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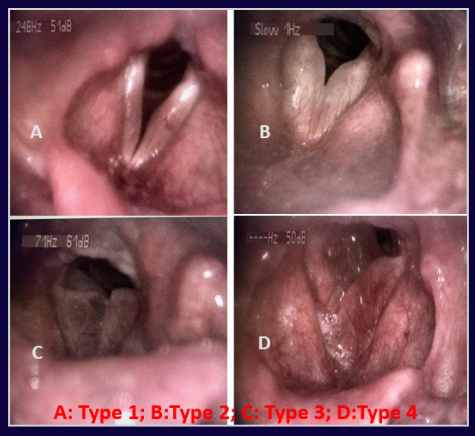

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Original Investigations

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Contents

Effects of Body Positioning on Laryngeal Penetration and Aspiration in Children with Unilateral Vocal Cord Paralysis

Original Investigation

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Abstract

Objective: To evaluate laryngeal penetration and aspiration in upright and side-lying positions in children with unilateral vocal cord paralysis (VCP) who underwent modified barium swallow study (MBSS).

Methods: A retrospective chart review (Pro00089051) of pediatric patients who were diagnosed with unilateral VCP and underwent MBSS was performed. Patients were identified using diagnostic code for VCP and based on diagnosis via flexible laryngoscopy. Once identified, MBSS notes were reviewed for data regarding laryngeal penetration, tracheal aspiration, and body position during the exam. Information was collected on the various consistencies of liquids used. The order of positioning was recorded in patients who had undergone both positions during the study. Data was analyzed using chi-square analysis.

Results: 811 patients had undergone MBSS between 2011 and 2014. Of these, 90 patients were isolated with unilateral VCP, and of those 90 patients, 23 (26%) had undergone MBSS in both side-lying and upright positions. When all 90 patients were evaluated, there was no difference in penetration or aspiration noted in the side-lying or upright position with thin liquids. Importantly, among the 23 (26%) patients that had been studied in both positions, there were no significant differences in penetration or aspiration relating to body position with any consistency.

Conclusion: Rates of penetration and aspiration were not associated with body position in patients who had undergone MBSS at our institution. However, due to an incomplete data set and a small sample size of those who underwent MBSS in both positions, these results should be further explored in prospective studies.

Keywords: Vocal cord paralysis, children, aspiration, feeding, body position, modified barium swallow study

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Introduction

Vocal cord paralysis (VCP) is the second most common laryngeal anomaly in children and accounts for 10–20% of laryngeal disorders (1). Unilateral VCP has many underlying causes, often resulting from damage to the recurrent laryngeal nerve, with particularly high rates of unilateral VCP noted in children undergoing intervention for congenital heart disease due to the proximity of the recurrent laryngeal nerve to the aortic arch (2, 3). Other potential sources of VCP in children include viral infections, neoplasms, cardiac outflow tract disease, and idiopathic etiologies (3-5).

Swallowing is a complex motor skill that is largely driven by branches of the vagus nerve. During swallowing, respiration ceases and the airway closes at three levels: approximation of the true vocal cords to close the glottis, adduction of the false vocal cords and movement of the arytenoids superiorly and anteriorly to meet the base of the epiglottis, and close the laryngeal vestibule. These various levels of closure each serve to protect the airway during swallowing by preventing material from entering the airway (6). Without appropriate airway protection, swallowing can result in penetration (material enters the laryngeal vestibule but remains above the vocal folds) or aspiration (material enters the airway below the vocal folds) (7). Chronic tracheal aspiration is associated with several complications including recurrent pneumonia and lung injury (8, 9). In the setting of unilateral VCP, decreased laryngeal function places the patient at risk for reduced airway protection leading to aspiration (10-13). Recent studies have examined the effects of unilateral VCP on airway protection and swallowing in children. In 2019 Irace et al. (14) found that 16 of 28 children with VCP had silent aspiration in modified barium swallow study (MBSS), but any positional differences utilized during the examination were not reported. Additionally, in 2000, Heitmiller et al. (11) found the prevalence of aspiration in adults with unilateral VCP to be 18%.

Several studies have compared the effects of the elevated side-lying versus upright positions on variability in respiration and heart rate during bottle feeding in preterm infants. These studies had smaller sample sizes and demonstrated conflicting results on the benefits of the side-lying versus the upright positions. A systematic review examining the effects of positioning during bottle feeding in preterm infants determined that the evidence to define the role of positioning on physiological stability was still insufficient (15). Furthermore, these studies did not include infants with unilateral VCP or directly examine the effects of the elevated side-lying position versus the upright position on airway protection using measures such as the MBSS (16-18).

The reasoning for placing children with unilateral VCP in a side-lying position (functioning side down) is largely based on theory. The theory involves gravity helping to decrease aspiration by directing the flow of the liquid that enters the larynx down the side of the functioning cord as well as gravity helping passively adduct the non-functioning cord (19). Additionally, there is likely an element of improved coordination and slowed flow as evidenced by children taking fewer swallows per breath when placed in a side-lying position compared to an upright position (20).

One study by Hunt and Olney (21) in 2022 found that side-lying positioning "affects feeding success" in children with unilateral VCP, and stated that these children were more likely to be able to wean to oral feeding without thickening agents upon hospital discharge. However, there is no known study looking at the effects of positioning specifically on airway protection during swallowing in children with unilateral VCP.

The objective of our investigation was to evaluate laryngeal penetration and aspiration in upright and side-lying positions in children with unilateral VCP who underwent MBSS.

Methods

Ethical approval was obtained from the Office of Research Integrity at the Medical University of South Carolina Institutional Review Board for Human Research (Pro00089051, approval date: 10.10.2018).

Patient Selection

A retrospective review was performed on the charts of the children who had a diagnosis of VCP and underwent a MBSS at our institution. Patients were identified by diagnosis of VCP via laryngoscopy.

Data Collection

We conducted a retrospective chart review of MBSS performed on children less than 14 months of age to identify patients with a diagnosis of unilateral VCP. The data extracted included demographics, diagnosis, indications for MBSS, and comorbid conditions. MBSS data including penetration, aspiration, positioning, and liquid consistencies were collected. If a patient underwent multiple MBSS, only the first study was utilized for this review.

MBSS Procedures

MBSS examinations were conducted by trained speech language pathologists (SLPs) in conjunction with radiologists. Varibar® barium products of thin, nectar, or honey-thick liquids were administered as determined appropriate by the SLPs conducting the examination. Examinations were completed using continuous videofluoroscopy at 30 frames per second. Collimation protocols specify using the lips, hard/soft palate, posterior pharyngeal wall, and cervical esophagus as borders for the field of view. When available, the child's home bottle system was used to dispense the

barium. Dr. Brown's bottles and nipples were the most used bottle system if the child's bottle system was not sufficient. If the child refused to drink the barium, it may have been mixed with a preferred liquid to achieve cooperation. This was decided at the SLP's discretion and was not consistently documented in the MBSS report.

Statistical Analysis

All analyses were conducted using version 27.0 of SPSS (IBM Corporation, Armonk, NY) and GraphPad (GraphPad Software, San Diego, CA). Continuous variables were summarized by mean ± standard deviation/range or median and interquartile range (25–75th) where appropriate. All continuous variables were tested for normal distribution as determined by the Kolmogorov–Smirnov test. Categorical variables were summarized by frequency (N) and percentage (%). Comparisons between categorical variables were performed with a Fisher's or chi–square test. A p-value of <0.05 was considered statistically significant for all statistical tests.

Results

Of the 811 patients screened who underwent MBSS between 2011 and 2014, 90 were isolated with unilateral VCP. The median age of the patients was 5 months (range: 2 weeks–14 months). Forty eight (53%) patients were male, 42 (47%) were female. 93% (n=84) of patients' paralysis were left-sided, 7% (n=6) were right-sided (Table 1). 76% (n=68) of patients had cardiac comorbidities, 21% (n=19) had a history of prematurity, 17% (n=15) of patients had a diagnosis of GERD, 9% (n=8) of patients had neurological comorbidities, and 8% (n=7) were syndromic (Table 2). Of those 90 patients that were included, 23 (26%) underwent MBSS in both side-lying and upright positioning (Tables 3-7). Ninety

Table 1. Median age and sex of patients, and laterality of unilateral VCP as identified via flexible laryngoscopy

Patient characteristics	
Median age	5 months (range: 2 weeks–14 months)
Sex	48 male (53%), 42 female (47%)
Left-sided paralysis	84 of 90 (93%)
Right-sided paralysis	6 of 90 (7%)

VCP: Vocal cord paralysis

Table 2. Comorbid conditions identified among patients

Comorbidities	
Cardiac	68 of 90 (76%)
Prematurity	19 of 90 (21%)
Gastroesophageal reflux disease	15 of 90 (17%)
Neurological	8 of 90 (9%)
Syndromic	7 of 90 (8%)

Table 3. Comparison of laryngeal penetration and aspiration in upright (UR) and lateral decubitus/"side-lying" (LD) positioning in all patients with thin consistency. Penetration: p=0.2002, aspiration: p=0.1562

All patients Thin	**Penetration UR**	**Penetration LD**	**Aspiration UR**	**Aspiration LD**
Yes	74	22	58	19
No	16	1	32	4
Total	90	23	90	23

Table 4. Comparison of laryngeal penetration and aspiration in upright (UR) and lateral decubitus/"side-lying" (LD) positioning in the subset of patients that underwent the study in both positions with thin consistency. Penetration: p=0.6078, aspiration p=0.9999

Both positions Thin	**Penetration UR**	**Penetration LD**	**Aspiration UR**	**Aspiration LD**
Yes	20	22	18	19
No	3	1	5	4
Total	23	23	23	23

Table 5. Comparison of laryngeal penetration and aspiration in upright (UR) and lateral decubitus/"side-lying" (LD) positioning in all patients with nectar-thick consistency. Penetration: p=0.6960, aspiration: p=0.6008

All patients Nectar-thick	**Penetration UR**	**Penetration LD**	**Aspiration UR**	**Aspiration LD**
Yes	39	12	26	5
No	44	10	57	17
Total	83	22	83	22

Table 6. Comparison of laryngeal penetration and aspiration in upright (UR) and lateral decubitus/"side-lying" (LD) positioning in the subset of patients that underwent the study in both positions with nectar-thick consistency. Penetration: p=0.7507, aspiration p=0.326

Both positions Nectar-thick	**Penetration UR**	**Penetration LD**	**Aspiration UR**	**Aspiration LD**
Yes	14	12	9	5
No	7	9	12	16
Total	21	21	21	21

Table 7. Comparison of laryngeal penetration and aspiration in upright (UR) and lateral decubitus/"side-lying" (LD) positioning in all patients with honey-thick consistency. Penetration: p=0.222, aspiration: p=0.5304

All patients Honey-thick	**Penetration UR**	**Penetration LD**	**Aspiration UR**	**Aspiration LD**
Yes	4	2	3	1
No	12	1	13	2
Total	16	3	16	3

patients received the thin liquid consistency in total and 23 received thin liquid in both positions (Table 3). Eighty three patients received the nectar-thick liquid consistency in total and 21 received thin liquid in both positions (Table 5). Sixteen patients received the honey-thick liquid consistency in total (Table 7). For those receiving thin liquid, 90 were in the upright position, 23 in the lateral decubitus position, and 23 underwent the study in both positions (Tables 3, 4). For those receiving nectar-thick liquid, 83 were in the upright position, 22 in the lateral decubitus position, and 21 underwent the study in both positions (Tables 5, 6). For those receiving honey-thick liquid, 16 were in the upright position, three in the lateral decubitus position, and three underwent the study in both positions (Table 7). Among those who underwent the study in both positions, we found no significant difference in penetration or aspiration between body positions with any consistency (Tables 3-7).

Discussion

While commonly used in practice at our institution, there is a lack of significant scientific evidence supporting body positioning for airway protection in dysphagic infants with unilateral VCP, highlighting the need for further investigation.

While anecdotal and theoretical benefits to patient positioning in unilateral VCP have been noted, our pilot data, as seen in Tables 3-7, did not reveal a significant difference in airway protection between upright or side-lying positioning in this population. Limited by a small number of eligible MBSS, this data would suggest that further investigation of patient positioning is warranted.

The study has several limitations that primarily relate to the retrospective study design and the absence of a standardized protocol for evaluating laryngeal penetration and aspiration in upright and side-lying positioning in children with unilateral VCP who underwent MBSS. As a retrospective chart review, we are confined to the contents of the chart, as well as the quality and information included in the medical record which can result in a potential selection bias. MBSS in the infant population is often challenging, with difficulties noted with patient cooperation, ability to change positioning, and modification of liquid consistencies and flow rates. Additionally, patients were not randomized to starting position, meaning that fatigue could be a confounding factor, and we were unable to assess the order of positioning for all individuals in this study. Finally, MBSS relies on subjective interpretation of data collected during the study, which needs to be considered when interpreting this data.

It should also be noted that a large number of children in this study had cardiac comorbidities. This population is known to be at high risk for unilateral VCP following cardiothoracic procedures, with rates in the literature reported to be as high as 56% (22). At our institution, children undergoing cardiac procedures are routinely examined postoperatively to determine vocal cord mobility before oral feeding. This likely explains the high percentage of patients with cardiac comorbidities in our study. Given this highly complex patient population, it is reasonable to consider that other factors beyond vocal cord function may be playing a role in the airway protection of our sample.

Finally, this study is limited by the retrospective nature and inability to control for confounding factors associated with swallowing pathology during each MBSS. In the future, a prospective study designed to isolate changes in swallow with respect to positioning during the same bottle feed is needed. It has been demonstrated that swallowing physiology throughout feed changes in as little as 1.5 minutes in infants, therefore controlling for the variable of time is also important (23). Additionally, nipple flow rate control was not possible in our study. While our study was not able to address these issues, we believe this is important pilot data supporting the need for further analysis. This was the first study of its kind in children with unilateral VCP, so we did not have preliminary data from which to formulate highly specific a priori hypotheses or perform formal power analyses. As a result, we may have missed the associations due to a lack of statistical power (Type II errors) or identified spurious associations (Type I errors). Also, explanations of findings were limited by the survey level of data. Thus, our interpretations should not be considered conclusive, but rather hypothesis-generating for future investigations.

We believe this data could impact the way we educate patients' families on best feeding practices and impact how we perform MBSS, however, further prospective analyses are needed to draw these conclusions. Additionally, further research with stratification of specific populations would be of interest.

Conclusion

Rates of penetration and aspiration were not associated with body position in pediatric patients who underwent MBSS at our institution. However, due to an incomplete data set and small sample size of those who underwent MBSS in both positions, these results should be explored further prospectively.

Ethics Committee Approval: Ethical approval was obtained from the Office of Research Integrity at the Medical University of South Carolina Institutional Review Board for Human Research (Pro00089051, approval date: 10.10.2018).

Informed Consent: Informed consent was waived due to the retrospective nature of the investigation.

Authorship Contributions

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

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

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Main Points

- We do not identify a significant difference in laryngeal penetration or aspiration between upright and side-lying positioning on modified barium swallow study.
- Body positioning may not affect airway protection during feeds in this population.
- Further prospective analysis is needed to make strong conclusions.

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Optimizing Early Detection: Validating Obstructive Sleep Apnea-18 (OSA-18) in Turkish-Speaking Pediatric Patients

Original Investigation

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Abstract

Objective: Quality of life (QoL) assessments are increasingly important for evaluating the well-being of children with Obstructive Sleep Apnea Syndrome (OSAS). This study's objective is to culturally adapt and validate the Turkish version of the OSA-18 questionnaire, a commonly used tool for assessing QoL in children with OSAS.

Methods: The OSA-18 questionnaire was translated and culturally adapted for use in the Turkish-speaking population. The study was conducted with 180 participants, 100 boys and 80 girls, with a mean age of 6.16±2.14 years. The participants were divided into two groups. The patient group comprised individuals with symptoms of OSAS based on clinical evaluation, including anamnesis, physical examination, and video recording of apnea and snoring. The patient group underwent adenotonsillectomy and their caregivers completed the Turkish version of the OSA-18 scale postoperatively. The control group comprised 90 children who were similar to the patient group in terms of gender and age. These children had no major complaints such as snoring, apnea, fatigue during the day, irritability, or distraction. In the physical examination of this group, no major tonsillar or adenoid hypertrophy, which causes significant stenosis in the upper airway, was observed. Internal consistency, reliability, validity, responsiveness, and factor analysis were assessed.

Results: The Turkish version of the OSA-18 questionnaire demonstrated excellent reliability, with a Cronbach's alpha of 0.929. The test-retest results were not statistically different. Validity was confirmed through a positive correlation between the OSA-18 score and external parameters, such as the Mallampati score, and tonsil and adenoid size. We found a statistically significant reduction in OSA-18 scores postoperatively, signifying a robust responsiveness to the intervention.

Conclusion: Our study confirms the suitability of the Turkish OSA-18 questionnaire for assessing the QoL in children with OSAS. This quick and easy-to-use tool will be valuable for future research on Turkish-speaking children with OSAS, aiding in the evaluation of pediatric OSAS and QoL.

Keywords: Obstructive sleep apnea, children, quality of life, sleep-related breathing disorders, validation

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Introduction

Obstructive sleep apnea syndrome (OSAS) is the most critical clinical condition in the sleep-related breathing disorder spectrum. It is characterized by recurrent episodes of prolonged blockage of the upper airway during sleep, despite continued or increased respiratory effort, which leads to complete (apnea) or partial (hypopnea) cessation of airflow and disturbed sleep (1, 2). Studies have suggested that both habitual snoring and childhood OSAS are associated with behavioral problems, particularly impulsiveness, aggressiveness, and inattentive behaviors (3-9).

Quality of life (QoL) surveys are crucial for diagnosing and monitoring various diseases, including pediatric obstructive sleep apnea (OSA). Different assessment tools, such as the Obstructive Sleep Disorders-6 (OSD-6), Tonsil and Adenoid Health instrument, Pediatric Sleep Questionnaire (PSQ), and OSA-18, have been developed and validated to gauge the QoL in children with OSA. In a 2021 meta-analysis comparing various pediatric OSA questionnaires, 37 studies evaluating 20 different questionnaires met the criteria for qualitative analysis and none were considered to be of low quality. Among these reviewed articles, 13 studies assessed two specific questionnaires, the PSQ and the OSA-18, and both met the criteria for quantitative synthesis.

The findings revealed that the PSQ exhibited a higher sensitivity of 0.76 compared to the OSA-18 which showed a sensitivity of 0.56. Conversely, the OSA-18 demonstrated higher specificity with a value of 0.73, while the PSQ exhibited a specificity of 0.43. Notably, other questionnaires included in the analysis displayed lower sensitivities and specificities (10). Kang et al. (11) reported that the efficacy of the OSA-18 questionnaire varied across age groups. In toddlers, the questionnaire exhibited high accuracy (sensitivity: 78.6%, specificity: 85.7%). For preschoolers, robust sensitivity (78.8%) was accompanied by a trade-off in specificity (62.5%). In school-age children, the questionnaire performed exceptionally well, with a sensitivity of (81.0%) and perfect specificity (100%). Among adolescents, there was a moderate sensitivity (60%) while maintaining high specificity (100%). These findings emphasize the importance of tailoring screening methods based on age for effective detection of OSA in children (11).

The OSA-18, widely used in both research and clinical settings, is a reliable and quick survey applicable across various medical specialties (12-15). It provides insights into the impact of OSA on children's QoL, aiding physicians in assessing treatment outcomes in conjunction with other clinical parameters. The OSA-18 questionnaire was originally developed for an English-speaking population, and its use in non-English-speaking countries requires translation and validation in the target population's language (11, 13, 16-19). Currently, a validated Turkish version of the OSA-18 questionnaire is absent. Thus, the objectives of the present study revolve around the translation and subsequent validation of the OSA-18 questionnaire for its utilization among Turkish-speaking children. This initiative holds the potential to facilitate comprehensive assessments of the impact of OSAS on the QoL in this specific population.

Methods

Study Design

This prospective instrument validation study was conducted between June 2022 and March 2023 according to the ethical standards specified in the Helsinki Declaration of Good Clinical Practices. The study received approval from the Institutional Review Board of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-09-08, date: 09.05.2022), and informed consent was obtained from the caregivers of all participants, allowing for the processing of personal data and publication of study results.

