



Association of *Actinomyces* with Allergic Rhinitis, Adenotonsillar Hypertrophy and Chronic Recurrent Tonsillitis and Its Histopathological Findings

Actinomyces'in Alerjik Rinit, Adenotonsiller Hipertrofi ve Kronik Rekürren Tonsillit İlişkisi ve Histopatolojik Bulguları

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ABSTRACT

Aim: To evaluate the prevalence of adenotonsillar *Actinomyces* with histopathological findings and to determine the relationship of *Actinomyces* with allergic rhinitis (AR), adenotonsillar hypertrophy (ATH) and chronic recurrent tonsillitis (CRT).

Materials and Methods: Histopathological sections were retrospectively analyzed in 228 patients who underwent adenoidectomy, bilateral tonsillectomy, and adenotonsillectomy. The presence of *Actinomyces*, cryptitis, and severity of inflammation were determined. Data were analyzed with the Statistical Package for the Social v.21.0 package software. The statistical significance level was accepted as $p < 0.05$.

Results: *Actinomyces* was detected in 39 (17.1%) patients. *Actinomyces* was seen at a similar rate in ATH and CRT ($p=0.08$) (14.6% and 24.6%, respectively). The diameter of the tonsils with *Actinomyces* were larger than those without *Actinomyces* ($p < 0.01$). The frequency of cryptitis in tonsils with *Actinomyces* histopathologically ($p=0.03$) and the degree of inflammation in the surface epithelium ($p < 0.01$) were increased. *Actinomyces* was found more frequently in patients with AR than in patients without AR ($p=0.02$) (25.7% and 13%, respectively).

Conclusion: Our study shows that adenotonsillar *Actinomyces* colonization may cause ATH, CRT and AR, and AR may be one of the factors in the etiology of ATH.

Keywords: *Actinomyces*, adenotonsillar hypertrophy, allergic rhinitis, recurrent tonsillitis

ÖZ

Amaç: Adenotonsiller *Actinomyces* prevalansını histopatolojik bulgularla değerlendirmek ve *Actinomyces*'in alerjik rinit (AR), adenotonsiller hipertrofi (ATH) ve kronik tekrarlayan tonsillit (CRT) ile ilişkisini belirlemektir.

Gereç ve Yöntem: Adenoidektomi, bilateral tonsillektomi ve adenotonsillektomi uygulanan 228 hastanın histopatolojik kesitleri retrospektif olarak incelendi. *Actinomyces* varlığı, kriptit ve enflamasyonun şiddeti belirlendi. Veriler Statistical Package for the Social v.21.0 programı ile analiz edildi. İstatistiksel anlamlılık düzeyi $p < 0,05$ olarak kabul edildi.

Bulgular: Otuz dokuz (%17,1) hastada *Actinomyces* saptandı. *Actinomyces* ATH ve CRT'de benzer bir oranda ($p=0,08$), sırasıyla %14,6 ve %24,6 olarak görüldü. *Actinomyces* görülen tonsillerin çapı, olmayanlardan daha büyüktü ($p < 0,01$). Histopatolojik olarak *Actinomyces*'in görüldüğü tonsillerde kriptit sıklığı ($p=0,03$) ve yüzey epitelindeki enflamasyon şiddeti ($p < 0,01$) artmıştı. *Actinomyces*, AR'li hastalarda AR olmayanlara göre daha sık bulunmuştur ($p=0,02$) (sırasıyla %25,7 ve %13).

Sonuç: Çalışmamız, adenotonsiller *Actinomyces* kolonizasyonunun ATH'ye, CRT ve AR'ye neden olabileceğini ve AR'nin ATH'nin etiyolojik faktörlerinden biri olabileceğini göstermektedir.

