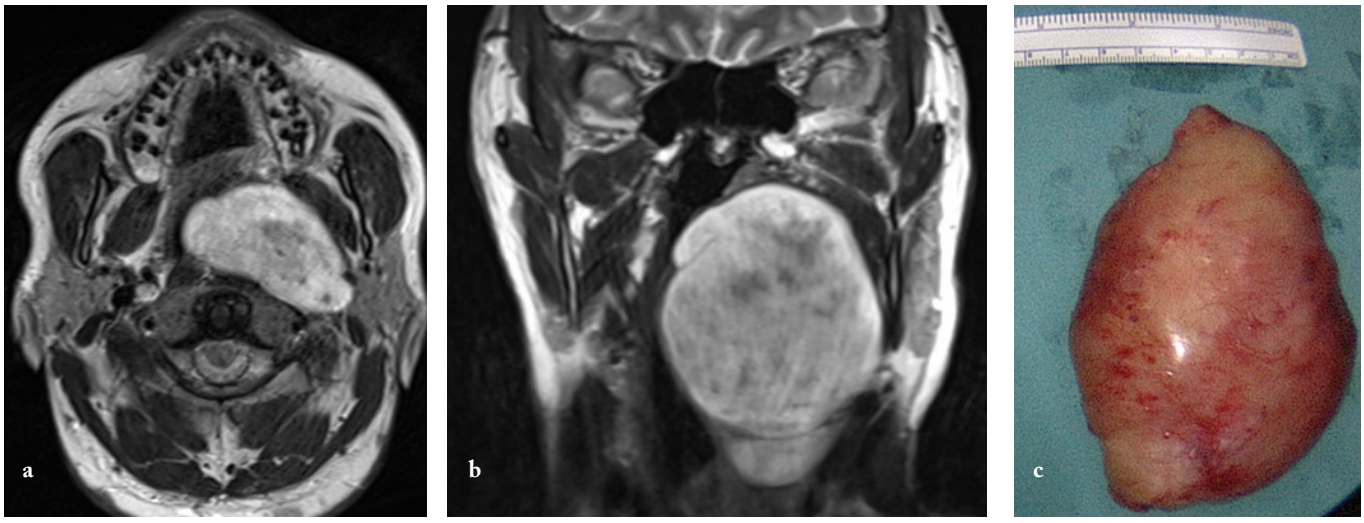

Figure 1. a, b) MRI scan showing tumor with a clear plane from the left parotid gland and skull base, **c)** specimen removed measured 8x7 cm with an intact capsule
MRI: Magnetic resonance imaging