Participants

The determination of the sample size or power calculation for psychometric validation of questionnaires lacks a widely accepted theoretical basis (20). As a result, in this study, we employed a general rule of thumb for sample size calculation. This rule suggests that the minimum recommended number of participants should be within the range of 5 to 10 times the number of questionnaire items (20, 21). In our presented research, we have chosen a sample size of 180 participants for a questionnaire with 18 items, complying with the minimum ratio of 10 to 1.

One hundred and one children were examined in the outpatient clinic from June 2022 onwards. Excluding five patients who did not meet the inclusion criteria, 96 participants were enrolled in the study and successfully completed the questionnaire during their initial visit. Of these, 90 children fully participated in both the initial questionnaire and the retest evaluation after two weeks, comprising the final sample. The control group comprised 90 healthy children, chosen to align with the patient group in terms of both quantity and gender. These individuals were free from any health issues and exhibited no symptoms. In the physical examination of this group, no cases of major tonsillar or adenoid hypertrophy were observed that could cause significant stenosis in the upper airway.

Inclusion and Exclusion Criteria

The participants, 100 boys and 80 girls aged between 3 and 15 years, were divided into two groups; the patient group comprised individuals with symptoms of OSAS based on clinical evaluation, including anamnesis, physical examination, and video recording of apnea and snoring and

were subsequently treated with surgical intervention for tonsil and adenoid hypertrophy. The control group included 90 children who were similar to the patient group in terms of gender and age. These children had no major complaints such as snoring, apnea, fatigue during the day, irritability, or distraction. The participants were also examined for tonsillar and adenoid hypertrophy which causes significant stenosis in the upper airway.

The exclusion criteria for the study were as follows: prior surgery on the head and neck region, any central nervous system disease, congenital malformations related to the head and neck region, presence of syndromic disease, and the inability of the caregiver to read and understand Turkish. These criteria were established to ensure the sample population was free of any conditions that could potentially interfere with the study's objectives and results.

Adaptation and Translation Into Turkish

The original authors of OSA-18 were conducted via e-mail, and their permission to use the questionnaire in this research was obtained. OSA-18 consists of five domains: sleep disturbance, physical symptoms, emotional symptoms, daytime function, and caregiver concerns. Respondents are asked to rate each item on a scale of one to seven, with one indicating "never" and seven indicating "always." The minimum possible score is 18, while the maximum is 126. The OSA-18 questionnaire is easy to administer and suitable for use in various clinical and research settings (12-15).

In designing the study's methodology, our primary focus was to ensure the validity and the cultural relevance of the Turkish adaptation of the OSA-18 questionnaire. Securing official approval from the original authors underscored our commitment to maintaining the questionnaire's integrity. Two proficient bilingual Turkish physicians meticulously translated the questionnaire, leveraging their linguistic dexterity to ensure accuracy. A consolidation process followed, addressing any disparities in the Turkish translation through collaborative discussions with the research team. A rigorous back-translation, performed by a native English speaker, guaranteed linguistic and conceptual equivalence. Discrepancies were scrutinized and resolved by an independent expert, ensuring the adapted questionnaire's accuracy and cultural suitability. These meticulous procedures resulted in a final OSA-18 Turkish adaptation that attests to its precision and cultural relevance. This adapted questionnaire is poised to significantly contribute to understanding and assessing QoL in Turkish-speaking children with OSAS, enhancing research and clinical care in the Turkish context (Appendix).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 25.0 software (IBM SPSS Statistics for Windows; Armonk, NY: IBM Corp). Demographic and clinical data, including age, gender, Friedman tongue position and Mallampati classification, degree of tonsillar hypertrophy, and adenoid hypertrophy assessment, were reviewed in the analysis. The normality of the variables was assessed using histogram graphics and the Kolmogorov-Smirnov test. Descriptive analyses were presented using mean, standard deviation, median, and minimum-maximum values. Categorical variables were compared using Pearson's chi–square test, Fisher's exact test, and Mann–Whitney U test for non-normally distributed variables. An independent t-test was used to compare normally distributed variables between the two groups. Repeated measures analysis was performed to evaluate the change in the scale score between groups, while the dependent t-test was used to evaluate the change within the group. Spearman's correlation test was utilized to analyze the measurement data. Statistical significance was set at p-value <0.05.

Validity and Reliability for the OSA-18 Scale

A total of 180 individuals completed the OSA-18 questionnaire. Exploratory factor analysis was conducted to determine the factor structure of the 18-item measurement tool. The analysis resulted in grouping all 18 items of the scale under a single factor. To confirm the factor structure, confirmatory factor analysis (CFA) was conducted. In addition, Cronbach's alpha coefficient was calculated to assess the reliability of the scale and its subdimensions.

Results

The study included a total of 180 participants, 100 boys and 80 girls, with a mean age of 6.16±2.14 years (range: 3–15 years). The mean age of the patient group was 6.11±1.9 years, while that of the control group was 6.21±2.35 years. No significant differences were observed between the patient and control groups in terms of gender (p=0.764), age (p=0.878), or comorbidities (p=0.081). In the patient group, three out of 90 had asthma. There were no comorbid diseases in the children in the control group. There were 10 and seven underweight, 53 and 65 normal weight, 16 and 13 overweight, and 11 and five obese patients in the patient and control groups, respectively. After applying the chi-square test, we found that there was a significant association between weight and OSA (χ^2= 33.87, df: 3, p<0.0001).

Our study found a significant difference between the patient and control groups in terms of OSA-18 scores, with patients having higher scores than the controls (Table 1).

We evaluated the internal consistency of the Turkish translation of the OSA-18 scale, which measures how well the scores of individual items in the instrument correlate with each other (22). We used Cronbach's alpha to analyze

internal consistency, which was found to be 0.929, indicating excellent reliability for the overall questionnaire and each domain (Table 1). The exclusion of any item or domain did not significantly affect the overall score (Table 2).

Test-retest reliability is a crucial metric for assessing the consistency of calculated scores with repeated testing, which can be accomplished by examining the correlation between initial test scores and subsequent retest scores. In the presented study, we randomly enrolled 36 children from both the OSAS and the control groups. Using Wilcoxon correlations, we analyzed test-retest reliability and found that the total OSA-18 score was significantly reliable (p=0.0155; R=0.759). The test and retest evaluations were conducted with an average two weeks apart. We assessed the validity of the OSA-18 scale by examining the correlation between the OSA-18 scores and external parameters such as the Mallampati score, tonsil size, and adenoid size. Spearman's rank correlation analysis revealed a positive correlation between the OSA-18 score and Friedman Mallampati score, tonsils and adenoid grade in the patient group (Tables 3, 4).

The Kaiser–Meyer–Olkin test yielded a value above 0.7, indicating good sample adequacy (0.912) in terms of inter-item relationships. Since the significance value of the Bartlett sphericity test was below 0.001 (χ^2=1901.050), the matrix with inter-item relations was different from the unit matrix without relations. Therefore, the assumptions were met in terms of scale. In addition, when the relationships between the items were examined, the number of items with an acceptable relationship (r>0.30) was quite high, and multicollinearity between the items (items with r>0.8) was not observed.

CFA was conducted to examine whether the factor structure of the OSA-18 scale was confirmed in the current sample. Several fit indices were used to assess the adequacy of the model. The results of the CFA for the one-dimensional factor structure of the scale revealed a ratio of chi–square

Table 1. Demographic data and OSA-18 scores (each item and total) according to groups

	Patient (n=90)		Control (n=90)		Total (n=180)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p-value
Age	6.11±1.9	6 (3–15)	6.21±2.35	6 (3–15)	6.16±2.13	6 (3–15)	0.878
Gender (boy-%)	41 (45.56%)		39 (43.33%)		80 (44.44%)		
Gender (girl-%)	49 (54.44%)		51 (56.67%)		100 (55.56%)		0.764
OSA-18 scores items							
Snoring	5.81±1.4	6 (1–7)	2.74±1.78	2 (1–7)	4.28±2.22	4 (1–7)	**<0.001**
Breath holding	3.94±1.93	4 (1–7)	1.53±1.09	1 (1–6)	2.74±1.98	2 (1–7)	**<0.001**
Choking/gasping	3.34±1.93	3 (1–7)	1.36±0.75	1 (1–4)	2.35±1.77	1 (1–7)	**<0.001**
Fragmented sleep	4.14±1.97	4 (1–7)	1.98±1.36	1 (1–7)	3.06±2.01	3 (1–7)	**<0.001**
Mouth breathing	5.97±1.28	6 (1–7)	3.32±1.98	3 (1–7)	4.64±2.12	5 (1–7)	**<0.001**
URTI/colds	4.88±1.82	5 (1–7)	3.18±1.8	3 (1–7)	4.03±2	4 (1–7)	**<0.001**
Nasal discharge	4.8±1.83	5 (1–7)	3.08±1.7	3 (1–7)	3.94±1.96	4 (1–7)	**<0.001**
Dysphagia	4.21±1.99	4 (1–7)	1.77±1.32	1 (1–6)	2.99±2.08	2 (1–7)	**<0.001**
Temper tantrums	3.33±1.93	3 (1–7)	1.74±1.43	1 (1–7)	2.54±1.87	2 (1–7)	**<0.001**
Aggressiveness	4.06±2.02	4 (1–7)	1.99±1.45	1 (1–7)	3.02±2.04	2 (1–7)	**<0.001**
Discipline problems	3.26±1.93	3 (1–7)	1.7±1.18	1 (1–7)	2.48±1.77	2 (1–7)	**<0.001**
Excessive daytime drowsiness	2.81±1.77	2 (1–7)	1.44±0.78	1 (1–4)	2.13±1.52	1 (1–7)	**<0.001**
Attention deficit	3.99±2.01	4 (1–7)	1.44±0.84	1 (1–4)	2.72±2	2 (1–7)	**<0.001**
Difficulty waking up	3.36±2.18	3 (1–7)	1.72±1.17	1 (1–5)	2.54±1.93	2 (1–7)	**<0.001**
Caregiver worried about child's health	4.83±1.82	5 (1–7)	2.12±1.44	2 (1–6)	3.48±2.13	3 (1–7)	**<0.001**
Caregiver worried about the child does not get enough air	5±1.96	6 (1–7)	1.77±1.37	1 (1–7)	3.38±2.34	3 (1–7)	**<0.001**
Caregiver missed activities	3.2±1.94	3 (1–7)	1.62±1.18	1 (1–6)	2.41±1.78	1 (1–7)	**<0.001**
Caregiver frustration	2.67±1.92	2 (1–7)	1.53±1.15	1 (1–6)	2.1±1.68	1 (1–7)	**<0.001**
OSA-18 (total)	73.6±16.26	73 (39–120)	36.04±12.87	33 (18–72)	54.82±23.84	54 (18–120)	**<0.001**

OSA-18: Obstructive Sleep Apnea-18, SD: Standard deviation, min-max: Minimum-maximum, URTI: Upper respiratory tract infection

Table 2. Internal consistency analysis of OSA-18 scores items

OSA-18 scores items	Cronbach's alpha if item is deleted*	OSA-18 scores items	Cronbach's alpha if item is deleted*
Snoring	0.924	Aggressiveness	0.926
Breath holding	0.924	Discipline problems	0.928
Choking/gasping	0.924	Excessive daytime drowsiness	0.927
Fragmented sleep	0.924	Attention deficit	0.924
Mouth breathing	0.924	Difficulty waking up	0.927
URTI/colds	0.928	Caregiver worried about child's health	0.923
Nasal discharge	0.928	Caregiver worried about the child does not get enough air	0.921
Dysphagia	0.926	Caregiver missed activities	0.925
Temper tantrums	0.927	Caregiver frustration	0.928

*Cronbach's alpha for 18 items is 0.929

OSA-18: Obstructive Sleep Apnea-18, URTI: Upper respiratory tract infection

Table 3. The positive correlation between the total OSA-18 score and the Friedman–Mallampati score, tonsils and adenoid grade in the patient group

		Mallampati score	Tonsil grade	Adenoid grade
OSA-18	r	0.668	0.747	0.575
	p	<0.001	<0.001	<0.001

OSA-18: Obstructive Sleep Apnea-18

Table 4. Table indicates the mean OSA-18 score according to tonsil and adenoid grades

		OSA-18 score
Grade 1	Tonsil	41.15
	Mallampati	56.6
Grade 2	Tonsil	58.07
	Mallampati	70.8
Grade 3	Tonsil	76.34
	Mallampati	87.2
Grade 4	Tonsil	92.87
	Mallampati	96.16

OSA-18: Obstructive Sleep Apnea-18

statistics to degrees of freedom (χ^2/df) of 4.372 (χ^2=590.2; df=135; p=0.000), a root mean square error of approximation of 0.137, and a comparative fit index of 0.750. These findings indicate that the one-dimensional factor structure of the scale provided adequate fit values.

To assess the responsiveness of the questionnaire, we utilized the Wilcoxon test to compare OSA-18 scores before and after adenotonsillectomy in a cohort of pediatric patients. In the control group, comprising individuals without symptoms of OSAS, the mean OSA-18 score was 36.04. Among the patient group, which consisted of ninety individuals, adenotonsillectomy procedures were performed, and their caregivers completed the Turkish version of the OSA-18 questionnaire within a period of 1–3 months following the procedure. Remarkably, the OSA-18 scores exhibited a statistically significant reduction postoperatively (T1) compared to preoperative levels (T0), signifying robust responsiveness to the intervention. The mean OSA-18 score at T1 was 33.9±10.2, while the mean OSA-18 score at T0 was 73.53±15.88 (p<0.001).

Discussion

Our study intended to adapt and validate the OSA-18 score in the Turkish context. The study encompassed a diverse group of 180 participants, including both genders, and spanning an age range from 3 to 15 years. This comprehensive sample size aligns with the recommended guidelines for questionnaire validation studies (20, 21). The distribution of the participants into patient and control groups allowed for a robust evaluation of the adapted questionnaire's performance. The validation process involved rigorous analysis of various aspects, such as internal consistency, reliability, validity, and responsiveness.

The Turkish version of the OSA-18 questionnaire exhibited excellent internal consistency, with a Cronbach's alpha coefficient of 0.929. This signifies strong inter-item correlations, indicating that the adapted questionnaire consistently measures the construct it intends to assess. Our results are consistent with earlier findings in the literature. The Chinese version showed a range of Cronbach alpha values, ranging from 0.62 to 0.84. The Portuguese version

had a Cronbach's alpha of 0.82, the Spanish version scored 0.91, the Greek version 0.94, and the Italian version 0.93 (13, 16-18, 20).

Validation of the adapted questionnaire involved examining its correlation with external parameters related to OSAS symptoms. Positive correlations between the OSA-18 score and parameters such as the Mallampati score, and tonsil and adenoid size confirmed its validity, as similar to the literature (11, 13, 17). These correlations underline the questionnaire's ability to capture relevant aspects of OSAS symptoms and their impact on patients' lives.

The responsiveness of the adapted questionnaire was evaluated in a cohort of pediatric patients who underwent adenotonsillectomy. Notably, the statistically significant reduction in OSA-18 scores postoperatively highlights the tool's sensitivity to changes resulting from therapeutic interventions. In the Italian version of the questionnaire, a marked reduction in the mean OSA-18 score from 76.36 to 26.89 was observed, reaffirming its responsiveness to the surgical intervention. In our study using the Turkish version, we similarly found a substantial reduction in the mean OSA-18 score from 73.53 to 33.9 postoperatively, demonstrating the questionnaire's effectiveness in detecting treatment-related improvements (19). This outcome indicates that the adapted OSA-18 questionnaire can effectively reflect improvements in QoL following surgical procedures for OSAS.

In our study, we found that physical symptoms (items 5–8) were rated as the most severe domain, followed by sleep disturbances (items 1–4). Interestingly, in children from the United States and Portugal, sleep disturbances were identified as the primary concern based on the existing literature, with physical symptoms ranking second (12-14). In contrast, in our research, daytime function (items 12–14) and emotional distress (items 9–11) were rated as the least severe domains, which aligns with previous research findings (11-14).

The primary drawback of our study is the absence of polysomnography (PSG) as a diagnostic tool. PSG is the gold standard for diagnosing OSAS, but it is expensive, time-consuming, and has limitations in predicting the risk of adverse outcomes or response to treatment (13). In our study, the diagnosis of pediatric OSAS was made on a clinical basis. As an alternative to PSG, the use of tonsil and adenoid grade and the Friedman–Mallampati score have been proposed. Since parent-reported surveys to assess childhood OSAS depend on caretakers' observation ability, these surveys are inherently limited. Parent responses may not fully capture the child's subjective experience, potentially introducing bias in the data. It is important to recognize these when interpreting our findings and consider future research to address these issues.

QoL surveys have become increasingly important in the diagnosis and follow-up of various diseases. Various assessment tools, including both general and disease-specific questionnaires, have been employed to evaluate QoL in children diagnosed with OSA. Disease-specific instruments, such as the OSD-6 survey, the Tonsil and Adenoid Health instrument, the PSQ, and the OSA-18, have been specifically developed and validated for assessing QoL in pediatric OSAS. These instruments are utilized to measure the impact of OSAS on QoL and to evaluate treatment outcomes. Among these instruments, the OSA-18 is most commonly utilized in both research and clinical settings, which was developed for the English-speaking population. The OSA-18 is a reliable and valid survey that is quick and easy to administer (12-15).

The OSA-18 survey can be used by physicians of various specialties, not only otolaryngologists, to assess the neurobehavioral statements and problems of children affected by OSAS. This survey allows physicians to better understand the impact of OSAS on the QoL of affected children and their caregivers when combined with other clinical parameters.

Conclusion

Our study validates the Turkish version of the OSA-18 questionnaire as a reliable, valid, and responsive tool for assessing QoL in children with OSAS. This adapted questionnaire holds promise for facilitating further research on OSAS in the Turkish-speaking population, aiding in the comprehensive evaluation of pediatric OSAS and its impact on QoL. As the field of sleep medicine continues to advance, the adapted OSA-18 questionnaire will contribute to enhanced understanding and improved care for children with OSAS in Turkey.

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Ethics Committee Approval: The study received approval from the Institutional Review Board of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2022-09-08, date: 09.05.2022).

Informed Consent: Informed consent was obtained from the caregivers of all participants, allowing for the processing of personal data and publication of study results.

Authorship Contributions

Surgical and Medical Practices: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Concept: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Design: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Data Collection and/or Processing: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Analysis and/or Interpretation: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Literature Search: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S., Writing: Z.M.Y., F.B.B., B.K.İ., M.A.A., İ.S.

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Main Points

- The study aimed to culturally adapt and validate the Turkish version of the Obstructive Sleep Apnea-18 (OSA) questionnaire to assess the quality of life (QoL) in Turkish-speaking children with obstructive sleep apnea syndrome (OSAS), an important aspect of pediatric health.
- The Turkish adaptation of the OSA-18 questionnaire demonstrated excellent reliability and validity, with a Cronbach's alpha coefficient of 0.929, and it was found to be responsive to changes following adenotonsillectomy, making it a valuable tool for assessing OSAS impact and treatment outcomes in Turkish-speaking children.
- The primary domains affected by OSAS in Turkish-speaking children, as indicated by OSA-18 scores, were physical symptoms and sleep disturbances, while daytime function and emotional distress were rated as the least severe.
- The Turkish version of the OSA-18 questionnaire holds promise for enhancing research on OSAS in Turkey, contributing to a better understanding of its impact on pediatric QoL and improving care for affected children.