Anahtar Kelimeler: *Actinomyces*, adenotonsiller hipertrofi, alerjik rinit, rekürren tonsillit

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INTRODUCTION

Palatine, tubal, pharyngeal (adenoid) and lingual tonsils form Waldeyer ring, which is an important lymphatic structure of the upper airway¹. Adenoidectomy and tonsillectomy are the most common surgical procedures in both pediatric and adult patients. The most common indications for surgery are adenotonsillar hypertrophy (ATH) and chronic recurrent tonsillitis (CRT), which may cause obstructive sleep-related breathing disorders^{2,3}. Although the causes of ATH are still unclear, there are studies in the literature showing that allergy may be a risk factor⁴.

Actinomyces are Gram-positive, anaerobic, immobile, filamentous and rod-shaped commensal bacteria in the normal flora of the oropharyngeal, genitourinary and gastrointestinal tract⁵. They can resemble fungi because of their filamentous structure. In the literature, the incidence of *Actinomyces* in tonsil and adenoid has been reported in very variable rates, ranging from 0.3% to 40.7%^{2,5-9}. There are different opinions on the role of *Actinomyces* in the etiology of tonsil/adenoid hypertrophy and CRT. In addition to the studies suggesting that *Actinomyces* plays a role as an etiologic agent in these pathologies^{7,9-12}, there are also studies suggesting that it is only a saprophyte agent¹³. However, few studies have examined the histopathological effects of *Actinomyces* on tonsil and adenoid tissues^{14,15}. Allergic rhinitis (AR) is an inflammatory disease caused by IgE-mediated type 1 hypersensitivity reaction. AR has many factors in etiopathogenesis, including various fungi¹⁶. To date, no studies have investigated the relationship between AR and the presence of adenotonsillar *Actinomyces* in the literature. However, it is known that *Actinomyces* plays a role in the etiology of hypersensitivity pneumonia (extrinsic allergic alveolitis)¹⁷.

This study aims to determine the prevalence of *Actinomyces* in adenoidectomy, tonsillectomy and adenotonsillectomy materials, to investigate the relationship of *Actinomyces* with AR, ATH and CRT, and to discuss all findings in the light of literature. This is the first study in the literature to investigate the relationship between AR and adenotonsillar *Actinomyces*.

MATERIALS AND METHODS

Patient Selection

This retrospective study included 228 patients who underwent adenoidectomy (n=143), bilateral tonsillectomy (n=29), and adenotonsillectomy (n=56) at Silifke State Hospital between January 2013 and December 2015. The study were approved by the Hatay Mustafa Kemal University of Local Ethics Committee (protocol number: 10, date: 16.01.2020). Unilateral tonsillectomies were excluded because of different surgery indications. Data on age, sex, diagnosis of AR, indications for

operation, the largest diameters of tonsils and adenoids were obtained from the patient files and pathology reports.

Histopathological Evaluation

Hematoxylin-eosin stained histopathological sections of a total of 369 tissue materials taken from 228 patients were re-evaluated on the Olympus BX53 (Olympus, Tokyo, Japan) light microscope and photographed with the Olympus DP20 digital imaging system (Olympus, Tokyo, Japan). Tonsillar *Actinomyces* diagnosis is made either by the presence of sulfur granules in the form of a basophilic mass with a granular center and the radial fringes around it or by the presence of a unique *Actinomyces* filament in the tonsillar tissue and/or crypt¹⁵ (Figure 1).

The presence of *Actinomyces*, cryptitis (evaluated only in palatine tonsils because there was no crypt in adenoid tissue), inflammation in the surface epithelium and lymphoid hyperplasia were re-evaluated. Inflammation in the surface epithelium was scored semiquantitatively as 0: none, 1: mild, 2: moderate, and 3: severe. Lymphoid hyperplasia was classified as follicular hyperplasia, paracortical hyperplasia and mixed hyperplasia (follicular + paracortical).