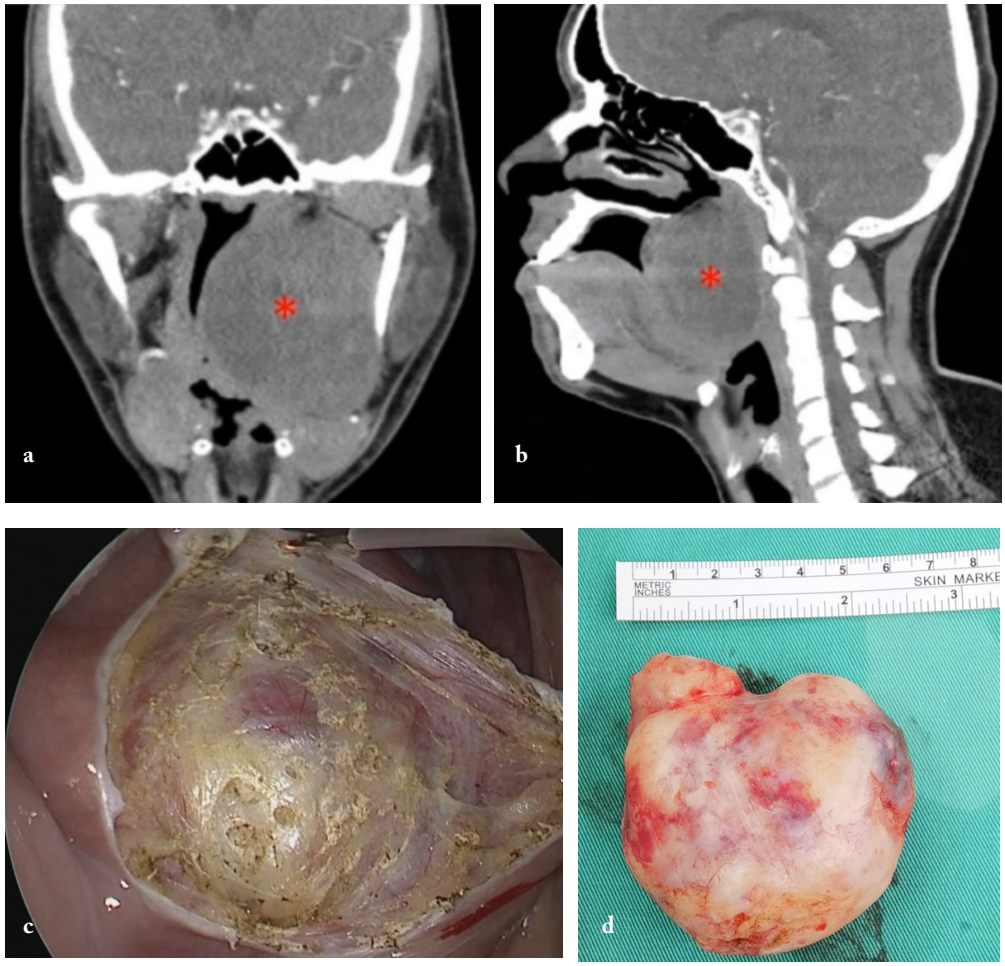

Figure 2. a, b) CT scan showed a huge tumor obstructing the upper aerodigestive tract, **c)** layers of incision slowly exposing the tumor capsule transoral, **d)** tumor removed was reported as schwannoma
CT: Computed tomography

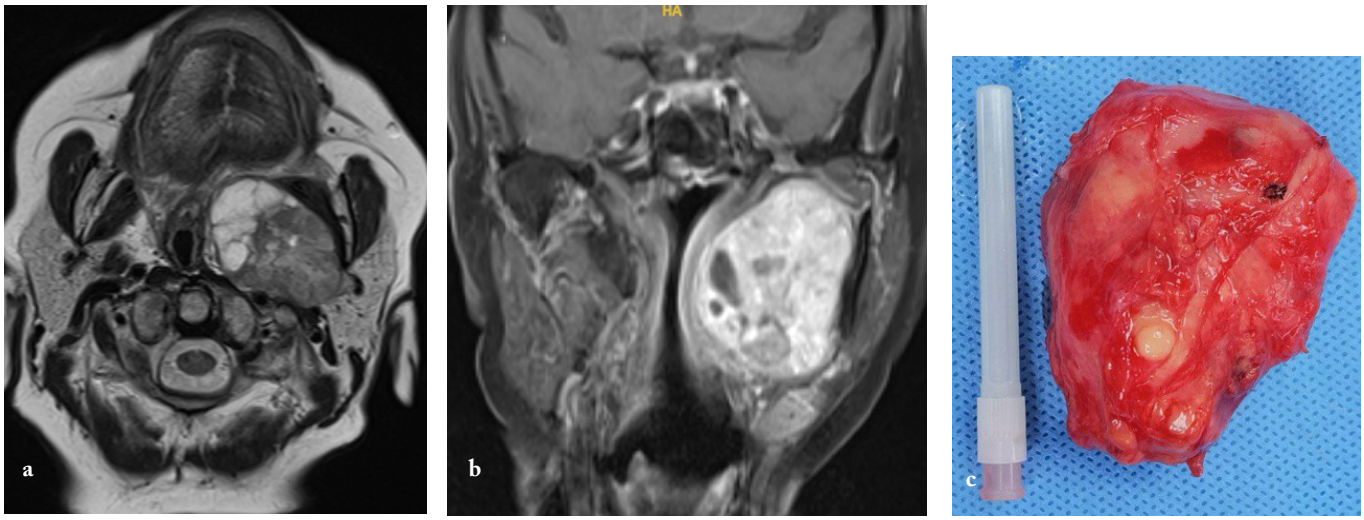

Figure 3. a, b) MRI scan showed multilobulated tumor originating from the deep lobe of the left parotid gland with clear margins superiorly, **c)** surgical specimen with intact capsule was reported as pleomorphic adenoma
MRI: Magnetic resonance imaging