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Appendix. Turkish Version of the OSA-18

	Hiçbir Zaman	Çok Nadiren	Nadiren	Bazen	Genellikle	Çoğu Zaman	Her Zaman
Uyku Sorunları							
Geçtiğimiz 4 hafta içerisinde çocuğunuz/çocuğunuzun ne sıklıkla…							
1) Sesli horladı?	1	2	3	4	5	6	7
2) Gece nefes tutma atağı veya solunum duraksaması yaşadı?	1	2	3	4	5	6	7
3) Uyurken boğulma veya nefes nefese kalma sesi çıkardı?	1	2	3	4	5	6	7
4) Dinlendirmeyen uykusu veya sık uyanması oldu?	1	2	3	4	5	6	7
Fiziksel Belirtiler							
Geçtiğimiz 4 hafta içerisinde çocuğunuz/çocuğunuzun ne sıklıkla…							
5) Burun tıkanıklığı nedeniyle ağızdan nefes aldı?	1	2	3	4	5	6	7
6) Nezle veya üst solunum yolu enfeksiyonu geçirdi?	1	2	3	4	5	6	7
7) Burun akıntısı oldu?	1	2	3	4	5	6	7
8) Yutmada zorluk yaşadı?	1	2	3	4	5	6	7
Duygusal Belirtiler							
Geçtiğimiz 4 hafta içerisinde çocuğunuz/çocuğunuzun ne sıklıkla…							
9) Ruh hali değişiklikleri veya öfke krizi oldu?	1	2	3	4	5	6	7
10) Agresif veya hiperaktif davranışları oldu?	1	2	3	4	5	6	7
11) Disiplin problemi oldu?	1	2	3	4	5	6	7
Günlük İşlev							
Geçtiğimiz 4 hafta içerisinde çocuğunuz/çocuğunuzun ne sıklıkla…							
12) Gündüz aşırı uyku hali oldu?	1	2	3	4	5	6	7
13) Dikkatini vermede veya konsantre olmada zorluk yaşadı?	1	2	3	4	5	6	7
14) Sabah uyanmada zorluk yaşadı?	1	2	3	4	5	6	7
Aile/Bakım Veren Kaygıları							
Geçtiğimiz 4 hafta içerisinde yukarıdaki problemler ne sıklıkla…							
15) Çocuğunuzun genel sağlığı hakkında sizi endişelendirdi?	1	2	3	4	5	6	7
16) Çocuğunuzun yeterli nefes alamadığını düşündürüp sizi endişelendirdi?	1	2	3	4	5	6	7
17) Günlük işlerinizi yapmanıza engel oldu?	1	2	3	4	5	6	7
18) Sizi hüsrana uğrattı?	1	2	3	4	5	6	7
İsim Soyisim:		Puan:					
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Predictors and Time Interval of Chronic Rhinosinusitis Recurrence After Endoscopic Sinus Surgery

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Abstract

Objective: Chronic rhinosinusitis (CRS) is a common inflammatory disease that significantly impacts the quality of life. Endoscopic sinus surgery (ESS) is indicated for refractory CRS. This study aims to estimate the predictors of CRS recurrence, and the rates with time intervals of recurrent CRS and revision ESS.

Methods: A retrospective cohort study included 516 patients who underwent ESS for CRS at King Abdulaziz Medical City in Riyadh between January 2017 and May 2020. Patients were followed up for 12–48 months postoperatively. The study sample was divided into two groups based on the recurrence status and compared using the appropriate statistical tests. Significant variables were included in the logistic regression model to determine the predictors of CRS recurrence.

Results: The recurrence rate of CRS following ESS was 14.5%, with a time interval of 28.31 months, and standard deviation (SD) =18.76. On the other hand, the rate of revision ESS for recurrent CRS was 6.8%, with a time interval of 34.18 months, SD =16. In the multivariable logistic regression model, the significant predictors of recurrent CRS were a high Lund–Mackay (LM) score [odds ratio (OR): 1.055, p=0.04] and a high eosinophil count (OR: 3.619, p=0.03). Almost half of the patients who developed recurrent CRS underwent revision surgery (46.7%).

Conclusion: CRS has a considerable recurrence rate despite the high success rate of ESS, and nearly half of the recurrent CRS patients need revision surgery. A high LM score and eosinophilic count significantly increase the likelihood of CRS recurrence.

Keywords: Sinusitis, chronic disease, recurrence, endoscopic surgical procedure, surgical revision, multivariate analysis

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Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the lining mucosa of the nasal cavity and paranasal sinuses. It is classified based on the presence of nasal polyps through nasal endoscopy into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) (1, 2). It is also classified based on inflammatory patterns into two endotypes: type 2 and non-type 2 immune responses. The type 2 immune response involves eosinophils, IgE, and upregulation of type 2 cytokines, constituting most of CRSwNP. On the other hand, non-type 2 CRS is primarily considered a type 1 to type 3 immune response and is characterized by neutrophilic inflammation in the nasal mucosa (3). The treatment goals in patients with CRS are directed to improve patients' symptoms and quality of life. Currently, the standard appropriate medical therapy (AMT) consists of saline nasal irrigation and intranasal corticosteroids with a short course of oral corticosteroids (1). Endoscopic sinus surgery (ESS) is considered once AMT is unsuccessful and the patient is symptomatic (4).

ESS involves adequately enlarging the natural paranasal sinus drainage pathways via the surgical removal of the diseased mucosa and the bony partitions. This leads to the improvement of CRS symptoms by reducing the amount of sinonasal mucosal disease and facilitating the delivery of postoperative topical medications. It has a high success rate ranging from 75% to 95% in improving patients' symptoms and overall quality of life (1, 5). However, almost 9–34% of patients will develop recurrent disease, and 9–27% will undergo revision ESS (6-14). Multiple factors were documented in the literature to increase the rates of recurrence and revision surgery. These include patient-related factors [e.g., atopy, aspirin-exacerbated respiratory distress (AERD), immunodeficiency], disease-related factors (e.g., presence of polyps, presence of fungal mucin, eosinophil count, and extent of disease), and treatment-related factors (surgical technique, postoperative care, postoperative adhesions) (8, 10, 11, 15, 16).

Published studies on the rate and predictors of recurrent CRS and revision ESS showed variable results and are limited in Saudi Arabia. Therefore, this study aims to estimate the rate, predictors, and time interval of CRS recurrence post-ESS.

Methods

Study Design and Subjects

A retrospective cohort study was conducted at King Abdulaziz Medical City in Riyadh, Saudi Arabia. All adult patients (aged 18 years or older) who underwent ESS for the treatment of primary CRS between January 2017 and May 2020 were included in the study. Patients who underwent ESS for secondary CRS (i.e., fungal ball, neoplasm, odontogenic infection, or selective immunodeficiency) were excluded from the study.

Data Collection

The patients' electronic records were reviewed using the hospital's healthcare information system. The data collection flowsheet included patients' demographics, CRS-related conditions, immunodeficiency (i.e., uncontrolled diabetes, chemotherapy, acquired immunodeficiency syndrome, or post-transplant), CRS-related features (e.g., extent of disease, phenotype, preoperative laboratory tests, and imaging), and postoperative management with follow-up. Serum eosinophil count was considered low if the value was <50 per mm^3, normal if between 50–500 per mm^3, and high if >500 per mm^3. Lund-Mackay (LM) score was created based on computed tomography scan and categorized as low if the value was <15 and high if the value was ≥15. The patients were followed up for 12–48 months postoperatively at three-month intervals to detect the rates of recurrence and revision surgery. The disease was considered recurrent if the patient fulfilled the criteria of CRS, according to EPOS 2020, after a period without symptoms. Revision surgery was considered for recurrent CRS as a last resort after the failure of AMT for at least three months (17).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS®) version 25. The categorical variables were presented as frequencies and proportions, while the numerical variables were reported as means and standard deviations. The study sample was divided into two groups based on the recurrence status. The groups were compared using the chi–square test and the independent t-test for categorical and continuous variables, respectively. The variables were included in a multivariable logistic regression model to determine the predictors of CRS recurrence. A p-value of <0.05 was declared as statistically significant.

Ethics and Permissions

The institutional review board (IRB) of King Abdullah International Medical Research Center approved the study (study no: NRC21R/471/10, date: 22.11.2021).

Results

The study included 516 patients who underwent ESS for primary CRS. The mean age of our patients was 37.32 (±13.07) years, and male gender was the dominant gender (59.5%). Out of all patients with primary CRS, most patients (76.9%) were diagnosed with CRSwNP. CRS was unilateral in 28 (5.8%) patients; none were due to odontogenic infections, fungal infections, or neoplasms. Immunodeficiency disease and asthma were found in 11.2% and 8.3%, respectively. The recurrence rate of CRS post-ESS was 14.5%, while the revision surgery rate was 6.8% (Table 1).

The comparison between recurrent CRS and non-recurrent CRS groups is summarized in (Table 2). The recurrent CRS group has significantly higher rates of CRSwNP and lower rates of CRSsNP than the non-recurrent CRS group (p=0.001). The recurrent CRS group has higher rates of asthma and asthma and AERD with a significant p-value (<0.05 level). Moreover, high eosinophil count and LM score were significantly associated with CRS recurrence with a p-value of 0.006 and 0.002, respectively.

In the multivariable logistic regression model, the only significant predictors of recurrent CRS were high LM scores and high eosinophil counts (Table 3). An elevated eosinophil count increased the probability of CRS recurrence by 3.62 times [odds ratio (OR): 3.62, p=0.03]. Moreover, a high LM score was significantly associated with high CRS recurrence (OR: 1.055, p=0.04).

Table 4 demonstrates a sub-analysis of patients with recurrent CRS. The mean time intervals between primary ESS and recurrent CRS and between primary ESS and revision ESS were 28.31 (±18.76) and 34.18 (±16.82) months, respectively. Nearly half of the patients with recurrent CRS (46.7%) underwent revision ESS, and most patients with recurrent CRS had a lower LM score than their primary disease score.

Table 1. Clinical characteristics of the study sample

Variables	Full cohort (n=516)
Age (mean ± SD)	37.32 (±13.07)
Gender (n%)	
Male	307 (59.5%)
Female	209 (40.5%)
BMI (mean ± SD)	28.41 (±5.74)
Rhinosinusitis (n%)	
CRSsNP	119 (23.1%)
CRSwNP	397 (76.9%)
Immunodeficiency diseases (n%)	58 (11.2%)
Allergic rhinitis (n%)	55 (10.7%)
AERD (n%)	12 (2.3%)
Asthma (n%)	43 (8.3%)
Eosinophil count (n%)	
High	25 (4.8%)
Normal	353 (68.4%)
Low	58 (11.2%)
Extent of disease (n%)	
Unilateral	28 (5.4%)
Bilateral	488 (94.6%)
LM score (mean ± SD)	14.13 (±6.59)
Recurrence (n%)	75 (14.5%)
Revision surgery (n%)	35 (6.8%)

SD: Standard deviation, BMI: Body mass index, CRSsNP: Chronic rhinosinusitis without nasal polyps, CRSwNP: Chronic rhinosinusitis with nasal polyps, AERD: Aspirin-exacerbated respiratory distress, LM: Lund-Mackay

Discussion

The presented study investigated the rate and predictors of CRS recurrence and revision ESS. In our study, the most common diagnosis was CRSwNP (76.9%), which was expected as most nasal polyps tend to regrow despite AMT and eventually require surgical intervention (18). Our findings revealed an overall recurrence rate of 14.5%, consistent with the published literature, and a revision rate of 6.8% (6-14). The revision ESS rate reported in our study is low compared to the published literature, and only 46%

Table 2. Clinical characteristics of recurrent versus non-recurrent CRS

Variables	Recurrent CRS (n=75)	Non-recurrent CRS (n=441)	p-value
Age (mean ± SD)	35.65 (±12.78)	37.61 (±13.11)	0.232
Gender (n%)			
Male	40 (53.3%)	267 (60.5%)	0.240
Female	35 (46.7%)	174 (39.5%)	
Rhinosinusitis (n%)			
CRSsNP	8 (10.7%)	111 (25.2%)	0.006*
CRSwNP	67 (89.3%)	330 (74.8%)	
Smoking (n%)	9 (12%)	85 (19.3%)	0.131
Immunodeficiency (n%)	8 (10.7%)	50 (11.3%)	0.865
Allergic rhinitis (n%)	10 (13.3%)	45 (10.2%)	0.417
Asthma (n%)	13 (17.3%)	30 (6.8%)	0.002*
AERD (n%)	6 (8.0%)	6 (1.4%)	0.000*
Eosinophil count (n%)			
High	9 (14.5%)	16 (4.3%)	0.006*
Normal	46 (74.2%)	307 (82.1%)	
Low	7 (11.3%)	51 (13.6%)	
Extent of disease (n%)			
Unilateral	1 (1.3%)	27 (6.1%)	0.091
Bilateral	74 (98.7%)	414 (93.9%)	
LM score (mean ± SD)	16.29 (±6.00)	13.76 (±6.62)	0.002*

*Significant at p<0.05 level.

CRS: Chronic rhinosinusitis, SD: Standard deviation, CRSsNP: Chronic rhinosinusitis without nasal polyps, CRSwNP: Chronic rhinosinusitis with nasal polyps, AERD: Aspirin-exacerbated respiratory distress, LM: Lund-Mackay

Table 3. Predictors of CRS recurrence in logistic regression analysis

Variable	Odd ratio	p-value	95% LCI	95% UCI
LM score	1.055	0.040*	1.003	1.111
Eosinophil count	3.619	0.037*	1.080	12.128

*Significant at p<0.05 level.

CRS: Chronic rhinosinusitis, UCI: Upper confidence interval, LCI: Lower confidence interval, LM: Lund-Mackay

Table 4. Sub-analysis of patients with recurrent CRS

Variables	Recurrent CRS (n=75)
Time interval between primary ESS and recurrence (mean ± SD)	28.31 (±18.76)
LM score compared to primary disease (n%)	
Higher score	23 (30.7%)
Same score	18 (24.0%)
Lower score	34 (45.3%)
Management (n%)	
Revision surgery	35 (46.7%)
Medical treatment	33 (44.0%)
Patient refused revision surgery	7 (9.3%)
Time interval between primary ESS and revision ESS (mean ± SD)	34.18 (±16.82)

CRS: Chronic rhinosinusitis, SD: Standard deviation, ESS: Endoscopic sinus surgery, LM: Lund-Mackay

of the patients with recurrent disease underwent revision surgery. The lower revision rate may be due to social reasons, as 9.3% of patients with recurrent CRS refused revision surgery. Moreover, the presented study showed that most patients with recurrent CRS had a lower LM score than their primary disease score. This finding might also justify the low revision rate, as most patients had milder recurrent CRS than their primary disease. The mean durations between primary ESS and recurrence and between primary ESS and revision ESS were 28.31 and 34.3 months, respectively. This finding highlights the importance of regular follow-up of CRS patients for at least 28 months postoperatively for early detection of the recurrent disease.

Several studies investigated the recurrence of CRS post-ESS, aiming to identify the prognostic factors that play a role in the recurrence process (9, 13, 19). The presented study identified eosinophil count and LM score as predictors of CRS recurrence. It has been shown that prominent eosinophil infiltration plays a massive role in CRS development and tissue eosinophilia is seen in most CRS cases with or without polyps (20, 21). A study done in 2008 in Tokyo showed a similar association between eosinophil count and CRS recurrence (19). Moreover, the presented study showed that a high LM score increases the probability of recurrence threefold. Similarly, De Corso et al. (22) found that a high LM score (>12) was associated with a lower disease control at 12 months of follow-up, leading to an increased recurrence rate. A higher LM score typically indicates a more extensive disease with a higher degree of sinus opacification, which explains the higher recurrence rate. A higher LM score is also associated with the presence of nasal polyps; Tan et al. (23) showed that patients with CRSwNP had a higher presenting LM score than patients with CRSsNP. Our findings of high recurrence rate in patients with high blood eosinophilia and high LM score are explained by the type 2 immune response in these patients, as it tends to be extensive with a high recurrence rate that usually needs revision surgeries.

The need for revision of ESS can be of particular concern in patients with CRSwNP. CRSwNP has been shown to have a high regrowth rate, probably due to the nasal polyp interference with mucociliary clearance in addition to its mechanical obstruction (8, 10, 12). Stein et al. (11) conducted a large retrospective cohort study that involved over 61,000 patients and concluded that the diagnosis of CRSwNP is a positive predictor of the need for revision surgery. Furthermore, multiple studies have supported the same positive correlation between the presence of nasal polyps and the need for revision ESS (24, 25). Some patients may need more than one revision surgery, which increases the risks of intraoperative and postoperative complications (26). Therefore, multiple biological agents (e.g., dupilumab, mepolizumab, and omalizumab) are now approved and recommended for recurrent CRSwNP. The introduction of these biological agents might improve the outcome of CRSwNP and decrease the need for revision ESS in patients with type 2 CRS, thus avoiding the risk of intraoperative complications (3). On the contrary, several studies showed a revision rate ranging between 11% to 27% in both CRSsNP and CRSwNP groups with no significant difference between both groups (7, 12, 14). In our study, the recurrent CRS group had a higher rate of CRSwNP than the non-recurrent group. However, this finding was not significant in the multivariate analysis.

AERD were documented frequently in the literature as risk factors for CRS recurrence (2, 11, 25). This association is thought to be due to the shared pathophysiology of asthma and CRSwNP, as both conditions have the same type 2 immune response (2). Sella et al. (25) identified asthma as the only factor that affected the recurrence of CRS in both patients with CRSsNP and CRSwNP. Moreover, Mendelsohn et al. (8) found that patients with AERD have a higher risk of CRSwNP recurrence post-ESS compared to other prognostic factors, such as asthma and the presence of fungal mucin. However, our study showed no association between asthma and AERD with the recurrence of CRS in the multivariate analysis.

The presented study has some limitations, including its retrospective design and being conducted in one tertiary healthcare center, which may affect the generalizability of the study. However, the strengths of our study include the sample size and the long follow-up duration.

Conclusion

CRSwNP has a considerable recurrence rate despite the high success rate of ESS, and nearly half of the recurrent CRS cases need revision surgery. In this study, a high LM score and eosinophil count significantly increased the likelihood

of CRSwNP recurrence. We recommend prolonged regular follow-ups of CRSwNP patients postoperatively for early detection of recurrence.

Ethics Committee Approval: The institutional review board (IRB) of King Abdullah International Medical Research Center approved the study (study no: NRC21R/471/10, date: 22.11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.K.A., B.A., S.A., J.A., R.A., Concept: A.K.A., B.A., S.A., J.A., R.A., Design: A.K.A., B.A., S.A., J.A., R.A., Data Collection and/or Processing: A.K.A., B.A., S.A., J.A., Analysis and/or Interpretation: A.K.A., B.A., S.A., J.A., R.A., Literature Search: A.K.A., B.A., S.A., J.A., R.A., Writing: A.K.A., B.A., S.A., J.A., R.A.

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Main Points

• This study aimed to estimate the rate, predictors, and time interval of chronic rhinosinusitis (CRS) recurrence post-endoscopic sinus surgery.

• 516 patients were included in this study, 75 patients developed recurrent CRS and nearly half of this group needed revision surgery.

• This study showed that CRS has a considerable recurrence rate and that two predictors significantly increase the likelihood of CRS recurrence; namely, high Lund Mackay score and eosinophilic count.

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Impact of the Severity of Reinke's Edema on the Parameters of Voice

Original Investigation

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Abstract

Objective: This study aimed to classify the degree of edema in patients with Reinke's edema (RE) and examine its impact on their voice parameters using both objective and subjective assessment methods.

Methods: Objective and subjective voice data of 104 patients diagnosed with RE between 2018 and 2021 were evaluated retrospectively. RE is classified into 4 groups (types 1, 2, 3, and 4). The evaluation included videolaryngostroboscopic examination, acoustic voice analysis, and aerodynamic measurements, GRBAS, Voice Handicap Index-10 (VHI-10), Voice-Related Quality of Life Scale (V-RQOL), and Reflux Septum Index (RSI).

Results: Patients with type 1 RE had a significantly lower mean age than those with types 3–4. Although there were no significant differences in acoustic and aerodynamic parameters between the groups, it was observed that F0 and the maximum phonation time decreased as the degree of edema increased. The $GRBAS_{Total}$, G, and R scores of types 1 and 2 were significantly lower than those of types 3 and 4, as were the scores of type 1 S. There were no statistically significant differences between the RE groups in terms of VHI-10, V-RQOL, and RSI scores.

Conclusion: It has been observed that as the severity of RE increases, voice perception and quality (especially types 3 and 4) are negatively affected. Determining the degree of edema will guide the clinician in both the planning of the intervention phase and the follow-up phase.

Keywords: Larynx, dysphonia, vocal fold, Reinke's edema, classification, voice quality, laryngology

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Introduction

Reinke's edema (RE) is a common and benign laryngeal condition resulting in polypoid degeneration due to edema, vascular congestion, and venous stasis in Reinke's space (1). Its prevalence in the general population was found to be 0.347% (2). Although women are more

likely to have RE, some studies show that men are more likely to have it (2, 3).

RE can occur in one or both vocal folds (4). It is hypothesized that RE is caused by chronic inflammation, which affects the permeability of the capillary wall and causes fluid to seep into Reinke's cavity. The cover layer of the vocal fold becomes edematous and less stiff due to these changes (5). Chronic inflammation of the larynx can develop secondary to many conditions, such as smoking, phonotrauma, and gastroesophageal reflux (6). In the management of RE, smoking cessation, anti-reflux medication, and voice therapy are recommended to help reduce the edema; however, patients whose voice quality does not improve with these therapies need surgery. To ensure improved voice rehabilitation after surgery, it is essential to continue voice therapy and anti-reflux treatment for a long period and avoid smoking (7).