Statistical Analysis

All clinical, histopathological and demographic data obtained from this study were analyzed with Statistical Package for the Social (SPSS) v.21.0 software package program (SPSS Inc, Armonk, NY, US). The Pearson chi-square test was used for the analysis of qualitative data. For quantitative data that were not normally distributed were statistically analyzed with the Kolmogorov-Smirnov and the Mann-Whitney U tests. Correlation analyses were performed with the Spearsman's rank correlation test. Statistical significance was accepted as p<0.05 in all analyses.

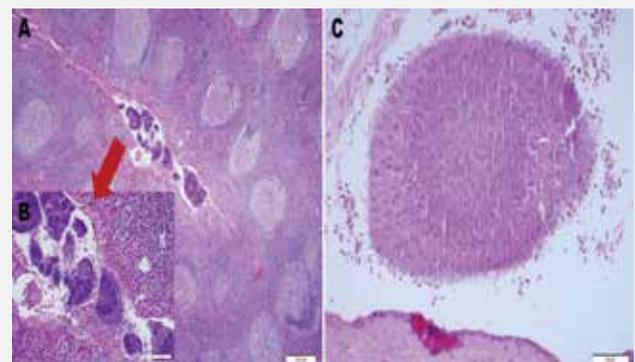


Figure 1. A) Irregularly shaped *Actinomyces* colonies in the tonsil crypt (hematoxylin-eosin, x200). B) On higher power, characteristic sulfur granules of *Actinomyces* (hematoxylin-eosin, x400). C) Filamentous branching of the bacteria at the periphery of the colonies (hematoxylin-eosin, x400)

RESULTS

The median age of all patients (n=228) was 8±5.06 years (minimum: 4, maximum: 39). 132 of them were male (57.9%) and 96 were female (42.1%). *Actinomyces* was detected in 39 patients (17.1%). *Actinomyces* was seen in 29 (34.1%) of 85 patients with tonsillectomy when adenoidectomy was excluded. The incidence of *Actinomyces* was similar in both sexes (p=0.20). The median age of the patients with *Actinomyces* was higher than that of those without *Actinomyces* (p<0.01). The median age of the patients with *Actinomyces* was 11±7.8 years and the median age of the patients without *Actinomyces* was 8±3.6 years. *Actinomyces* was seen in 25 (14.6%) of 171 patients who underwent surgery for ATH and in 14 (24.6%) of 57 patients who had surgery for CRT, and no significant difference was observed (p=0.08). The diameters of the tonsils (palatine + pharyngeal) with *Actinomyces* were larger than those without

Actinomyces (p<0.01). Histopathologically, cryptitis was observed more frequently in tonsils with *Actinomyces* (p=0.03) and the degree of inflammation in the surface epithelium was increased (p<0.01). There was no difference in lymphoid hyperplasia types (p=0.45). Follicular hyperplasia was high in both groups. Comparison of the presence of *Actinomyces* with other data and statistical test results are summarized in Table 1. *Actinomyces* was localized only in the right tonsil in 11 (28.8%) of 39 patients with *Actinomyces*. Other localizations of *Actinomyces* are shown in Table 2.

Actinomyces was observed in 19 (25.7%) of 74 patients with AR, while 20 (13%) of 154 patients without AR had *Actinomyces*, and the difference was statistically significant (p=0.02). The diagnosis of AR was higher in patients operated for ATH than in patients operated for CRT (p=0.013). Adenoid diameters of patients with AR were larger than those without AR (p=0.046).