The blood loss during the surgeries was all less than 50 cc. Operative time was not more than one hour in every case without any complications. The majority of our patients experienced tolerable pain and were discharged after three to four days once they were able to resume a regular diet. We did not resort to inserting a drainage tube to minimize discomfort and to allow earlier weaning off the nasogastric tube. Hitherto, we have observed no signs of recurrence during the years of follow-up. All the patients' wounds healed well, and they regained normal swallowing after surgery.

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

Discussion

External approaches including transcervical, transparotid and combined transmandibular were the main workhorses employed in the removal of PPS tumors. Lately, with the evolution of endoscopic technology, endoscopic transoral surgery has garnered more attention and is being used more frequently due to its many advantages. Among them, the endoscopes allowed enhanced and clearer anatomical structures and a wide-angle visual field with better lighting. It allowed superior appreciation of the anatomical planes, and easier identification of microvessels to allow precise, en bloc resection. Moreover, a recent meta-analysis concluded that PPS pre-styloid benign tumors were most suited for this approach, considering that patients benefited from shortened surgical times, lesser bleeding, faster postoperative recovery, shorter hospitalization, scar-free surgery, and fewer complications with comparable outcomes (2). In particular, it reduced the morbidity led by external approaches, especially regarding the significantly higher risk of facial nerve deficit, first-bite syndrome, sialocele, and functional disability (3).

Some surgeons do not favor the transoral approach mainly because of the limited exposure space, poorer hemostatic control, and purported higher risk of tumor spillage and carotid sheath injury (4). The reduced maneuverability of instruments in the surgical field may also be associated with an increased likelihood of capsular disruption, tumor recurrence and neurovascular damage (5). Direct contact with oral flora during surgery often requires temporary fasting and prophylactic antibiotics to prevent postoperative infections (5). These are the important considerations when choosing a suitable patient in a center with an experienced surgeon and backup. Interestingly, there has been no reported complication of major vascular injury during transoral endoscopic surgery. Many authors have also described a nearly non-existent complication rate using this approach through proper tumor and patient selection (6,7).

Therefore, rigorous patient selection is the most crucial step for successful endoscopic transoral PPS tumor removal. It begins with a thorough history and physical examination to assess the state of the upper aerodigestive tract including the airway, speech, and swallowing. Any tell-tale signs of malignancy, such as significant weight loss, cervical lymphadenopathy, and cranial nerve dysfunction, are cardinal features to note. Imaging will usually consist of both CT and MRI scans to analyze the tumor characteristics, tumor-normal tissue plane, tumor hypervascularity, and importantly, its relationship to the major neurovascular structure and skull base. Certainly, any features that suggest malignancy, such as irregular tumor margins, poor tissue fascial planes, lymphadenopathy and invasion into adjacent muscle, fat or bone, would not have an equally good clinical outcome.

Our patients' tumor sizes were significantly larger than the conventional ones that underwent endoscopic transoral excision as described in the literature (1). Other than having the advantage of a skilled surgeon, we avoided this approach if the tumor was located lateral or posterolateral to the carotid sheath. We also made sure that the tumor had a clear margin from the skull base without any features of malignancy. In this day and age, with the expanded usage of transoral robotic surgery, a better understanding of radical tonsillectomy, and ever-improving endoscopic instrumentation, this approach deserves its merits for obviating the need for a mandibular split, especially in tumors extending superior-medially to the skull base. A good command of the external approaches and appropriate counselling on the possible need to convert to them is vital to avoid medical entanglement.

Our experiences with large benign pre-styloid PPS tumors challenged the conventional surgical boundaries for an endoscopic transoral approach. Certainly, our small patient sample limits drawing any conclusions about how precisely valuable the surgical technique is. However, with the advancement of endoscopic instrumentation and minimally invasive approaches, we believe it will only become more widely deployed and allow future better-designed clinical studies to evaluate its credibility.