There are several RE classifications in the literature (1, 4, 8). Yonekawa (8) made the first clinical classification based on the morphological features of the vocal fold and classified it into types 1, 2, and 3. Another classification was made by Tan et al. (1) as grades 1, 2, 3, and 4 according to the size of the lesion. Different degrees of dysphonia are seen in patients with RE. It has also been noted that patients could develop dyspnea depending on the extent of the edema and the airway obstruction (7). The most typical symptoms in these patients are thickening of the voice, vocal fatigue, a reduced vocal range, and the inability to produce high-pitched voices. During a phone call, the voices of female patients, in particular, can be perceived as masculine. One study showed that the voices of female patients with type 1 RE were more easily distinguishable from those with types 2 and 3 in terms of gender identification (9). Lim et al. (10) reported that acoustic analysis parameters such as jitter, shimmer, and harmonic-to-noise ratio did not differ between patients with RE types 1, 2, and 3. Even though the maximum phonation time (MPT) of patients with type 3 RE was not statistically significantly different from the other types, MPT was found to be shorter. Yonekawa (8) looked at the auditory-perceptual relationship between the voice and the degree of RE and reported that the degree of hoarseness in patients with type 3 RE was more severe than in types 1 and 2. Patients with vocal fold lesions (leukoplakia, cysts, polyps, and RE) had high GRBAS and Voice Handicap Index-10 (VHI-10) scores in the preoperative auditory-perceptual evaluation of voice (11). There is no information in the literature about auditory-perceptual changes based on the classification of RE.

The purpose of this study was to examine the impact of the severity of RE on voice quality using objective and subjective evaluation methods. Our study questions were:

- Does the severity of RE change with age?

- Are there differences in acoustic and aerodynamic voice parameters based on RE classification?

- Which parameters are more effective in the auditory-perceptual evaluation according to the RE classification?

- Is there a difference between reflux symptom findings and the severity of RE?

Methods

The study was conducted with approval from the Ministry of Health, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 110/06, date: 03.05.2021), and all subjects gave their informed consent. We conducted a retrospective study of patients who presented to the University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Voice Clinic between 2018 and 2021 with a complaint of dysphonia and were diagnosed with RE as a result of the evaluation.

The RE patients included in our study were classified according to the classification made by Tan et al. (1): minimal polypoid degeneration of the vocal fold up to 25% of the glottic airway was grade 1; enlarged polypoid lesions occupying 25% to 50% of the glottic airway was grade 2; enlarged polypoid lesions of 50% to 75% of the glottic airway was grade 3; and obstructive lesions occupying more than 75% of the glottic airway, regardless of laterality, was grade 4 (Figure 1).

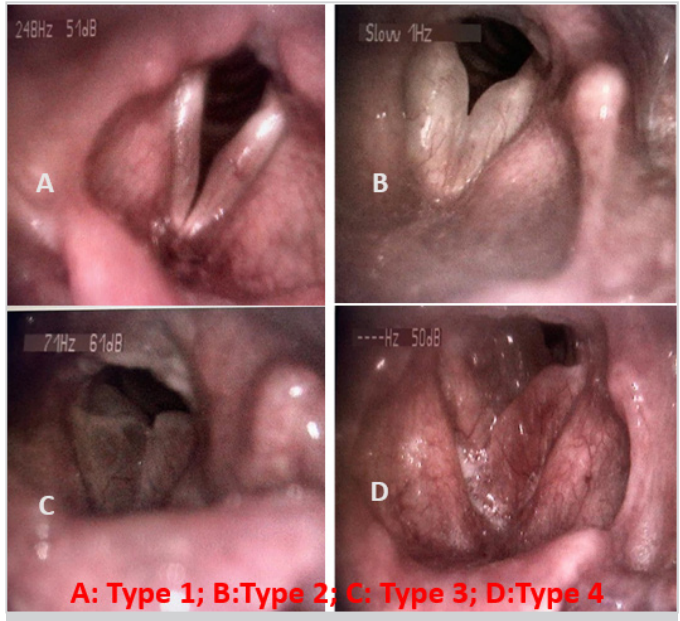

Figure 1. Classification of Reinke edema

Inclusion criteria for patients in the study were: a) being diagnosed with RE type 1, 2, 3, or 4; b) being between the ages of 18 and 65 years; c) the absence of a neurogenic disorder that would cause a voice disorder; d) not having undergone neck or laryngeal surgery. Our study included 104 patients who met these inclusion criteria.

Evaluation

Demographic data of all patients, such as age, gender, and smoking status recorded in the medical charts, and their objective/subjective voice parameters in the videolaryngoscopy, voice, and questionnaire records were retrieved and reviewed.

Videolaryngoscopic examination: All patients had undergone a videolaryngoscopic (XION; Berlin, Germany) examination with a rigid endoscope. Patients were asked to produce the vowel "i" with constant pitch and intensity throughout the assessment. The laryngologists who are the authors of this paper classified RE (types 1, 2, 3, and 4) according to the retrospective videolaryngostroboscopy record evaluation.

Acoustic voice analysis measurements: Acoustic analysis was conducted in a quiet room using a Computerized Speech Lab (CSL Model 4500-Kay Elementrics, Lincoln Park, N-LC, New Jersey) device and a Shure brand (Shure SM48-LC) microphone (12). The "Multi-Dimensional Voice Program" in the CSL device was used for acoustic voice measurement. A long /a/ vowel was recorded in a comfortable tone by adjusting the distance between the patient's mouth and the microphone to 10 cm and an angle of 45 degrees. The middle 3 seconds of the recording in the phonation range were analyzed (13). For this study, numbers were used to record the RE patients' fundamental frequency (F0), noise-to-harmonic ratio (NHR), jitter (%), shimmer (%), voice turbulence index (VTI), and soft phonation index (SPI).

Aerodynamic measurements: The s/z ratio and MPT durations of the RE patients were taken from the records. It gives an objective assessment of the respiratory mechanism's effectiveness during phonation (14). The s/z ratio expresses the ratio of the maximum phonation of the /s/ sound to the maximum phonation of the /z/ sound. While this ratio is approximately 1.00 in individuals with healthy vocal folds, it is over 1.4 in individuals with glottic closure defects (15). Both measurements were calculated using a stopwatch.

The subjective evaluations of the dysphonia patients, clinicians (GRBAS), and patient self-assessment tools [VHI-10, Voice-Related Quality of Life Scale (V-RQOL)] were used for the auditory-perceptual assessment.

GRBAS is a five-dimensional scale used to assess voice quality. These are defined as Grade (G), Roughness (R), Breathiness (B), Asthenia (A), and Strain (S) (16). All patients' GRBAS assessments were conducted by a 10-year-veteran speech-language pathologist who is an expert in the area. The patients were asked to read a passage and produce the vowel "a" in a relaxed tone. Each parameter was scored on a 4-point scale between 0 and 3.

VHI-10 is a scale on which the patient evaluates his or her voice in terms of physical, functional, and emotional aspects. There are 30- and 10-item versions of the scale (17, 18). The short version of VHI-10 was administered in our clinic. Each item was scored between 0 and 4.

V-RQOL has ten items divided into two subscales: physical functioning (6 items) and social-emotional (6 items). The overall score obtained from both subscales indicates the voice-related quality of life (19).

Reflux symptom index (RSI) is a 9-item self-assessment questionnaire to assess laryngopharyngeal reflux symptoms. An RSI score of more than 13 indicates laryngopharyngeal reflux (20).

Statistical Analysis

Statistical analysis was performed with the IBM SPSS 26.0 package program (Armonk, NY: IBM Corp.) The numerical variables were shown as mean, standard deviation, and percentage (frequency). In the normality test, data with skewness and kurtosis coefficients in the range of +2.0 and -2.0 were accepted as not exhibiting a substantial divergence from the normal distribution (21). Normally distributed data were analyzed using independent-sample t-tests and ANOVA, while non-normally distributed data were analyzed using the Kruskal–Wallis and Mann–Whitney U tests. In addition, post-hoc analyses were performed using Tukey to investigate notable disparities among the different groups. A significance threshold of 0.05 was established.

Results

There were 29 patients in the type 2 group and 25 patients in each of the types 1, 3, and 4. Of the 104 patients, 18.3% were male (n=19), and 81.7% were female (n=85). When we looked at the smoking status of the patients, 88.5% (n=92) were smokers, and only 11.5% (n=12) were not smokers. Non-smoking patients had a history of previous smoking.

The mean age of all patients was 49.096±9.324 years (minimum: 19–maximum: 65). Mean age was 45.080±12.158 years in the type 1 group; 46.896±8.393 in the type 2 group; 52.600±7.041 in the type 3 group; and 52.160±6.950 in the type 4 group. A substantial difference was found between the RE groups in terms of mean age scores (p=0.005) (Table 1).

When the mean ages of the RE groups were compared, the type 1 group was substantially younger than the type 3 (p=0.021) and type 4 (p=0.035) groups (Table 2).

In acoustic voice analysis, no statistically significant difference was found between the groups in terms of F0, jitter, shimmer, NHR, VTI, and SPI parameters (p=0.238; p=0.840; p=0.248; p=0.127; p=0.202; p=0.259, respectively). However, the acoustic voice analysis results by gender showed significant differences in the F0 scores (p=0.000). Accordingly, the F0 scores (mean =119.600 Hz) of the male patients were significantly lower than those of the female patients (mean = 158.619 Hz). The comparison of RE groups and gender in terms of acoustic voice analysis findings is shown in Table 3.

Aerodynamic analysis showed no statistically significant differences between the RE groups in terms of MPT and s/z ratios (p=0.094; p=0.466) (Table 4).

There was a statistically significant difference between the RE groups concerning G, R, S, and $GRBAS_{Total}$ (p=0.000 for all). The average $GRBAS_{Total}$, G, and R scores for types 1 and 2 were lower than those for types 3 and 4, as was type 1's average S score. There were no statistically significant differences between the RE groups in terms of patients' VHI-10, V-RQOL, and RSI scores (p=0.192; p=0.178; p=0.164, respectively) (Table 5).

Discussion

RE develops from chronic and widespread swelling of the superficial lamina propria of the vocal fold (22, 23). It is defined as polypoid degeneration of the vocal folds. RE is usually bilateral. However, sometimes it can be more prominent on one side (22). The etiologic factors of RE include smoking, vocal abuse, and other factors often closely associated with laryngopharyngeal reflux (4, 22, 24). In our study, a majority of the patients had a history of smoking in their etiology (88.5%), and 81.7% were female. In addition, the scores obtained from the RSI were considerably higher than the cut-off point (RSI >13) (20). These findings of our study are consistent with the literature.

In one study of 69 patients with RE, the mean age was 55.9 years; in another study, the mean age of 38 patients was found to be 50 years (34–64 years old) (1, 8). In our study, the mean age of 104 patients was 49 years. According to the classification of RE, the mean age of the type 1 group was younger than the type 3–4 group. This finding indicates that the degree of RE increases with age. Moreover, the increase in edema may depend on many etiological factors, such as smoking and severe reflux symptoms.

Table 1. Distribution of mean age according to RE groups

Groups	N	Age			F	p-value
		Mean	SD	Min–max		
Type 1	25	45.0800	12.15840	20–64		
Type 2	29	46.8966	8.39364	19–60		
Type 3	25	52.6000	7.04154	38–62	4.596[a]	**0.005**
Type 4	25	52.1600	6.95030	33–65		
Total	104	49.0962	9.32428	19–65		

RE: Reinke's edema, [a]ANOVA test, F: The ratio of the between-group mean squares to the within-group mean square, Min: Minimum, Max: Maximum, SD: Standard deviation. Results in bold represent statistically significant values with p-value <0.05

Table 2. Comparison of mean age findings by RE groups

RE group (I)	RE group (J)	Mean difference (I–J)	SE	p-value
Type 1	Type 2	-1.81655	2.42110	1.000
	Type 3	-7.52000	2.50917	**0.021**
	Type 4	-7.08000	2.50917	**0.035**
Type 2	Type 1	1.81655	2.42110	1.000
	Type 3	-5.70345	2.42110	0.123
	Type 4	-5.26345	2.42110	0.192
Type 3	Type 1	7.52000	2.50917	**0.021**
	Type 2	5.70345	2.42110	0.123
	Type 4	0.44000	2.50917	1.000
Type 4	Type 1	7.08000	2.50917	**0.035**
	Type 2	5.26345	2.42110	0.192
	Type 3	-0.44000	2.50917	1.000

RE: Reinke's edema, SE: Standard error, Tukey post-hoc analysis. Results in bold represent statistically significant values with p-value <0.05

RE is generally known to have a low F0 (10). Yonekawa (8) indicated that as type 2 or type 3 progressed, in other words, as the severity of the edema increased, the F0 decreased significantly in both genders. Colizza et al. (25) found that the mean F0 in males and females with RE was 101.06 Hz and 147.58 Hz, while it was 131.58 and 224.35 Hz, respectively, in healthy males and females. This study also reported that the jitter (2.254% and 3.733%), shimmer (9.037% and 11.172%), and NHR (0.235 and 0.278) values of males and females with RE were significantly higher than the healthy group. A related study found that acoustic parameters like harmonic-to-noise ratio, shimmer, and jitter did not differ between the types of RE. However, these parameters were significantly different in individuals with healthy vocal folds

Table 3. Comparison of acoustic voice analysis findings by RE groups and gender

Parameter Group/gender (n)		Mean ± SD	Mean rank	Test values	p-value
F0	Type 1 (n=25)	163.922±49.8		1.431[a]	0.238
	Type 2 (n=29)	155.174±42.0			
	Type 3 (n=25)	147.135±49.5			
	Type 4 (n=25)	139.143±35.9			
	Male (n=19)	119.600±33.7		3.686[b]	**0.000**
	Female (n=85)	158.619±44.0			
Jitter	Type 1 (n=25)	2.350±1.45	49.04	0.840[c]	0.840
	Type 2 (n=29)	2.731±1.84	53.72		
	Type 3 (n=25)	3.320±4.99	50.80		
	Type 4 (n=25)	3.624±4.16	56.24		
	Male (n=19)	2.649±1.9	50.37	-0.341[d]	0.733
	Female (n=85)	3.073±3.6	52.98		
Shimmer	Type 1 (n=25)	6.752±3.09	43.56	4.128[c]	0.248
	Type 2 (n=29)	7.864±3.63	54.16		
	Type 3 (n=25)	8.006±4.42	51.40		
	Type 4 (n=25)	9.400±5.00	60.62		
	Male (n=19)	8.808±4.6	57.74	-0.837[d]	0.403
	Female (n=85)	7.819±4.0	51.33		
NHR	Type 1 (n=25)	0.175±0.08	40.44	5.701[c]	0.127
	Type 2 (n=29)	0.204±0.07	56.07		
	Type 3 (n=25)	0.214±0.12	53.64		
	Type 4 (n=25)	0.259±0.15	59.28		
	Male (n=19)	0.211±0.11	50.39	-0.337[d]	0.736
	Female (n=85)	0.213±0.11	52.97		
VTI	Type 1 (n=25)	0.081±0.04	46.84	4.616[c]	0.202
	Type 2 (n=29)	0.080±0.04	46.27		
	Type 3 (n=25)	0.093±0.05	55.14		
	Type 4 (n=25)	0.118±0.09	60.44		
	Male (n=19)	0.121±0.08	62.13	-1.540[d]	0.124
	Female (n=85)	0.086±0.05	50.35		
SPI	Type 1 (n=25)	11.740±5.10	50.76	4.020[c]	0.259
	Type 2 (n=29)	14.416±7.76	59.11		
	Type 3 (n=25)	13.428±7.86	54.04		
	Type 4 (n=25)	9.966±4.83	43.24		
	Male (n=19)	11.643±6.2	48.58	-0.627[d]	0.531
	Female (n=85)	12.649±6.8	53.38		

RE: Reinke's edema, F0: Fundamental frequency, NHR: Noise-to-harmonic ratio, VTI: Voice Turbulence Index, SPI: Soft Phonation Index, [a]ANOVA test, [b]Independent-Samples T, [c]Kruskal–Wallis, [d]Mann–Whitney U test, SD: Standard deviation. Results in bold represent statistically significant values with p-value <0.05

(10). Our study showed that the F0 average of male and female patients was low, and jitter (2.649% and 3.073%), shimmer (8.808% and 7.819%), and NHR (0.211 and 0.213) values of male and female patients were close to the study findings in the literature. In addition, F0, frequency, and amplitude perturbation measurements (jitter and shimmer parameters), NHR, and SPI parameters were not statistically significant among the RE subtypes. However, as the severity of RE increased (especially in types 3 and 4), F0 decreased numerically. Although the changes in all acoustic parameters are not statistically significant between the RE groups, deviations from normal values in these parameters indicate that the presence of edema causes deterioration in the patient's voice quality. The other parameter we evaluated in acoustic analysis is SPI, which is a parameter that indicates whether the vocal folds are fully closed during phonation. A high output of this parameter is thought to indicate insufficient closure of the vocal folds during phonation (26). In our study, especially in the group with type 4 edema, SPI findings were lower than in the other groups. Due to the obstruction of more than 75% of the glottic airway in this group due to polypoid degeneration, it appears that there is no problem in closing the vocal folds during phonation.

In one study, it was reported that as the degree of RE increased, the average flow rate increased and the MPT decreased (8). Salmen et al. (27) compared MPT before and after surgery in 60 patients with RE. Whereas the mean MPT was 9±5 seconds before surgery, it increased by 2±5 seconds after surgery. In our study, there was no significant difference in MPT between the groups, but patients with types 3 and 4 edema had lower MPT than the other groups. As reported in the literature, in our study, too, we found that MPT had decreased when the degree of edema rose. Similarly, there is no significant difference between the groups in s/z ratios.

Via the auditory-perceptual assessment of a patient with complaints of voice impairment, the clinician reaches a subjective opinion about the severity of the overall impairment, the appropriateness of pitch and volume levels, and the quality of the voice. In the measurements made by the patient, it is important to obtain information about how the patient perceives the communication problems caused by pain, fatigue, and voice problems that cannot be directly observed by others (28). Taşar et al. (29) evaluated the vocal performances of 21 RE patients before and after surgery and found that their vocal performances had improved after surgery. In another study, researchers found that those with various vocal lesions (RE, cyst, or polyp) had a preoperative GRBAS score of 9.50±2.34 and a VHI-10 score of 18.19 (11). The information available in the literature on the effect of auditory-perceptual and voice-related quality of life according to the degree of RE is insufficient.

In our study, the G, R, S, and $GRBAS_{Total}$ scores of the group with types 1 and 2 edema were statistically significantly lower than the type 3 and 4 groups. This shows that as the degree of RE increases, so does the general severity, roughness, and tension of the voice disorder. In addition, no significant differences were found between the groups in how patients perceived their voices and the effect of their voices on quality of life. However, both VHI and V-RQOL scores were high in all patients. This indicates that the presence of edema was sufficient to negatively impact the auditory perception and voice-related quality of life of the patients. Therefore, knowing the degree of edema will guide the clinician both in planning the intervention phase and in the follow-up phase with the patients. We believe that a surgical decision is more appropriate, especially in cases where the voice quality is severely deteriorated (especially in types 3–4).

Damage to the vocal fold mucosa from laryngopharyngeal reflux makes the mucosa more sensitive to injury, which leads to the formation of benign vocal fold lesions such as RE, nodules, and polyps. It is also reported that the prevalence of laryngopharyngeal reflux symptoms is high in patients with RE (30). In another study, it was found that the RSI scores of patients with RE in the groups with and without pharyngitis were 23.05 and 22.65, respectively (24). In our study, RSI scores did not differ significantly between the

Table 4. Comparison of aerodynamic analysis findings by RE groups

Parameter	Groups (n)	Mean rank	Kruskal–Wallis–H	p-value
MPT	Type 1 (n=25)	56.66	6.402	0.094
	Type 2 (n=29)	61.74		
	Type 3 (n=25)	46.32		
	Type 4 (n=25)	43.80		
s/z rate	Type 1 (n=25)	49.66	2.553	0.466
	Type 2 (n=29)	48.41		
	Type 3 (n=25)	52.06		
	Type 4 (n=25)	60.52		

RE: Reinke's edema, MPT: Maximum phonation time, Kruskal–Wallis test. Result, p≤0.05, H: Kruskal–Wallis statistical values. Results in bold represent statistically significant values with p-value <0.05

groups. However, it is also reported that the RSI scores of every group were higher than the cut-off value (cut-off point: RSI >13) (20).