Table 1. Presence of <i>Actinomyces</i> and comparison of other data			
	<i>Actinomyces</i> (-) n (%)	<i>Actinomyces</i> (+) n (%)	p value
Gender			
Male	113 (85.6)	19 (14.4)	0.20
Female	76 (79.2)	20 (20.8)	
Age (median)	8	11	<0.01
Allergic rhinitis			
No	134 (87)	20 (13)	0.02
Yes	55 (74.3)	19 (25.7)	
Indication for surgery			
Adenotonsillar hypertrophy	146 (85.4)	25 (14.6)	0.08
Chronic recurrent tonsillitis	43 (75.4)	14 (24.6)	
Type of surgery			
Adenoidectomy	133 (93)	10 (7)	<0.01
Tonsillectomy	15 (51.7)	14 (48.3)	
Adenotonsillectomy	41 (73.2)	15 (26.8)	
The largest diameter of the right tonsil (cm-median)	3	4	<0.01
The largest diameter of the left tonsil (cm-median)	2.5	4	<0.01
The largest diameter of the adenoid (cm-median)	2.5	4	<0.01
Histopathological findings			
Presence of cryptitis			
(-)	23 (82.1)	5 (17.9)	0.03
(+)	33 (57.9)	24 (42.1)	
The intensity of inflammation in the surface epithelium			
None	56 (91.8)	5 (8.2)	<0.01
Mild	65 (87.8)	9 (12.2)	
Moderate	58 (76.3)	18 (23.7)	
Severe	10 (58.8)	7 (41.2)	
Types of lymphoid hyperplasia			
Follicular hyperplasia	124 (84.9)	22 (15.1)	0.45
Paracortical hyperplasia	20 (83.3)	4 (16.7)	
Mixed hyperplasia	45 (77.6)	13 (22.4)	
Total	189 (82.9)	39 (17.1)	228

Table 2. *Actinomyces* localizations

<i>Actinomyces</i> localization	n (%)
Right tonsil	11 (28.2)
Left tonsil	7 (17.9)
Pharyngeal tonsil (adenoid)	10 (25.6)
Both tonsils	5 (12.8)
Right tonsil + adenoid	2 (5.1)
Left tonsil + adenoid	2 (5.1)
Both tonsils + adenoid	2 (5.1)

DISCUSSION

Actinomyces spp. are found in normal flora of the oropharyngeal, genitourinary and gastrointestinal tract⁵. Histopathological examination is more valuable than microbiological culture in the diagnosis of *Actinomyces*¹⁸. There is a wide range in the literature regarding the frequency of tonsillar *Actinomyces* ranging from 0.3% to 40.7%. We wanted to investigate the incidence of *Actinomyces* in our series. Coban et al.² found only 3 (0.3%) *Actinomyces* in 1,078 tonsillectomy cases. Riffat and Walker⁶ found 221 (18.2%) *Actinomyces* of 1,213 tonsillectomy cases. Ashraf et al.⁵ found 83 (40.7%) *Actinomyces* of 204 tonsillectomy cases. We found *Actinomyces* at the rate of 17.1% (n=36) in our series. Since *Actinomyces* is found as saprophyte in oral flora, the general opinion is that it is also found as saprophyte in tonsils. Therefore, there may be different attitudes among pathologists to specify tonsillar *Actinomyces* in the report and this may lead to differences in the results of retrospective studies using the archive of reports. In fact, if only pathology reports were taken as the basis in our study, *Actinomyces* was reported in 11 (4.8%) of 228 patients, but when preparations were re-evaluated, the number of patients with *Actinomyces* was revised to 39 (17.1%). In some studies, it was reported that tonsillar *Actinomyces* was seen more frequently in adults than in children^{5,11,12,19,20}, particularly in older children^{5,21}. Some studies have shown that *Actinomyces* is not age-related^{15,22}. In this study, the median age value (median age: 11) of those with *Actinomyces* colony was greater than that of those without *Actinomyces* (median age: 8 years) ($p<0.01$).

In most of the studies in the literature, the rate of tonsillar *Actinomyces* was found to be similar in both sexes^{5,15,21,22}. Similar findings were obtained in this study, which is consistent with the literature.