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

Authorship Contributions

Surgical and Medical Practices: C.C.L., Y.T.L., S.G., P.N., Concept: C.C.L., Y.T.L., S.G., P.N., Design: C.C.L., Y.T.L., S.G., P.N., Data Collection and/or Processing: C.C.L., Y.T.L., S.G., Analysis and/or Interpretation: C.C.L., Y.T.L., S.G., P.N., Literature Search: C.C.L., Y.T.L., S.G., P.N., Writing: C.C.L., Y.T.L., S.G., P.N.

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

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Main Points

- Endoscopic transoral surgery has been limited to only small benign parapharyngeal space tumors.
- External approaches including transcervical, transparotid and combined transmandibular were more routinely employed.
- Endoscopic surgery allows a clearer wide-angled visual field for superior appreciation of the anatomical planes and en bloc resection.
- Patients benefit from shortened surgical times, lesser bleeding, shorter hospitalization, faster recovery, and scar-free surgery, with fewer complications and morbidities.
- Large tumors can be removed with good outcomes by having accurate patient selection and surgical strategy.

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Patulous Eustachian Tube Accompanied by Internal Carotid Artery Anomalies

Case Report

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Abstract

Patulous Eustachian tube is a physical disorder in which the normally closed Eustachian tube remains open intermittently. Internal carotid artery (ICA) anomalies accompanied by Eustachian tube anomalies have been described very rarely in the literature. To the best of our knowledge, the presented case is the second case in the literature. In this report, we present a rare case of ICA anomalies accompanied by a bilateral patulous Eustachian tube in a 51-year-old woman.

Keywords: Eustachian tube, internal carotid artery, congenital anomalies, computed tomography, otology, case report

Introduction

The Eustachian tube (ET) is a delicate anatomical structure that connects the middle ear to the nasopharynx. The ET acts as a pressure equalizer and mucus drainer for the middle ear. Patulous Eustachian tube (PET) is a physical disorder in which the normally closed ET remains open intermittently. Internal carotid artery (ICA) anomalies accompanied by PET have been described very rarely in the literature (1, 2). In the presented case, we describe rare ICA anomalies accompanied by a bilateral PET.

Case Presentation

A 51-year-old female patient presented with a complaint of progressive hearing loss. It was learned from the patient's history that she had received treatment for ear infections and chronic cough at various times. Recently, she had a complaint of a sound coming from both ears while breathing. The patient had no known disease or operation history. Laboratory findings were within normal limits. On the patient's audiogram, conductive hearing loss was detected. There was a type C tympanometry curve in both ears on the tympanogram. On an otoscopic examination, bilateral dry tympanic membranes were detected. Depending on the patient's complaints, high-resolution temporal bone computed tomography (CT) and contrast-enhanced CT-angiographic (CTA) examinations were performed. High-resolution CT of the temporal bone showed prominent and wide ETs connecting both middle ears and nasopharynx (Figures 1a, b). Bilateral mastoid cell complex aerations were not observed. Soft tissue structures compatible with chronic otitis media were observed in

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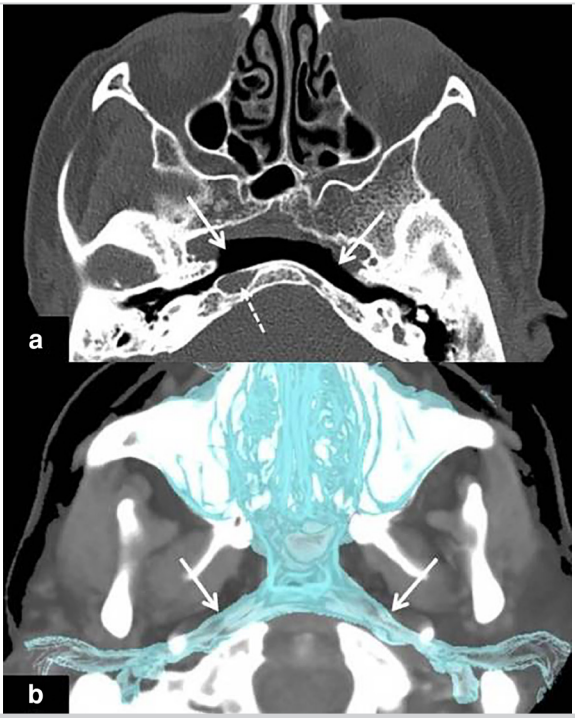