The treatment of RE involves a comprehensive approach that integrates surgical intervention with voice therapy (3). The intervention aims to ameliorate dysphonia symptoms with a primary focus on eliminating the underlying etiological factors. The primary strategy in its treatment is the elimination of all potential risk factors that could contribute to the condition. Surgery is indicated in cases where voice quality is severely affected and protective methods do not provide

Table 5. Auditory-perceptual analysis findings evaluated by clinician and patients

Parameter	Groups (n)	Mean	SD	F	p-value	Post-hoc
G	Type 1 (n=25)	1.5600	0.76811	13.988[a]	**0.000**	Type 1 < Type 3–4 Type 2 < Type 3–4
	Type 2 (n=29)	1.7586	0.63556			
	Type 3 (n=25)	2.3600	0.63770			
	Type 4 (n=25)	2.5600	0.50662			
R	Type 1 (n=25)	1.2000	0.81650	12.391[a]	**0.000**	Type 1 < Type 3–4 Type 2 < Type 3–4
	Type 2 (n=29)	1.4483	0.78314			
	Type 3 (n=25)	2.1200	0.78102			
	Type 4 (n=25)	2.3600	0.75719			
B	Type 1 (n=25)	0.5200	0.65320	0.615[a]	0.607	
	Type 2 (n=29)	0.4828	0.50855			
	Type 3 (n=25)	0.6000	0.50000			
	Type 4 (n=25)	0.6800	0.62716			
S	Type 1 (n=25)	0.4800	0.77028	7.067[a]	**0.000**	Type 1 < Type 3–4
	Type 2 (n=29)	0.8621	0.87522			
	Type 3 (n=25)	1.1200	0.60000			
	Type 4 (n=25)	1.4000	0.64550			
$GRBAS_{Total}$	Type 1 (n=25)	3.7600	2.29637	15.491[a]	**0.000**	Type 1 < Type 3–4 Type 2 < Type 3–4
	Type 2 (n=29)	4.5517	1.93808			
	Type 3 (n=25)	6.2800	1.72047			
	Type 4 (n=25)	6.9600	1.61967			
VHI-10	Type 1 (n=25)	19.0400	8.87168	1.609[a]	0.192	
	Type 2 (n=29)	19.1724	10.03234			
	Type 3 (n=25)	20.2400	9.13911			
	Type 4 (n=25)	24.2400	10.60770			
V-RQOL	Type 1 (n=25)	22.240	6.8086	1.673[a]	0.178	
	Type 2 (n=29)	23.793	9.4278			
	Type 3 (n=25)	24.440	10.5478			
	Type 4 (n=25)	27.800	9.0921			
RSI	Type 1 (n=25)	15.8800	12.12889	1.739[a]	0.164	
	Type 2 (n=29)	17.0690	12.52407			
	Type 3 (n=25)	18.0400	13.21766			
	Type 4 (n=25)	23.2000	11.17288			
Parameter	**Groups (n)**	**Mean rank**	**df**	**Kruskal–Wallis–H**	**p-value**	**Post-hoc**
A	Type 1 (n=25)	52.00	3	3.160[b]	0.368	
	Type 2 (n=29)	52.00				
	Type 3 (n=25)	54.00				
	Type 4 (n=25)	52.00				

G: Grade; R: Roughness, B: Breathiness, A: Asthenia, S: Strain, VHI-10: Voice Handicap Index-10, V-RQOL: Voice-Related Quality of Life Scale, RSI: Reflux Symptom Index, [a]ANOVA Ttest, F: The ratio of the between-group mean squares to the within-group mean square, [b]Kruskal–Wallis, H: Kruskal–Wallis statistical values, SD: Standard deviation. Results in bold represent statistically significant values with p-value <0.05

improvement in dysphonia (5). Voice therapy and smoking cessation play an important role in the long-term treatment results of RE after surgery (3). In our study, we found that as RE increases, voice perception and quality are negatively affected. We can say that the classification of Reinke's edema is especially important in terms of planning the appropriate treatment approaches. Moreover, it is thought that knowing the effects on voice quality according to the severity of the edema will play an important role in providing accurate and reliable information for research in this field.

Our study had several limitations. Firstly, the retrospective nature of the study was a disadvantage. Secondly, there was insufficient data regarding the duration of smoking (years) and the number of daily cigarettes smoked by the patients. The other limitation was the inequality of the numbers of male and female participants in RE subgroups.

Conclusion

The severity of edema was found to increase with age, according to our study. It is worth noting that as the severity of Reinke's edema increases, F0 and the MPT decrease. In the perceptual evaluation of the clinician, the voice perception of patients with types 3 and 4 RE is more likely to be negatively affected. Therefore, knowing the degree of RE will guide the clinician in both the intervention phase and the follow-up phase of patients. It is further thought that knowing the deterioration of voice quality according to the severity of edema will play an important role in providing accurate and reliable information to clinicians working in this field, both in clinical practices and research.

Ethics Committee Approval: The study was conducted with approval from the Ministry of Health, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (decision no: 110/06, date: 03.05.2021).

Informed Consent: All subjects gave their informed consent.

Authorship Contributions

Concept: E.B., E.A., E.Ç.T., Design: E.B., E.A., M.H.K., Data Collection and/or Processing: E.B., E.A., Z.Y., M.H.K., E.Ç.T., Analysis and/or Interpretation: E.B., E.A., Z.Y., M.H.K., E.Ç.T., Literature Search: E.B., Z.Y., Writing: E.B., Z.Y., E.Ç.T.

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Main Points

- We found that the severity of edema increased with age.
- As edema increased in the clinician's auditory perceptual evaluation, voice quality and perception were negatively affected.
- Knowing the type of Reinke's edema will guide the clinician both during the intervention phase and during the follow-up phase of patients.
- F0 and MPT decreased proportionally to edema severity.

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Optimizing Surgical Management of Acute Invasive Fungal Sinusitis

Original Investigation

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Abstract

Objective: Early surgical debridement is vital for favorable outcomes in acute invasive fungal sinusitis (AIFS). Our study aimed to propose guidelines with tailored, conservative surgical procedures based on areas of involvement and evaluate their usefulness in avoiding repeated debridement.

Methods: This retrospective observational study was conducted on 150 AIFS patients operated on with the proposed surgical guidelines from May to June 2021 at a tertiary care hospital. Data including demography, comorbidities, surgical procedures, revision surgery, and outcome were collected and analyzed.

Results: All 150 patients underwent bilateral endoscopic sinonasal debridement. Among them, 108 patients (72%) had current or recent coronavirus disease (COVID) infection. Ninety-two patients (61.3%) required additional procedures based on disease extent. Twenty patients (15.4%) required revision debridement because of progressive or recurrent disease. Mean age of this group was 46.15 (standard deviation ±11.2) years with a strong male predominance (9:1). Seventeen had diabetes mellitus, 12 suffered from active COVID-19 infection and six had received corticosteroids. None of the 31 patients who had recovered from COVID-19 or had no comorbidities required revision surgery. Age, gender, and comorbidities were not significant predictors for revision surgery. Fourteen patients (70%) underwent second surgery within one month of primary surgery. Predominant disease locations were alveolus and palate (55% each), and in 80% the site was uninvolved at primary surgery. The most common revision procedure was inferior partial maxillectomy (60%). At follow-up, all were asymptomatic with no evidence of disease.

Conclusion: The proposed surgical guidelines for AIFS allow for adequate surgical debridement with preservation of optimum functional status. Low revision surgery rates and good outcomes with minimal morbidity validate its usefulness.

Keywords: Fungal sinusitis, mucormycosis, endoscopy, surgery, debridement, revision surgery, guideline

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Introduction

Acute invasive fungal sinusitis (AIFS) is rapidly progressive and angioinvasive, and often a fatal fungal infection that usually affects immunocompromised or immunosuppressed patients. The high prevalence of diabetes mellitus and widespread unsupervised use of steroids, culminated in an unprecedented escalation of cases with AIFS in a short time during the second surge of the coronavirus disease-2019 (COVID-19) pandemic, posing a big challenge to otolaryngologists (1). Early diagnosis, adequate surgical debridement, reversal of immunocompromising factors, and prompt initiation of systemic antifungal therapy are vital for a good outcome in AIFS.

Early and aggressive surgical debridement is thought to be the reason for the reduction in mortality associated with early diagnosis of AIFS (2, 3). Opening all sinuses endoscopically irrespective of clinico-radiological involvement along with debridement of affected areas at the very first instance has been shown to avoid repeated surgery and provide good outcomes (4). The extent of the disease determines the amount of debridement required and the ability to achieve complete surgical clearance. The maxillary sinus is the most common sinus involved in AIFS and compared to other sinuses is more amenable to radical debridement (5). Any advanced disease here with signs of bony erosion, palatal involvement or extraparanasal sinus spread has been traditionally addressed with total or partial maxillectomy. Though associated with minimal complications, the morbidity associated with maxillectomy can be functionally incapacitating, compromising the quality of life, and subsequent adequate rehabilitation can be challenging. A tailored, more conservative debridement procedure based on the areas of involvement is necessary to address this problem. A recent report showed the benefit of using an appropriately designed palatal flap to effectively separate the oral and nasal cavities after bilateral inferior partial maxillectomy in a case of mucormycosis involving the maxilla and the alveolus (6). The effectiveness of such approaches in a large number of patients with maxillary sinus mucormycosis has not been evaluated to date. Also, there are no evidence-based guidelines regarding specific surgical procedures to be used for each affected site in different clinical scenarios.

Since the majority of the patients during the second wave had an active COVID-19 infection, the patient's general condition and the hazards of general anesthesia had to be balanced with the benefits of aggressive surgical debridement. Considering the large number of otolaryngologists with varying experience in rhinology involved in the management of the condition, comprehensive surgical guidelines were put forward and implemented in our department. The presented study aims to propose guidelines for the surgical management of AIFS and evaluate its usefulness in avoiding repeated debridement. Patient characteristics were also analyzed to determine any predictors of revision surgery.

Methods

Patients and Methodology

This was a retrospective observational study of all patients operated on for suspected AIFS and had a final histopathological confirmation of AIFS during the period from May to June 2021 at the otorhinolaryngology department of a tertiary care hospital in South India. The authors confirm that approval from Christian Medical College, Vellore, Institutional Review Board (IRB number: 14181, date: 28.07.2021) and informed consent from the patients were obtained before the commencement of the study. The surgical outcome measured was the need for any revision surgery.

Data Collection

Details regarding demography, comorbidities, surgical procedures performed, any revision surgery, the outcome at the time of discharge and at last follow-up were collected.

All patients underwent surgical debridement based on a tailored surgical protocol depending on the extent of clinical and radiological involvement at initial evaluation as given in Table 1. Bilateral paranasal sinuses were opened in all patients irrespective of involvement seen on imaging. The endoscopic sinonasal debridement (ESND) procedure included uncinectomy, wide middle meatal antrostomy, anterior and posterior ethmoidectomy, sphenoidotomy and frontal sinusotomy. If the frontal sinus was normal on imaging with a normal intraoperative frontal recess, opening of the frontal sinus was optional based on the expertise and comfort of the surgeon.

External incisions were avoided as far as possible and a sublabial approach was used for patients requiring partial or total maxillectomy. If the overlying palatal mucosa was healthy, preservation was performed by elevating a U-shaped posterior-based palatal mucoperiosteal flap up to the hard and soft palate junction, removal of the underlying diseased bone and securing the palatal flap to the gingival and buccal mucosa. Patients with orbital and intracranial symptoms were simultaneously evaluated and managed by ophthalmology and neurosurgical teams with appropriate interventions.

After surgical treatment, all patients received adequate, appropriate antifungal therapy with amphotericin B followed by oral posaconazole or with voriconazole depending on the organism. Simultaneously associated comorbidities and COVID infection were managed as required. Patients were postoperatively initiated on thrice daily saline nasal douching and prospectively followed up every two weeks until complete healing occurred. Thereafter, every patient was seen every

month until antifungal therapy was complete. Subsequently, follow-up was planned once in three months for up to one year after surgery. At each outpatient visit, a complete clinical examination and endoscopic assessment were performed and secretions and crusts were removed. Follow-up with imaging was performed only when recurrence or disease progression was suspected. Revision surgery was mandated in patients who presented with new or progressive clinical symptoms or endoscopic evidence of disease like unhealthy mucosa or granulations not responding to antifungal therapy. Patients who expired in the course of treatment were excluded from the analysis of surgical outcomes. Therapeutic success was clinically and endoscopically defined as patients who were asymptomatic at follow-up after completing the antifungal therapy and had no evidence of residual disease.

Statistical Analysis

All descriptive statistics were reported as counts and percentages for categorical variables and mean and standard deviation (SD) or median and interquartile range for normally and non-normally distributed data, respectively. For all correlational analyses, a two-sample t-test was done for normally distributed variables and the Mann–Whitney U test for skewed variables. The chi–square test was used to study the association between revision surgery and all categorical variables of patient characteristics. All statistical analyses were done using SPSS 21.0.

Results

A total of 150 patients underwent surgery for AIFS during the study period. Of these, 113 patients were male and 37 were female. Their ages ranged from 18 to 80, with a mean of 51 years.

The most common comorbidity was diabetes mellitus (129 patients, 86%). One hundred eight patients (72%) had current or recent COVID infection. Seventy-seven patients (51.3%) tested positive for reverse transcriptase-polymerase chain reaction of the nasopharyngeal swab for severe acute respiratory syndrome coronavirus-2 at presentation, while another 31 (20.7%) had recently recovered from COVID-19 infection. Fifty-seven (38%) patients had received systemic corticosteroids for COVID-19 infection. Other comorbidities seen were hypertension (44 patients, 29.3%) and chronic renal failure. Four patients did not have any comorbidities (Table 2).

The most common presenting complaints were facial (118 patients, 78.7%) and orbital (112 patients, 74.7%) symptoms. At presentation, 68 patients (45.3%) had palatal symptoms, 62 (41.3%) had headaches, 46 (30.7%) had nasal complaints, and 29 (19.3%) had neurological symptoms.

All patients underwent bilateral ESND. In 58 patients (38.7%), it was the only surgical procedure done. The remaining patients required additional procedures based on the extent of the disease. Thirty-four patients (22.7%) required septectomy and 33 (22%) required pterygopalatine fossa clearance. Other surgical procedures performed are shown in Table 3. Forty-five patients (30%) had varying extent of resection of palate and maxilla with only five of them undergoing total maxillectomy. Among these, palatal mucoperiosteal flap preservation was achieved in the 12 patients (26.7%) with normal-looking palatal mucosa.

Of the 109 patients (72.7%) who had positive growth on fungal culture, 99 (90.8%) grew zygomycetes with 95 of them being rhizopus. Ten patients (9.2%) had invasive aspergillosis. Of the 150 operated patients, 20 (13.3%) expired in the course of treatment due to AIFS or COVID-

Table 1. Guidelines for surgical resection in patients with AIFS

Indication	Surgical protocol
All cases of AIFS	Endoscopic sinonasal debridement
Involvement of septum	Partial or total septectomy
Involvement of turbinates	Turbinate resection
Unhealthy or discolored palatal mucosa with normal appearance of palatal bone both on imaging and intraoperatively	Wide local excision of palatal mucosa with preservation of palatal bone
Unhealthy palatal bone with surrounding healthy alveolus	Palatectomy
Unhealthy palatal bone with limited involvement of alveolus	Palatectomy with partial alveolectomy
Unhealthy palatal bone and alveolus	Inferior partial maxillectomy
Involvement of maxillary suprastructure	Subtotal or total maxillectomy
Involvement of premaxillary soft tissue	Debridement through a sublabial approach and Caldwell Luc clearance of maxilla.
Involvement of pterygopalatine fossa and infratemporal fossa	Clearance through a transantral route via a sublabial or medial maxillectomy approach
Involvement of skull base	DO NOT attempt debridement of this area

AIFS: Acute invasive fungal sinusitis

19-related complications. The surviving 130 patients were analyzed to evaluate the adequacy of surgical treatment. Of these, 20 patients (15.4%) required a revision debridement because of progressive or recurrent disease. The mean age of this group was 46.15 (SD ±11.21) years and there was a strong male predominance (9:1). In patients requiring revision surgery the main comorbidity was diabetes mellitus (17 patients, 85%). Active COVID-19 infection was seen in 12 (60%) and corticosteroid use in 6 (30%), as shown in Table 2. Patients without comorbidities and those who had recovered from prior COVID-19 infection did not require revision surgery. However, neither age or gender nor the presence of comorbidities was a significant risk factor for revision surgery (Table 2).

Of the patients requiring re-debridement, 13 (65%) had AIFS alone. Another 6 patients (30%) had AIFS and chronic granulomatous fungal sinusitis. One patient had a fungal ball along with AIFS.

The time interval between the primary and the revision surgeries ranged from 4 to 96 days (median 23). Fourteen patients (70%) underwent the second surgery within one month of the primary surgery. Among them, six underwent revision surgery within two weeks. The interval between the

Table 2. Baseline characteristics

	Primary surgery (n=150)	Revision surgery		
		Yes (n=20)	No (n=110)	p-value
Mean age (SD)	51±12.2	46.15±11.2	51±11.7	0.069
Gender				
Male	113 (75.3%)	18 (90%)	79 (71.8%)	0.100
Female	37 (24.7%)	2 (10%)	31 (28.2%)	
Comorbidities				
None	4 (2.7%)	0	4 (3.6%)	-
Diabetes mellitus	129 (86%)	17 (85%)	94 (85.5%)	0.9571
Hypertension	44 (29.3%)	2 (10%)	36 (32.7%)	0.5012
Chronic kidney disease	4 (2.7%)	0	2 (1.8%)	-
Active COVID-19	77 (51.3%)	12 (60%)	52 (47.3%)	0.4277
COVID-19 recovered	31 (20.7%)	0	28 (25.5%)	-
Corticosteroid use	57 (38%)	6 (30%)	41 (37.3%)	0.7285

SD: Standard deviation, COVID-19: Coronavirus disease-2019

Table 3. Primary surgical procedure

Surgery	No. of patients (n=150)		Patients requiring revision surgery	
	No.	%	No.	%
ESND alone	58	38.7	8	13.8
Wide local excision	12	8	1	8.3
Septectomy	34	22.7	4	11.8
Alveolectomy	2	1.3	1	50
Palatectomy	1	0.7	0	0
Inferior partial maxillectomy	16	10.7	1	6.3
Subtotal maxillectomy	9	6	1	11.1
Total maxillectomy	5	3.3	0	0
Palatal mucosa preservation	12	8	0	0
Premaxillary clearance	11	7.3	2	18.2
Caldwell Luc	23	15.3	5	21.7
PPF clearance	33	22	6	18.2
ITF clearance	12	8	2	16.7
Tooth extraction	4	2.7	1	25

ESND: Endoscopic sinonasal debridement, PPF: Pterygopalatine fossa, ITF: Infratemporal fossa

Table 4. Surgical procedures in patients with revision surgery

Revision cases	First surgery	Site of recurrence	New/ old site	Revision surgery
1	ESND	Alveolus, palate PMS, ITF, zygoma	N	STM, PMP, PMS, ITF clearance, zygoma debridement
2	ESND	Alveolus	N	IPM, PMP, TE
3	ESND	Palate	N	Palatectomy
4	ESND	Alveolus	N	IPM, PMP
5	ESND	Palate	N	IPM
6	ESND	Palate	N	IPM
7	ESND	Palate, zygoma	N	IPM, PMP, TE, zygoma debridement
8	ESND	Maxilla	O	TM, PMP
9	ESND, WLE	Alveolus, PPF	N	IPM, PPF clearance
10	ESND, septectomy	Alveolus, palate	N	TM, PMP
11	ESND, septectomy	Alveolus	N	IPM, PMP, TE
12	ESND, septectomy	Alveolus	N	Alveolectomy, PMP, TE
13	ESND, Caldwell Luc	Frontal bone	N	Frontal debridement
14	ESND, PPF clearance	Alveolus, palate	N	IPM
15	ESND, PPF clearance	PPF	O	Caldwell Luc, PPF, ITF clearance
16	ESND, Caldwell Luc, TE	Alveolus	O	STM, PMP
17	ESND, Caldwell Luc, PMS, PPF, ITF clearance	Palate, alveolus	N	IPM
18	ESND, Caldwell Luc, PPF, ITF clearance	Palate	N	IPM, PMP
19	ESND, Caldwell Luc, PMS, PPF clearance	Palate	N	IPM, PMP
20	ESND, alveolectomy, septectomy, PPF clearance	Palate, alveolus	N	IPM, STM, PPF, ITF clearance

ESND: Endoscopic sinonasal debridement, PMS: Premaxillary space, ITF: Infratemporal fossa, PPF: Pterygopalatine fossa, WLE: Wide local excision, TE: Tooth extraction, IPM: Inferior partial maxillectomy, STM: Subtotal maxillectomy, TM: Total maxillectomy, PMP: Palatal mucosa preservation

primary and revision surgeries was between 1–2 months in four patients and more than two months in two patients.