The role of *Actinomyces* in the etiology of ATH and CRT remains unclear. In addition to the studies suggesting that *Actinomyces* has a role in the etiology of hypertrophy and recurrent tonsillitis^{7,10-12,23}, there are also studies suggesting that it is not associated with these diseases^{5,11,13,24}. In the study of Kutluhan et al.¹⁵, *Actinomyces* was found in 33.3% of tonsils and it was revealed that *Actinomyces* was more common in tonsillar hypertrophy

(61.5%) than in recurrent tonsillitis (21.9%). Besides, they found that the volume of tonsils found in *Actinomyces* was larger than in those without *Actinomyces*. Similarly, Daneshmandan et al.²² found that tonsil volumes with *Actinomyces* (mean 8.65 mL) were larger than in those without *Actinomyces* (mean 4.48 mL). In contrast to these studies, Jones et al.²⁵ found a negative correlation between tonsillar *Actinomyces* colonization and hypertrophy and found a higher rate of *Actinomyces* in patients with recurrent tonsillitis compared to hypertrophy patients. Toh et al.¹¹ reported that *Actinomyces* did not affect the tonsillar size. In this study, a similar rate of actinomyces was detected in patients operated for hypertrophy and recurrent tonsillitis ($p=0.08$). The diameters of the tonsils (palatine and pharyngeal tonsils) with *Actinomyces* were larger than in those without *Actinomyces* ($p<0.01$), suggesting that *Actinomyces* plays a role in the etiology of ATH. Tonsils with *Actinomyces* showed more cryptitis ($p=0.03$) and inflammation in the surface epithelium was more severe ($p<0.01$). This suggests that *Actinomyces* may be an effective pathogen in the etiology of recurrent tonsillitis.

AR is one of the most common chronic diseases in children²⁶. Few studies have investigated the relationship between AR and AH and there is no consensus between these studies. Sadeghi-Shabestari et al.²⁷ found a significant correlation between positive skin prick test and high serum IgE levels with ATH. Modrzynski and Zawisza²⁸ also reported that AR might cause AH. Similarly, Bozkurt et al.²⁹ found that adenoid volumes of patients with AR were higher than those of patients without AR. In contrast to these studies arguing that AR causes AH or exacerbates existing AH, Ameli et al.³⁰ found that patients with AR had smaller adenoid volumes than those without AR, suggesting that anterior nasal obstruction stopped adenoid growth. In our study, the adenoid size was higher in patients with AR ($p=0.046$) and there was a positive correlation between them ($p=0.04$). Our findings support the view that AR may cause or increase existing AH, as in the studies of Sadeghi-Shabestari et al.²⁷ and Modrzynski and Zawisza²⁸. Some fungi have been reported to play a role in the etiology of AR in the literature. In their study, Namyslowski et al.¹⁶ found *Candida albicans* in 3.8%, *Aspergillus fumigatus* in 11.5%, *Alternaria alternata* in 3.8%, *Mucor racemosus* in 7.6% and *Cladosporium herbarum* in 7.6% in patients with AR. *Actinomyces* is also known to be similar to fungi because of their filamentous structure, and *Actinomyces* like *Aspergillus* have been shown to act as active pathogens in allergic diseases such as hypersensitivity pneumonia¹⁷. In our study, *Actinomyces* was found to be more frequent in patients with AR (25.7% and 13%, respectively) than in those without AR, and there was a positive correlation between them ($p=0.02$).

Study Limitations

Our study's retrospective design and therefore, the lack of access to drug history and laboratory values of all patients constitute the limitations of our study.

CONCLUSION

ATH and recurrent tonsillitis, which can cause obstructive sleep-related respiratory disorders, are the most common diseases and adenotonsillectomy is one of the most common surgical procedures in the treatment of these diseases. However, the etiologic cause of ATH is still unclear. Our study shows that adenotonsillar *Actinomyces* colonization may cause ATH, recurrent tonsillitis, and AR. It also suggests that AR may be involved in the etiology of ATH. Establishing causal relationships will contribute to the development of both preventive and therapeutic approaches. Our study is the first study to investigate the relationship between AR and *Actinomyces*.

Ethics

Ethics Committee Approval: The study were approved by the Hatay Mustafa Kemal University of Local Ethics Committee (protocol number: 10, date: 16.01.2020).

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

Peer-review: Externally peer-reviewed.

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