Figure 1. a) On the axial unenhanced computed tomography image, both Eustachian tubes are observed to be wider than normal and with a horizontal course (white arrows), and both carotid canals are not observed. In addition, in the clivus localization, a bone defect in which the aberrant internal carotid artery course is noted (dotted white arrow). b) 3D-volume rendering computed tomography fusion image shows patulous Eustachian tubes (white arrows) connecting the nasopharynx and middle ear bilaterally

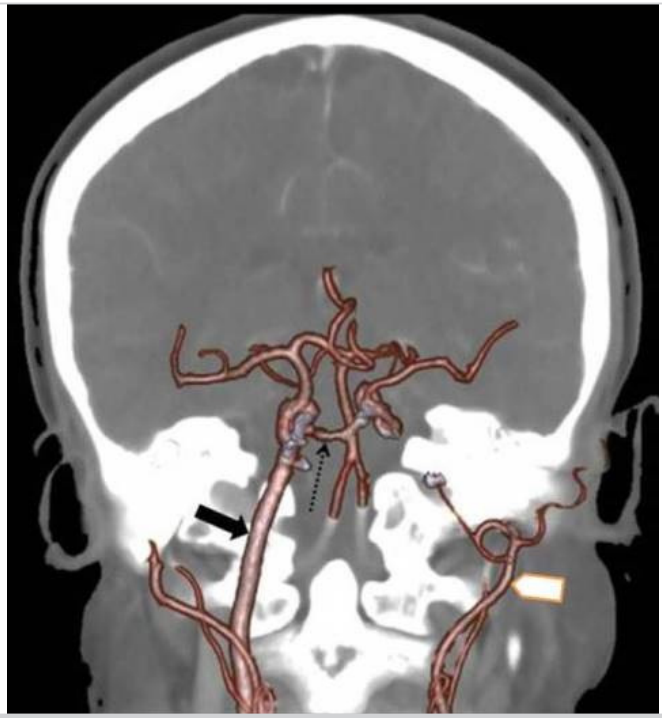

Figure 2. On the coronal contrast-enhanced computed tomography-angiographic fusion image, the internal carotid artery on the right is patent (black arrow) and has a tortuous appearance. The internal carotid artery is not observed on the left. The external carotid artery (short white arrow) is seen on the left. Furthermore, the aberrant arterial structure originating from the distal right internal carotid artery and extending to the left (aberrant left internal carotid artery, dotted black arrow) calls attention

bilateral mastoid cells. Both the middle and the inner ear structures were normal. Bilateral carotid channels were not observed. CTA examination revealed that the right ICA was patent. The left ICA was not seen in its normal location. The left ICA continued as a branch emerging from the right ICA at the level of the dorsum sellae and clivus. The right ICA had a tortuous appearance at a distal level. The A1 segment of the left anterior cerebral artery was observed as hypoplasic (Figure 2). No other accompanying vascular pathologies such as aneurysm or dissection were detected on CTA. In light of these findings, the patient was diagnosed with bilateral PET and ICA anomalies. The patient was informed about the present anomalies. Surgical treatment was recommended to the patient, but the patient did not accept surgical treatment. The patient was recommended conservative treatment and advised to gain weight.

An informed consent form was signed by the patient for the publication of this case.

Discussion

The ETs and the tympanic cavity originate from the first pharyngeal sac. The distal of the first pharyngeal sac forms the primitive tympanic cavity, while the proximal narrows to form the ETs. In case of damage at this stage, the ETs may be enlarged and associated with the tympanic cavity. An abnormal opening of the ET can lead to extreme changes in middle ear pressure and abnormal ossicular movements, resulting in hearing impairment. It may cause recurrent ear infections and chronic otomastoiditis attacks, as in our patient (2-4).