In a majority (16 patients, 80%), the site requiring revision surgery was previously uninvolved, and the most common locations were the alveolus and the palate (11 patients, 55% each). Two patients had disease in the pterygopalatine fossa and the zygoma, whereas the premaxillary tissue, the infratemporal fossa and the frontal bone showed pathology in one patient each. Among the 42 patients who had tailored, conservative resection of the palate and the maxilla, only four patients (9.5%) required revision surgery. None of the patients in whom the palatal mucosal flap was preserved needed a second surgery.

The most common procedure performed during revision surgery was inferior partial maxillectomy (12 patients, 60%). Three patients required subtotal maxillectomy and two required total maxillectomy. Other surgical procedures are shown in Table 4. In 11 patients (55%), palatal mucosal preservation could be achieved.

The site of recurrent disease showed involvement during primary surgery clinically in four (20%) and radiologically in only two (10%) patients. On reviewing the previous clinical reports and radiological images, the primary surgery performed based on the protocol described above was found to be appropriate in 17 patients (85%) who required revision debridement. In the remaining three patients, the areas where the disease was missed during initial surgery were the pterygopalatine fossa, the infratemporal fossa, the alveolus and the premaxillary soft tissue.

The mean follow-up duration was 6.86 months, and 78.5% of the patients had a follow-up period exceeding six months. At the last visit, all patients who had revision surgery were asymptomatic and had well-healed sinus cavities with no evidence of disease. Mild cheek swelling and forehead swelling were noticed at the last visit in one patient each. Seven patients had minor dehiscence of the palatal mucosal flap. The presented series showed an overall survival of 86.7%.

Discussion

Though endoscopic debridement of the paranasal sinuses is the primary treatment for AIFS, a delicate balance needs to be maintained between being too aggressive while at the

same time performing a thorough and adequate debridement. Retaining normal tissues to the extent possible with the help of good clinical judgment collaborated with imaging will help accelerate surgical recovery and optimize postoperative quality of life. Our study showed that with adherence to the surgical guidelines described above, only 20 patients (15.4%) required a revision debridement. In most of these (16 patients, 80%), the site requiring revision surgery was at a previously uninvolved site, the most common locations being the alveolus and the palate (11 patients, 55% each). Accordingly, the most common surgical procedure performed at revision surgery was varying types of maxillectomy depending on the extent of involvement. Palatal mucoperiosteal flap preservation could be achieved in 55% of the patients.

The study period was during the second wave of the COVID-19 pandemic which witnessed a sudden escalation of patients with AIFS and this explains the high number of cases in our series. Endoscopic debridement has been reported as an independent positive prognostic factor for survival in AIFS (7). This could be attributed to earlier tissue diagnosis, reduced fungal burden, better antifungal delivery following necrotic tissue removal, and improved postoperative sinonasal monitoring (8). In a previous study done at our institution on 51 patients, 11.8% of patients with radiological evidence of paranasal sinus disease only on one side were found to have bilateral disease on histopathology when all the sinuses were sampled (4). Unlike other types of fungal sinusitis where radiological changes are prominent, since AIFS tends to spread along vascular channels, changes in the paranasal sinuses are minimal in the initial stages of the disease. Hence bilateral sinonasal debridement was adopted as the standard basic procedure for all cases irrespective of the presence of clinico-radiological disease. In 38.7% of the cases, this was the only surgical procedure required since there was no extraparanasal spread.

The most common additional surgical procedure done was septectomy. More than one-fifth of the patients requiring pterygopalatine fossa clearance points to an increased occurrence of the disease in the area which may act as a primary reservoir for subsequent intraorbital and intracranial spread (8, 9).

Once AIFS extends beyond the sinonasal cavity especially when associated with orbital and intracranial extension, complete removal is sometimes not possible and may lead to serious morbidity and life-threatening postoperative complications. In a study by Roxbury et al. (10), looking at surgical resection and short-term survival, even patients with incomplete surgical resection of disease had a higher survival rate compared with those who were treated with medical therapy alone. Hence in all patients with AIFS, the feasibility of surgical resection should be considered aiming at complete surgical resection whenever possible. However, in cases with advanced disease when a surgical cure is less likely, it is important to assess the prognosis, consider the benefits versus the risks of the procedure, and determine the extent of surgical removal.

In addition to clinical and endoscopic examination, radiological assessment aids in determining the disease extension and clinical decision-making. Early computed tomography (CT) findings like unilateral sinus mucosal thickening are very nonspecific (11). Since the disease spreads by vascular invasion, it can cross bony partitions without any associated bone erosion and involve adjacent areas like the pterygopalatine fossa, the infratemporal fossa, the orbit and the premaxillary soft tissue. This extraparanasal spread may be evident as loss of orbital or periantral fat planes and later soft tissue infiltration. Fat stranding is considered an early sign of AIFS and radiographic evidence of bone destruction is seen in later stages (11, 12). Similarly, loss of contrast enhancement on Gadolinium-enhanced magnetic resonance imaging (MRI) is indicative of tissue infarction secondary to angioinvasion and vascular thrombosis (13). While CT acts as a roadmap for surgery and is ideal for the evaluation of bony erosions, MRI is better for soft tissue abnormalities and superior in the evaluation of vascular occlusions, intraorbital, intracranial and cavernous sinus involvements (8). MRI is also useful in the early detection of skull base osteomyelitis, with early detection of bone marrow infiltration (14). Diffusion-weighted imaging helps better delineate the formation of any abscess (15).

Debridement of necrotic sinonasal tissue is advised until bleeding is seen and often repeat surgical debridements are needed (7). In a study by Gardner et al. (16), the average number of debridements (or surgical procedures) required was 2.45. Nam et al. (13), in a study on AIFS with extrasinonasal involvement, reported the median number of operations as two (range, 1–5 times) with 52.0% of the patients undergoing surgery more than once. Despite adopting more conservative procedures, only 15.4% of the patients in our series required a revision debridement and none of them required more than one revision surgery.

Most of the patients in the cohort had a good outcome, even in cases where a complete clearance could not be achieved due to proximity to vital structures. 84.6% of the cases did not require any further surgical debridement. That revision surgery was not required for the patients in whom the palatal mucosal flap was preserved, and the rate of a second surgery was less than 10% among those with tailored resection of the palate and the maxilla suggest that the disease location-specific conservative approach does not affect the prognosis adversely.

The majority of the patients requiring a revision underwent surgery within one month. 80% of the patients showing disease at a new location suggests subclinical, radiologically

nonevident involvement which has become overt over time. This shows the importance of close follow-up with detailed clinical and endoscopic examination especially in the first two months after surgery. In high-risk individuals, the fungal spores in the nose and the paranasal sinuses germinate and the fungal hyphae tend to invade the adjacent mucosa, the blood vessels and the bone. Vascular invasion leads to thrombosis, tissue infarction, and later acute neutrophilic tissue infiltrates with rapid tissue necrosis which may not be evident on initial imaging (17). When clinically evident, surgical debridement of this necrotic tissue is vital to reduce the fungal load and improve the tissue penetration of antifungal agents (13, 18). So, any suspicion of new signs or clinical progression when on antifungal therapy warrants imaging and tissue sampling.

Four patients underwent revision surgery for disease progression after an appropriate primary surgery. However, in two of these patients, the involvement was not radiologically evident initially, suggesting radiology may lag behind clinical signs. In three patients, the primary surgery was inadequate and the areas missed were the pterygopalatine fossa, the infratemporal fossa, the alveolus and the premaxillary soft tissue. This highlights the importance of paying special attention to these areas while assessing patients with AIFS.

Inferior partial maxillectomy (12 patients) predominated the revision surgical procedures followed by subtotal maxillectomy in three patients and total maxillectomy in two. This can be attributed to the fact that the maxillary sinus is the most commonly involved sinus in AIFS and any extraparanasal sinus spread here can be addressed surgically with less morbidity and favorable results than the other sinuses. Also, prior pterygopalatine fossa involvement with angioinvasion may progress to areas supplied by the internal maxillary artery. However, the palatal mucoperiosteal flap was preserved in a majority of these patients. This allowed for maintaining the oronasal separation and thereby facilitated prompt rehabilitation. Even in the few patients who later developed minor dehiscence, normal swallowing and intelligible speech without any significant nasal aspiration could be achieved without compromising the prognosis. Our conservative approach tailored to resect only the diseased segmental unit complemented with preservation of a palatal mucoperiosteal flap helped avoid nuances of a large postoperative defect and achieve optimal postoperative physiological function in a single stage.

Conclusion

Our study highlights the feasibility of a tailored surgical approach in patients with AIFS based on the extent of the involvement. The proposed surgical guidelines allow for adequate surgical debridement while at the same time preserving optimum functional status. Patients requiring revision surgery had disease at a new site rather than a residual lesion. The low rate of revision surgery and good outcomes with minimal morbidity validate the usefulness of the proposed surgical guidelines in deciding the extent of surgical resection in the management of AIFS.

Ethics Committee Approval: All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Christian Medical College, Vellore, Institutional Review Board approval was obtained before the commencement of the study (IRB number: 14181, date: 28.07.2021).

Informed Consent: Informed consent was obtained from the patients included in the study.

Authorship Contributions

Surgical and Medical Practices: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Concept: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Design: L.V., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Data Collection and/or Processing: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Analysis and/or Interpretation: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Literature Search: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R., Writing: L.V., R.K., L.M.C., G.R., S.R., D.S.S.S., K.P.P.A., M.T., J.S.M., G.M.V., V.R.

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Main Points

- Though early and aggressive surgical debridement has a key role in the management of acute invasive fungal sinusitis (AIFS), the associated morbidity can often be functionally incapacitating, compromising the quality of life.
- Using the proposed tailored surgical approach, only 15.4% of the patients required a revision debridement with the site requiring revision being previously uninvolved in 80%.
- Age, gender, and presence of comorbidities were not significant risk factors for revision surgery.
- The most common sites of recurrent disease were the alveolus and the palate (11 patients, 55% each).
- Palatal mucoperiosteal flap preservation could be achieved in 55% of the patients who underwent maxillectomy.
- The low rate of revision surgery and good outcome with minimal morbidity validate the usefulness of the proposed surgical guidelines in deciding the extent of surgical resection in the management of AIFS.

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The Conundrum of Labyrinthitis Ossificans: An Etiology-Based Case Comparison and Review of Literature

Case Report

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Abstract

Labyrinthitis ossificans is the formation of pathological new bone within the membranous labyrinth of the inner ear due to various local and systemic pathologies. Most commonly it occurs as a sequelae of meningitis spreading to the labyrinth, from the subarachnoid space via the cochlear aqueduct and the internal auditory canal. We are comparing three different etiological presentations of labyrinthitis ossificans; namely, tympanogenic, meningitic, and traumatic, together with their management in the light of recent advances.

Keywords: Labyrinthitis, cochlear implantation, osteogenesis, labyrinthitis ossificans, case report

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Introduction

Labyrinthitis is the inflammation of the membranous labyrinth, commonly caused by infection. It can lead to the fibroblastic proliferation and ossification of the labyrinth, known as labyrinthitis ossificans (LO), resulting in irreversible profound sensory neural hearing loss (SNHL) (1). LO can be caused by tympanogenic, meningitic, or traumatic etiologies (2). Patients with labyrinthitis present with vertigo and hearing loss, which can be reversible if treated early (3). Age is a risk factor for LO. Rare causes of LO include Cogan's syndrome, otosyphilis, and meningitic LO. Comprehensive clinico-radiological analysis of LO based on etiology is limited, and the authors present three such rare cases.

Case Presentations

All three minor patients were included in the study after obtaining consent for publication from their parents.

Case 1

A 9-year-old boy presented with a history of left ear discharge for four years, which worsened in the last one year, becoming persistent and foul smelling. He also had gradually progressive hearing loss in the left ear, affecting his scholastic performance. On examination, there was purulent drainage from the left ear with granulation tissue in the posterosuperior quadrant of the pars tensa as well as in the pars flaccida region with scutum erosion. Pure tone audiometry showed profound SNHL on the left side. High-resolution computed tomography (HRCT) and

magnetic resonance imaging (MRI) showed ossicular erosion together with erosion of the bony walls in the middle ear and complete bony ossification in the apical turn of the cochlea and partial bony ossification in the middle and the basal turn of cochlea (Figures 1, 2). He underwent left canal wall down mastoidectomy, and bone-anchored hearing aid and bone conduction hearing aid were offered for the benefit of binaural hearing.

Case 2

A 6-year-old girl with a history of head injury and meningitis presented with impaired hearing for the past three years. An anterior cranial fossa cerebrospinal fluid (CSF) fistula was diagnosed as the culprit for meningitis and repaired by frontal craniectomy. Otological examination showed reduced absolute bone conduction bilaterally, and pure tone audiometry showed profound SNHL. HRCT and MRI of the inner ear showed bilateral cochlear ossification, and ossification of lateral semicircular canals, suggestive of LO as a sequalae to meningitis (Figures 3, 4). The parents were counselled about the prognosis of hearing loss and its impact on the child's development. The patient underwent cochlear implantation (CI) on the left side with the Veria technique, with drill-out procedure addressing partial ossification of basal turn of cochlea (Figure 5). The child recovered well, and CI switch-on was done on postoperative day 21, followed by rehabilitation therapy. Follow-up categories of auditory performance scores were promising.

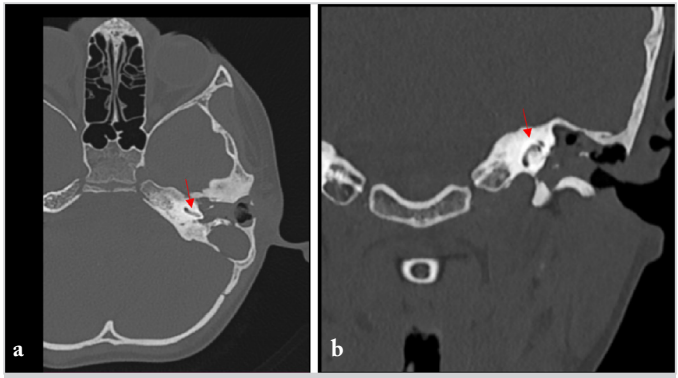

Figure 1. a) HRCT of temporal bones with axial cuts showing ossification within basal turn of left cochlea (red arrow), b) Coronal cut showing higher degree of ossification of middle turn and apical turn of left cochlea compared to basal turn (red arrow)

HRCT: High-resolution computed tomography

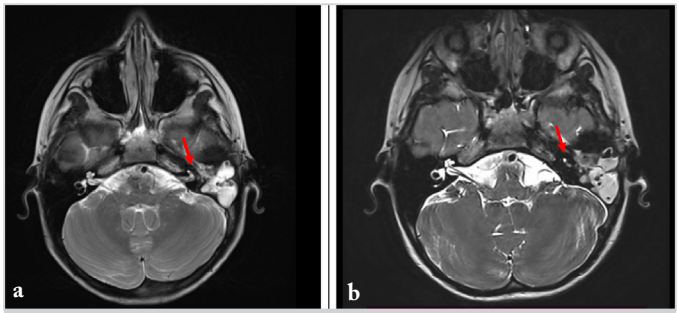

Figure 2. a, b) T2-weighted magnetic resonance images axial cuts showing the external auditory canal, the middle ear cavity, the aditus and mastoid air cells are filled with contents appearing T2 hyperintense with patchy restriction on diffusion, with loss of T2 hyperintensity in cochlear turns and semicircular canals on left side (red arrow)

Case 3

A 4-year-old girl with delayed speech and impaired hearing for two years following a head injury from a fall was evaluated. Bleeding from both ears was reported. Pure-tone audiometry and brainstem-evoked response audiometry confirmed profound SNHL. HRCT showed complete ossification of bilateral cochlea and the vestibule, and partial ossification of the semicircular canals. MRI showed complete loss of T2 hyperintensity in the cochlea and the vestibule, and partial loss in the semicircular canals (Figures 6, 7). After counselling the parents about the prognosis and the impact on the child's development, CI was done on the left side using the Veria technique. Drill-out procedure was used to address the ossification (Figure 8). However, post-implant

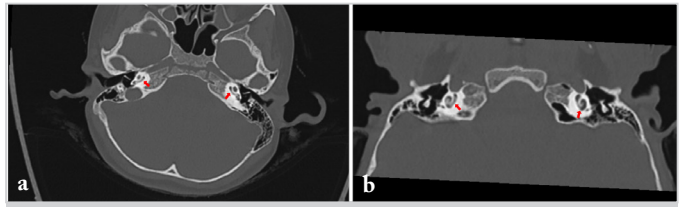

Figure 3. HRCT of temporal bones: a) axial cuts, and (b) coronal cuts showing mild ossification of basal turn and clear middle and apical turns bilaterally (red arrow)

HRCT: High-resolution computed tomography

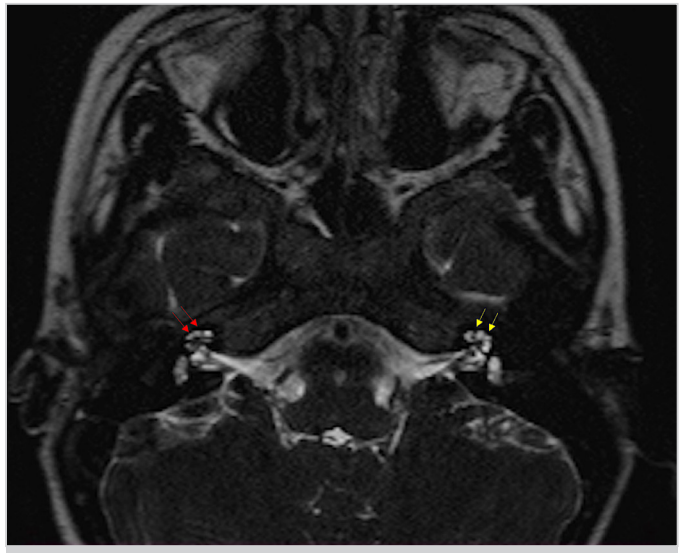

Figure 4. T2-weighted magnetic resonance images with axial cuts showing loss of hyperintensity in the basal turn of cochlea bilaterally (red arrow on the right and yellow arrow on the left)

responses were poor, and the child was planned for auditory brainstem implantation.

Discussion

Labyrinthitis, a rare complication of chronic otitis media, can be classified into different types (2, 3). Serous labyrinthitis is the best period for patients, as early diagnosis and treatment can reverse hearing loss and prevent complications like LO. Infective causes are more common than inflammatory, with the infection spreading via various pathways. LO is the end result of suppurative labyrinthitis, which can begin as early as three weeks after onset and progress up to nine months (1).

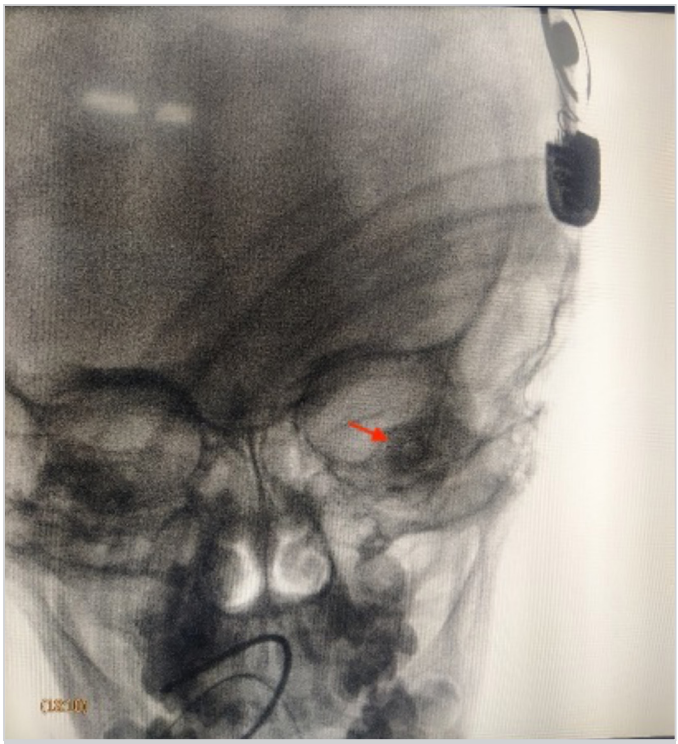

Figure 5. Postoperative X-ray of skull with trans-orbital view showing the position of electrode

Children with bacterial meningitis have a 5% chance of profound hearing loss, with up to 80% developing some degree of ossification (3). Infection spreads from the subarachnoid space to the labyrinth via the cochlear aqueduct, with LO occurring first and being worst where the aqueduct enters the labyrinth. A central nervous system etiology of LO typically presents bilaterally, unlike tympanogenic. Infection via the cochlear aqueduct causes intense inflammation and ossification at the basal turn of

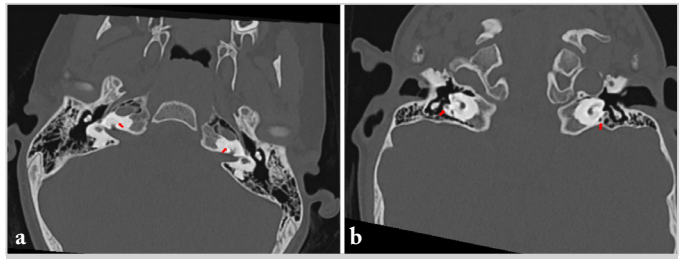

Figure 6. HRCT of temporal bones: a) axial cuts, and b) coronal cuts showing complete ossification of bilateral cochlea, and mild ossification of semicircular canals (red arrow)

HRCT: High-resolution computed tomography

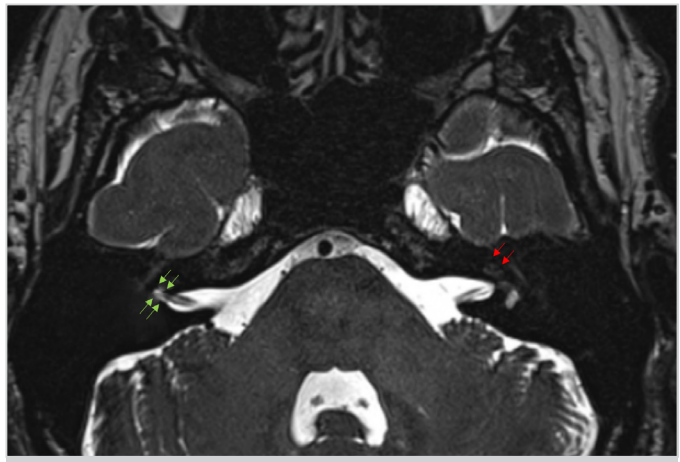

Figure 7. T2-weighted magnetic resonance images with axial cuts showing loss of hyperintensity in all turns of the cochlea bilaterally with mild hyperintensity in the vestibule and the semicircular canal (green arrows on the right and red arrows on the left)

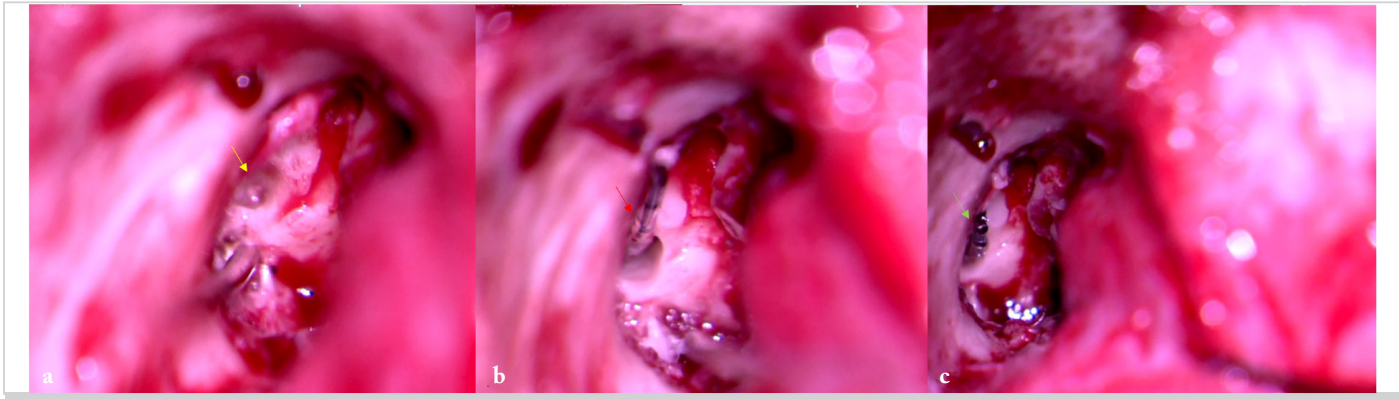

Figure 8. Intra-operative images: a) drill-out procedure (yellow arrow), b) electrode inserted after the drill-out (red arrow), c) insertion test device to assess the length of the electrode (green arrow)

the cochlea, while infection via the internal auditory canal (IAC) leads to more pronounced ossification in the first and second turns according to Aralaşmak et al. (4).

Tympanogenic LO is caused by middle ear pathologies and results in bone formation in the inner ear. Inflammation from the middle ear can spread to the inner ear through preformed pathways, membranes, or channels. The basal turn of the cochlea and lateral semicircular canal are most commonly affected. The disease progresses from inflammation to fibrosis and ossification. Typically, cholesteatoma in the middle ear serves as the nidus of infection. Lin et al. (5) found an incidence of 2% in a retrospective study of 195 patients who underwent mastoidectomy, with four patients testing positive for tympanogenic LO.

LO has three pathological stages: Acute (normal CT, labyrinthine enhancement on MRI), fibrous (loss of fluid signal intensity on T2-weighted MRI; normal CT), and ossification (membranous labyrinth replaced by bone). HRCT is commonly used to classify patients into mild, moderate, or severe stages for management purposes. Buch et al. (6) conducted a radiology study and found that patients with prior temporal bone surgery had significant ossification patterns. The semicircular canals were commonly affected in all etiologies, but no characteristic mineralization pattern was identified in any pathology.

In their histopathological study, Kaya et al. (7) found that LO was mainly observed in the scala tympani of the basal cochlear turn. They also discovered that increased endolymphatic hydrops led to a significant reduction in the spiral ganglion cell population, the outer and inner hair cells in all turns of the cochlea. Additionally, their study revealed differential atrophy of the stria vascularis and the spiral ligament, with the former being greater in all turns of the cochlea and the latter being greater in the basal and middle turns. Merchant et al. (2), in their book, similarly noted that the number of spiral ganglion cells decreased with increasing ossification and duration of deafness.

Tympanogenic LO is commonly found in aggressive cholesteatomas like pediatric cholesteatoma with labyrinth erosion and congenital cholesteatoma in the IAC or the petrous apex. Mesotympanic cholesteatoma cases can also extend to the IAC without LO via the supra-labyrinthine route, requiring extensive treatments like subtotal petrosectomy, translabyrinthine or middle cranial fossa approaches with radical mastoidectomy. In case 1, disease clearance was achieved through modified radical mastoidectomy since cholesteatoma was confined to the mesotympanum and the epitympanum.

Temporal bone trauma is an infrequent cause of LO and is classified into otic capsule sparing and otic capsule violating types (4, 8). The latter type is linked with SNHL, vestibular dysfunction, CSF leak, and peri-lymphatic fistula. However, there is currently no evidence to establish a correlation between otic capsule violating fractures and LO.

This article does not provide a detailed discussion on LO management, but prelingual children with LO are a significant subgroup of CI candidates. The classic drill-out procedure, introduced by Balkany et al. (9), involves drilling a 6–8 mm distance to allow 4–8 electrodes for CI. The compressed electrode array (Form series - MEDEL) and double/split array are commonly used. While the ideal number of spiral ganglion population for serviceable hearing is 3500, and histopathological studies show a decrease in spiral ganglion number, there is no evidence linking spiral ganglion population with auditory-verbal outcomes in CI patients, as supported by a large meta-analysis by Cheng and Svirsky (10). For patients with failed CI in LO, the auditory brainstem implant is an alternative option, although its efficacy remains uncertain and is generally poorer than that of CI.

Michel deformity, otosclerosis, and labyrinthine schwannoma are among the differential diagnoses for LO. Cochlear aplasia or hypoplasia, also known as Michel deformity, has a different labyrinth contour that is altered or absent. Otosclerosis, which causes osteodystrophy of the otic capsule, is classified into fenestral and retro-fenestral (cochlear) types. Although cochlear otosclerosis can radiologically mimic LO, the clinical presentation includes mixed hearing loss and differs in histopathological profile. Table 1 provides a comparison of all three etiologies of LO.

Conclusion

Patients with LO who have profound SNHL can be difficult to diagnose, as routine imaging modalities such as HRCT may not detect early stages of the condition. Therefore, it is recommended that centers with ample resources consider using MRI. Despite the different etiologies of LO, the pattern of mineralization is consistent among them. With recent advances, the drill-out procedure and CI are recommended for bilateral LO, especially in prelingual children.

Informed Consent: Informed consents were taken from the parents of the patients.

Authorship Contributions

Surgical and Medical Practices: N.D.K., V.S., A.G., Concept: N.D.K., V.S., A.G., Design: N.D.K., V.S., A.G., Data Collection and/or Processing: N.D.K., V.S., A.G., Analysis and/or Interpretation: N.D.K., V.S., A.G., Literature Search: N.D.K., V.S., A.G., Writing: N.D.K., V.S., A.G.

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

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Table 1. Etiology based comparison of labyrinthitis ossificans (LO)

Features	Meningitic LO	Tympanogenic LO	Traumatic LO
Clinical presentation	Children, Bilateral involvement, Preceding history suggestive of suppurative labyrinthitis.	No specific age group, Associated with squamosal type chronic otitis media, Vestibular symptoms are usually not evident in its history.	Unilateral > bilateral, Bimodal age groups - children and young adults, associated with otic capsule violating fracture.
Imaging features	CT: Irregularities/obliteration/sclerosis of labyrinth. MRI: T2 may show loss of normal fluid signal in the inner ear. T1 with contrast enhancement on MRI is seen in the early acute/subacute stage when there is inflammation-related hypervascularity. These features are more pronounced at the basal turn of the cochlea especially in the scala tympani where it meets the cochlear aqueduct. First and middle cochlear turn involvement with sparing of basal turn suggest spread via the IAC.	Same CT/MR features, with occasional erosive characteristics due to cholesteatoma. Lateral semicircular canal is more commonly involved.	Same as other three, enchondral layer demonstrates fibrous changes.

CT: Computed tomography, MRI: Magnetic resonance imaging, IAC: Internal auditory canal

Main Points

- Labyrinthitis ossificans is a rare but serious complication that can result from severe inner ear infection or inflammation which leads to the abnormal calcification or ossification of the delicate structures of the labyrinth.
- It can cause a range of symptoms, including hearing loss, dizziness, and tinnitus.
- Diagnosis typically involves imaging studies, such as a computed tomography scan or magnetic resonance imaging, to visualize the inner ear and identify any calcifications or ossifications.
- Treatment options for labyrinthitis ossificans are limited and can depend on the severity of symptoms. In some cases, hearing aids or cochlear implants may be recommended to improve hearing.

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Atypical Location of the Facial Nerve in a Patient with a First Branchial Cleft Fistula

Case Report

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Abstract

First branchial cleft anomalies are rare. Its estimated incidence is one in 100,000. Clinically, patients present with recurrent otorrhea, periauricular swelling, and/or flowing fistula in the neck. Surgical removal of the tract is considered the best treatment option for the first branchial cleft fistula. Due to the close relationship between the fistula tract and the facial nerve branches, facial nerve injury is one of the not uncommon complications of this surgery. Different variations in the relationship between the fistula tract and the facial nerve trunk and its branches have been mentioned in the literature. In this study, we presented the case of an atypical course of the facial nerve in a nine-year-old pediatric patient who underwent first branchial cleft fistula surgery, and discussed the importance of anatomic variations and measures to be taken to prevent facial nerve injury.

Keywords: Branchial cleft, facial nerve, anatomy, congenital, surgery, pediatric, case report

Introduction

First branchial cleft anomalies are rare, as the estimated incidence is one in 100,000 (1). Clinically, patients have recurrent swelling, hyperemia, pain, and inflammation whit periauricular swelling and/or flowing fistula in the neck.

Surgical removal of the tract is considered the best treatment option for first branchial cleft fistulas (2). Due to the close relationship between the fistula tract and the facial nerve branches, the parotid gland, and the external acoustic canal, the most common postoperative complications are parotid gland sialorrhea, facial paralysis, and external acoustic canal stenosis (3). Different variations in the relationship between the fistula tract and the facial nerve trunk and its branches have been mentioned in the literature (Figure 1).

The fistula tract, which is associated with the external auditory canal, usually passes through the superficial surface of the facial nerve. However, the probability of the fistula tract being located under the facial nerve or between its branches increases in younger patients (4).

The risk of nerve damage also increases in the surgery of these cases; therefore, these conditions should be taken into consideration, especially in patients presenting with the first branchial cleft fistula at a young age. Using intraoperative nerve monitoring helps surgeons identify the facial nerve and reduces the risk of nerve damage during the operation.

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In this case report, we present a pediatric patient who had a first branchial cleft fistula with an atypical location of the facial nerve (Figure 2).

Case Presentation

A nine-year-old female patient presented with occasional discharge and swelling in front of the left ear lobe, which was reported to have been present since infancy. In the clinical examination, a hyperemic lesion with a draining hole was observed at the level of the angle of the mandible (Figure 3).

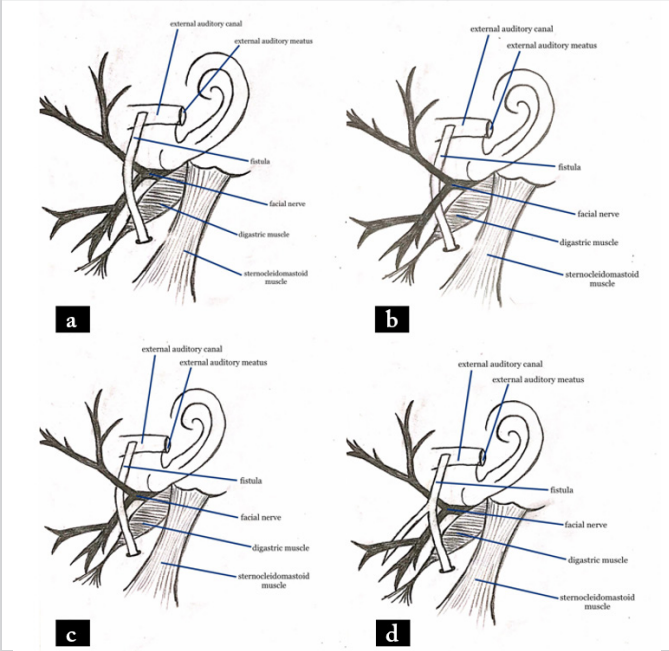

Figure 1. a) Fistula tract superficial to the facial nerve, b) Fistula tract deep to the facial nerve, c) Fistula tract between branches of the facial nerve, d) Fistula tract superficial to the facial nerve with additional deep extension

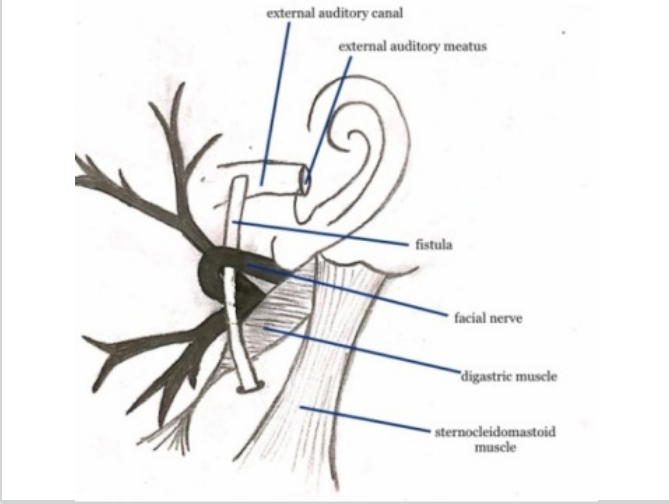

Figure 2. Facial nerve passing through the surface of the tragal pointer cartilage and rotating around the fistula tract (the situation in our patient)

Intraoral and otoscopic examinations were normal. There was no external auditory canal anomaly. Magnetic resonance imaging (MRI) of the neck revealed a 3x0.8x1 cm tubular structure extending from the left-sided skin to the parotid gland and further to the anteroinferior wall of the external auditory canal (Figure 4).

Although MRI revealed a fistula tract extending to the external auditory canal, the fistula orifice was not observed in the external auditory canal in otoscopic examination. The diagnosis of the first branchial cleft fistula, which opened under the skin of the external auditory canal on the left, was considered, and surgery was planned. Examination of the facial motor functions of the facial nerve in the preoperative period was evaluated as bilaterally normal. Superficial parotidectomy and total excision of the fistula tract were performed with intraoperative facial nerve monitoring (Figure 5). There was no need to perform a fistulogram or use methylene blue to identify the pathway during surgery.

During surgery it was found that the facial nerve trunk was more superficial than normal and had an atypical location compared to the fistula tract. After the facial nerve trunk passed through the surface of the tragal pointer cartilage, it was observed that it rotated around the fistula tract and

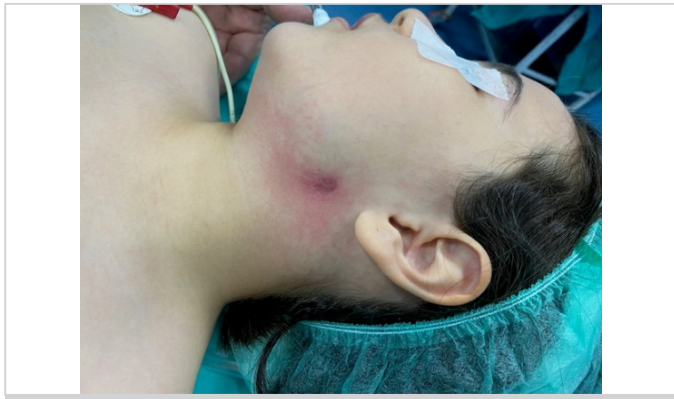

Figure 3. Hyperemic lesion appearance on clinical examination

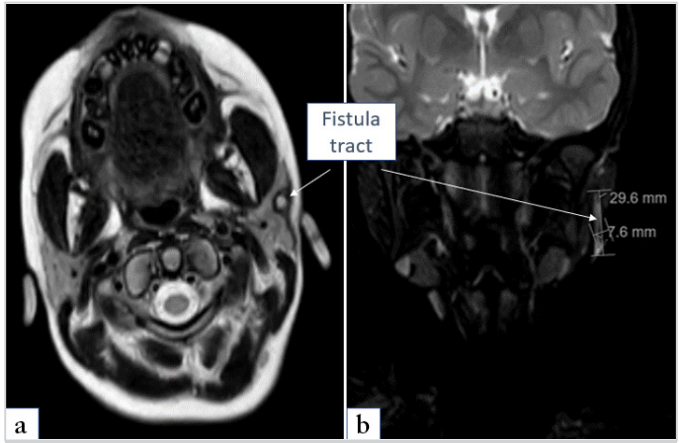

Figure 4. a, b) MRI T2 axial and coronal sections showing the fistula tract on the left side

divided into branches in the medial (deep) part of the tract (Figures 2, 6, 7).

After dissecting and removing the fistula tract with superficial parotidectomy, the facial nerve was identified with its main branches (Figure 8).

When the fistula tract was dissected, it observed that the fistula tract opened subdermally to the anteroinferior of the external auditory canal. The entire tract was excised.