PET was first described by Jago (5) in 1867, not as a defect in embryogenesis, but as acquired in patients with diabetes, extreme weight loss, otitis media, and malignancy. PET can also be seen in patients with Trisomy 13, 18, 21, 22, those with extreme weight loss, those using oral contraceptives, and patients with oculo-auriculo-vertebral spectrum and Klippel-Feil syndrome (1, 3, 4). In 1990, Tolley and Phelps (6) demonstrated the radiological findings of this pathology using CT images.

The incidence of PET varies between 0.3–6.6%. Patients with a PET often complain of autophony. In addition, tinnitus, which is felt in the form of a sound or humming synchronised with breathing, disturbs the patient. Patients' symptoms are relieved in the supine position or when they bring their head to knee level (1, 2, 4). In a recent study, long-term PET has been shown to be associated with sensorineural

hearing loss. The presence of PET causes pressure changes in the cochlea through abnormal ossicular movement in the middle ear, causing sensorineural hearing loss (7). Our case had conductive hearing loss. We think that this situation is due to ET dysfunction.

Our case can be categorized as agenesis according to the classification of developmental anomalies of the ICA. This is more common on the left side. Congenital ICA agenesis is very rare. Most of the cases are detected incidentally during imaging procedures. Three types of collateral networks have been described in patients with ICA agenesis. The most common type is the fetal form, in which the ipsilateral anterior and middle cerebral arteries are supplied respectively by the normal contralateral ICA via the anterior communicating artery and the basilar artery via the ipsilateral dominant posterior communicating artery. The second collateral type is the adult form, in which the contralateral anterior cerebral artery supplies the ipsilateral anterior and middle cerebral arteries of the affected side via the anterior communicating artery. In the third collateral type, blood flow is obtained from the external carotid system, the contralateral ICA, or some primitive vessels (8, 9).

In literature search, we found that Menyatsoe and Khan (10) described a case with PETs and ICA anomalies with imaging findings like our case. To the best of our knowledge, the presented case is the second case in the literature showing similar characteristics.

One study has shown that the ET/ICA/midline angle varies between 37.7° on average (11). The absence of carotid canals and the presence of abnormal ICAs, as in our case, may lead to a more horizontal orientation of the ETs, resulting in a patulous appearance. The relationship between the ET and the ICA is important during endoscopic surgery for the dysfunction of the ET. The distance from the ICA to the ET varies between men and women. ET-ICA distance is shorter in patients with abnormal aberrant ICA (11).

The diagnosis of a PET is usually made based on suggestive symptoms, physical examination, and audiological findings. However, there is currently no diagnostic gold standard method. Various special tests such as tubomanometry, sonotubometry, and tubotympanic aerodynamics have been developed for PET diagnosis; however, these methods do not provide information about the anatomical structure of the ET. Therefore, radiological methods, especially CT, can be used in diagnosing PET. A disadvantage of the standard CT in these cases is that the patient's symptoms usually disappear when lying in supine position. Therefore, there is a tendency to underdiagnose PET on standard CT scanning in the supine position. In the literature, it has been shown that horizontal cone-beam CT is more successful in the diagnosis of PET in terms of showing the long axis, short axis, cross-sectional area, and total volume of the ET lumen. The main disadvantage of horizontal cone-beam CT is that the soft tissue contrast resolution is lower than that of standard CT (12).

In treatment planning, the etiological factors should be eliminated. In conservative treatment, regaining lost weight, changing head position, and nasal irrigation with saline may be recommended. Surgical treatment options can be applied to symptomatic patients (1, 3, 4).

The presented case is a very rare condition. In cases with PET, craniocervical vascular structures, especially ICAs, should be evaluated radiologically in terms of possible variational conditions and accompanying pathologies. This evaluation will guide the surgeon before interventional invasive procedures in this region.

Informed Consent: An informed consent form was signed by the patient for the publication of this case.

Authorship Contributions

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

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

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

Main Points

- Patulous Eustachian tube (PET) is a physical disorder in which the normally closed ET remains open intermittently.
- Internal carotid artery anomalies accompanied by ET anomalies have been described very rarely in the literature.
- In cases with PETs, craniocervical vascular structures should be evaluated radiologically in terms of possible variational conditions and accompanying pathologies.

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