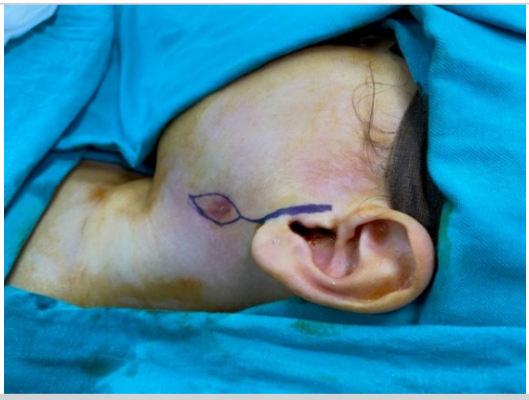

Figure 5. Planning the surgical incision

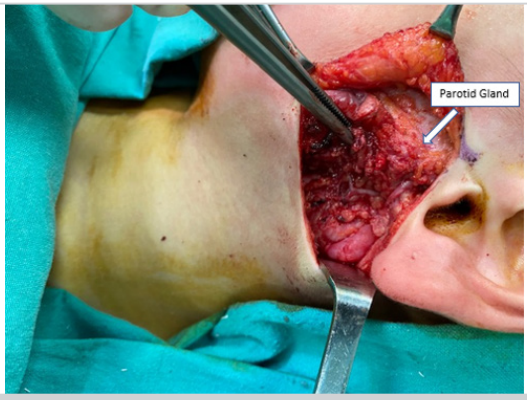

Figure 6. Exposure of the facial nerve

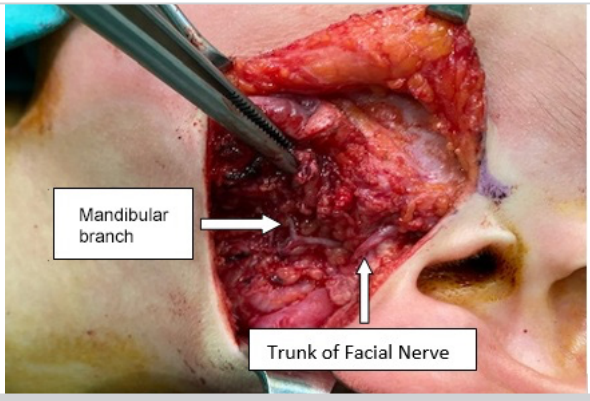

Figure 7. The facial nerve rotates around the fistula tract and divides into its branches

Electromyography responses were obtained by intraoperative facial nerve monitoring. Facial nerve examination was normal in the postoperative period. No signs of recurrence was observed during the six months follow-up of the patient.

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

Discussion

Branchial clefts are the embryological precursors of the face, neck, and pharynx. In children, branchial cleft anomalies are the second most common congenital lesion in the head and neck region. They are more common in females. Among the branchial cleft anomalies, second branchial cleft anomalies are the most common type. First branchial cleft anomalies are the second most common and constitute 1–8% of the four cleft types (5).

First branchial cleft anomalies are often misdiagnosed and managed inadequately before surgical excision. They are typically located as cysts/sinuses/fistulas between the external auditory canal and the submandibular area. They can occur in the form of a flowing pit in the angle of the mandible, an inflammatory mass in the parotid gland region, or a discharge in the external ear canal (6).

First cleft anomalies are classified as type I or type II lesions (7). Type I lesions are the continuation of the membranous part of the external auditory canal and contain only ectodermal tissues. Type II lesions consist of ectoderm and mesoderm and may contain cartilage. Type I lesions are located lateral to the facial nerve, while type II lesions are located medial to the nerve. Type II lesions may appear as preauricular, infraauricular, or postauricular swellings or cysts below the angle of the mandible.

In the literature, different localizations of the facial nerve and fistula tract compared to each other were previously stated in a case series study (4).

In this report, we discuss a case with an incompletely formed first branchial cleft fistula located atypically with the facial nerve. No such case is mentioned in the literature.

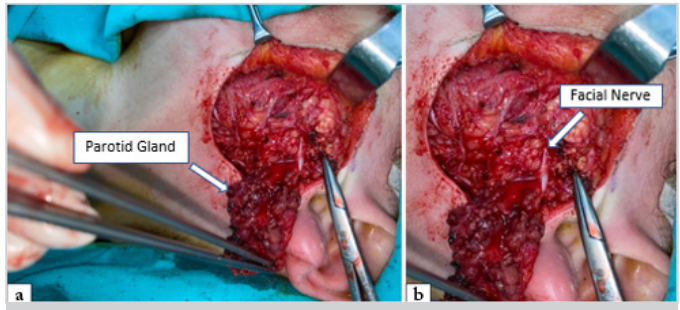

Figure 8. a) Appearance after superficial parotidectomy and removing the fistula tract, b) Exposure of the facial nerve branches

In the literature, it is stated that brachial cleft fistulas are more common on the left. When the position of the facial nerve and fistula tract are compared to each other, it is stated that the deeply located tract is more common at an earlier age than the facial nerve (4). In the presented case, the brachial cleft fistula was on the left, and the fistula tract was deeply located.

Radiological examinations provide important preoperative information for branchial anomalies. Ultrasonographic examination determines the structure and the size of the lesion. Computerized tomography and MRI help confirm the diagnosis and provide accurate anatomical information about the location. In MRI, axial and coronal T1 postcontrast imaging may show a cyst tract (8). In our case, a thick-walled fistula tract extending to the left external auditory canal was observed in the T1 and T2 MRI series (Figure 4).

First branchial cleft anomalies are at high risk for iatrogenic facial paralysis due to the proximity of the lesion to the facial nerve. Neither physical examination nor imaging techniques can clearly define the relationship between the lesion and the facial nerve (9). Several studies have been conducted on estimating the location of the facial nerve and its branches with MRI (10). However, no study has objectively shown the location of the facial nerve. Given the risk of injury to the nerve or its branches, it is critical to monitor the facial nerve during surgery.

First branchial cleft fistulas are rare. The fistula tract can cause anatomical variations in the extracranial location of the facial nerve, particularly in cysts from birth. Treatment includes surgical planning accompanied by facial nerve monitoring and total excision of the fistula tract, considering that it may be an atypically located facial nerve. Recognizing the facial nerve truncus at the early stage of dissection is critical. In young patients with fistula tract opening into the external auditory canal, variations in the atypical location of the fistula tract and facial nerve should be kept in mind, and attention should be given.

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

Authorship Contributions

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

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

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Main Points

- Different variations in the relationship between the fistula tract and the facial nerve trunk and its branches are mentioned in the literature.
- Different variations are seen especially in patients presenting with their first branchial cleft fistula at a young age.
- In this study, we present an atypically located facial nerve and the relationship between the fistula tract and the facial nerve in a nine-year-old pediatric patient with a first branchial cleft fistula.

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Cochlear Implantation in Primrose Syndrome with a Novel ZBTB20 Gene Variant

Case Report

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Abstract

In this article, we aim to present details of the cochlear implantation procedure performed in a patient with Primrose syndrome, which is a rare genetic condition characterized by physical deformities, sensorineural hearing loss, and metabolic disorders. While its long-term prognosis is still under investigation, the absence of intraoperative and postoperative complications indicates promising findings. This designates cochlear implantation as a viable therapeutic approach for sensorineural hearing loss linked to Primrose syndrome. As cochlear implantation in cases with Primrose syndrome has not been discussed previously in the literature and our patient has recently been operated on, additional investigation is imperative to broaden the understanding of cochlear implant outcomes in this patient population.

Keywords: Hearing loss, genetic disease, Primrose syndrome, cochlear implantation, otorhinolaryngology, case report

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Introduction

Primrose syndrome (PS) is a rare genetic disease characterized by a range of distinctive features including macrocephaly, hypotonia, developmental and speech delay, behavioral disorders, ocular anomalies, sensorineural hearing loss, distal muscle wasting, and abnormal glucose metabolism. Facial phenotypes associated with PS include a high anterior hairline, sparse eyebrows, downslanted palpebral fissures, ptosis, high palate, torus palatinus, broad jaw, and large ears. Imaging techniques can detect various abnormalities such as Wormian bones, platybasia, outer ear calcification, cerebral calcification, agenesis or dysgenesis of the corpus callosum, and mild cerebral atrophy (1). PS was first described by David Primrose in a 32-year-old male patient with intellectual disability, muscle weakness in the lower limbs, calcified ear flaps, bone abnormalities, and torus palatinus (2).

The diagnosis of PS is established with characteristic features, and a heterozygous pathogenic variant in the *ZBTB20* gene is identified through molecular genetic testing (1). Hearing is commonly affected in PS. Calcification of the outer ear

cartilage and enlarged auricles are also seen. Sensorineural hearing loss in patients with PS is usually prelinguistic and can range from mild to moderate (1).

In this report, we present a case of PS with severe sensorineural hearing loss for which cochlear implantation (CI) was performed in our clinic. The lack of data on CI in patients with PS in the literature suggests that the hesitations we experienced in our case could guide future candidates.

Case Presentation

The patient was born at term via normal spontaneous vaginal delivery, with a birth weight of 3370 grams. At her sixth-month postnatal control, the baby was referred to the genetic clinic for macrocephaly and hypotonia. Physical examination revealed macrocephaly, frontal bossing, downslanted palpebral fissures, and strabismus (Figure 1a, b) Microarray analysis using Affymetrix CytoScan Optima array platform yielded normal results. Subsequently, whole exome sequencing was performed to investigate the underlying etiology, which revealed a heterozygous state for the c.1930A>C variant in the *ZBTB20* gene. Segregation analysis confirmed that the variant was a *de novo* variant (Figure 2). Based on the guidelines of the American College of Medical Genetics and Genomics, this variant was classified as likely pathogenic, considering both the development of amplified consensus genetic markers and segregation analysis results (3).

After PS was diagnosed and the metabolic and endocrinological problems (central hypothyroidism, blood sugar regulation problems) were stabilized, the patient presented to our audiology department with sensorineural hearing loss, a commonly seen component of PS. Otoscopic examination revealed normal external auditory canals and tympanic membranes bilaterally. Brainstem evoked response audiometry showed untraceable 5th peaks in both ears even at 90 dB. The tympanometry results were type-A in both ears. The patient was evaluated as a CI candidate. High-resolution computed tomography (CT) and magnetic resonance imaging of the temporal bones showed normal bilateral cochlear anatomy, auditory canals, and facial nerves. There was no evidence of external ear cartilage calcification, agenesis or dysgenesis in the corpus callosum. The patient used a hearing aid for six months, with no improvement reported by the family or observed clinically. Due to the lack of data in the literature on the CI results of patients with PS, a CI decision was made in the CI council together with pediatric psychiatry, metabolism, endocrinology, and child development specialists. Preoperative psychiatric evaluation revealed language and speech retardation, yet no intellectual disability. Since the patient had additional metabolic problems and there were no clear data on the CI results, CI was planned initially for the right-side, and the family was informed that the left side could be planned six months later, based on the results. As metabolic disorders negatively affect surgical outcomes, patient's thyroid medication usage, and preoperative and postoperative blood glucose levels were closely monitored. Throughout the patient's hospitalization, regular monitoring of fasting blood glucose levels revealed that they remained within the reference range.

We placed the CI in the right ear under endotracheal general anesthesia when the patient was two years old. The device (Nucleus® CI 422 from Cochlear Ltd.) was fully inserted through the round window without any intraoperative complications. Impedance, stapes reflex, and neural response

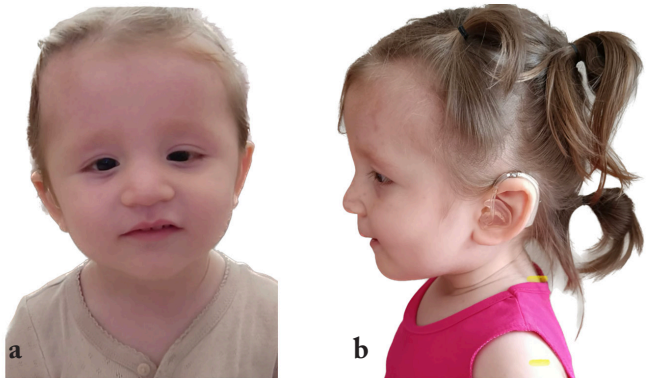

Figure 1. a, b. Clinical features of Primrose syndrome. Sparse body hair and eyebrows, macrocephaly, strabismus, high anterior hairline, downslanted palpebral fissures

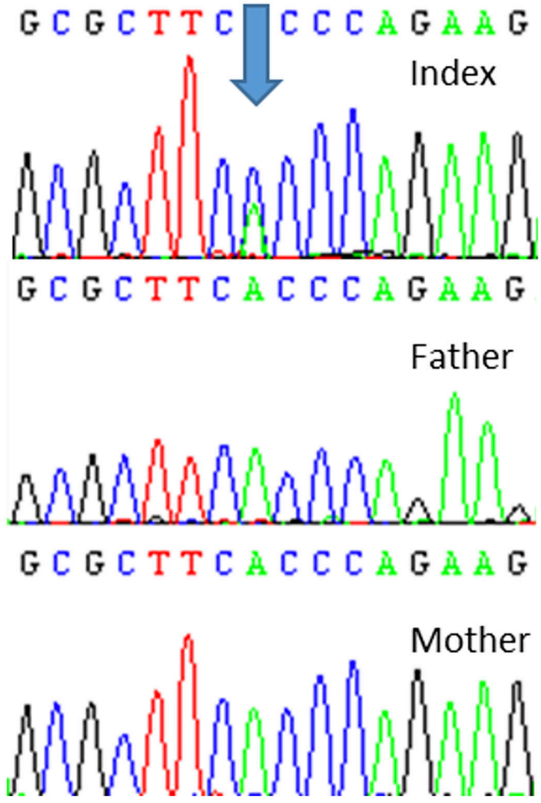

Figure 2. Sanger sequencing images of the family

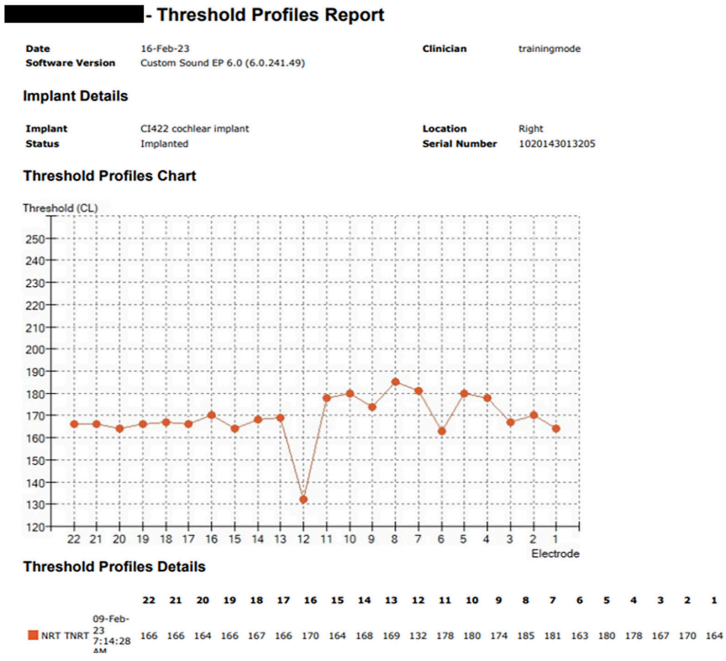

Figure 3. Intraoperative nerve monitoring showing the neural response telemetry responses in the right ear were within the normal limits

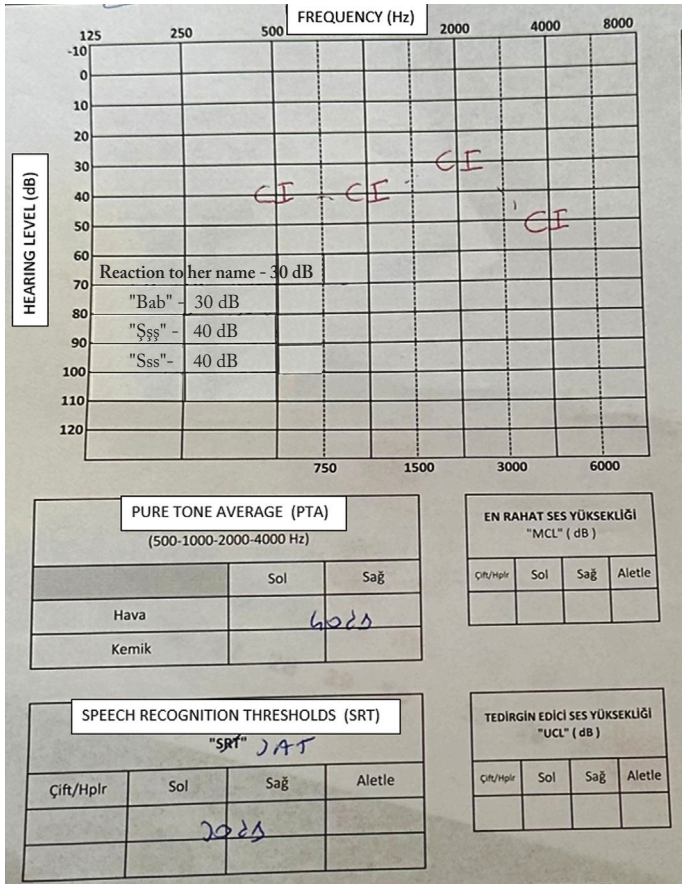

Figure 4. Postoperative third-month free field audiometry result

telemetry were within the normal limits (Figure 3). The Stenvers and transorbital radiographs obtained postoperatively confirmed the appropriate location of the CI. The patient was discharged without any complications on the postoperative fourth day. Visual reinforcement audiometry in free field setup was performed in the postoperative third month, monosyllabic word recognition and response to name test revealed a pure tone average of 40 dB (Figure 4). The patient's family reported that she can form basic one-to-three-word sentences, and eagerly uses the implant device throughout the day, taking it off only when sleeping. The process of evaluating long-term CI hearing and speech results continues since it has been only three months since the operation. However, the fact that we have not encountered any problems intraoperatively or postoperatively encouraged us to present this case, for which the patient's parents' written and verbal informed consent have been received.

Discussion

Our patient had sensorineural hearing loss, and there was no calcification in the outer ear. To date, no study has specifically addressed the treatment of PS-related sensorineural hearing loss or CI.

Xie et al. (4) conducted a study investigating the effect of ZBTB20 on cochlear development and hearing in mice. Their findings suggest that the *ZBTB20* gene is crucial for the growth of the cochlear lateral non-sensory epithelium, hearing perception, and for overall cochlear development.

In a study by van Beeck Calkoen et al. (5), which included 423 children with sensorineural hearing loss, genetic mutations were identified as the most common underlying pathology, with 87 of all patients having a genetic disorder. Among these, only one patient was diagnosed with PS.

Arora et al. (1) provided a comprehensive description of the clinical characteristics, diagnosis, genetic disorders, and management of PS. Their study revealed that 12 of 13 adult patients and 21 of 27 pediatric patients with PS experienced hearing loss. In most cases, hearing loss was prelingual and predominantly sensorineural, with only one patient having a mixed-type hearing loss due to recurrent ear infections.

Carvalho and Speck-Martins (6) presented a case study in which a patient with PS had bilateral moderate mixed hearing loss. CT scans of the head revealed extensive and uniform calcification of both the pinnae and part of the external ear canals.

Posmyk et al. (7) described a case of PS involving bilateral partial hearing loss and calcified ears, as observed on CT scans. In another case report by Grímsdóttir et al. (8), a patient with PS displayed decreased hearing but no calcification was observed in the ears.

CI surgery has not previously been reported in these patients. In our case, CI was indicated due to bilateral sensorineural hearing loss, unsuccessful hearing aid trial for six months, and

lack of improvement following conventional treatment. The fact that our case has no long-term results is a shortcoming on its own. On the other hand, systemic metabolic problems of the patient should not cause the surgeon to consider delaying CI, since CI is crucial in supporting normal developmental milestones.

CI should be considered as a viable treatment option for sensorineural hearing loss associated with PS. While hearing aids can be used, early CI is essential for patients with bilateral hearing loss, enabling them to achieve developmental milestones and speech capabilities. Given the limited information available on CI outcomes in PS, we performed unilateral implantation and planned to consider contralateral implantation based on our results.

Informed Consent: Informed consent was obtained from the patient's legal guardians.

Authorship Contributions

Surgical and Medical Practices: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Concept: B.A.T., İ.S., Z.M.Y., Design: B.A.T., İ.S., Z.M.Y., Data Collection and/or Processing: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Analysis and/or Interpretation: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y., Literature Search: B.A.T., A.G., İ.S., Z.M.Y., Writing: B.A.T., A.G., C.B.A., E.A., İ.S., Z.M.Y.

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

- Sensorineural hearing loss and calcification of the outer ear cartilage are common in Primrose syndrome.
- Cochlear implantation should be planned quickly to prevent disruption of language and speech development after systemic and metabolic problems are checked in suitable syndromic children.
- Early implantation is important in both syndromic and normal children.
- While making the implant decision in syndromic children, physicians in other related branches should be included in the cochlear implant councils.

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