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History of Tonsillectomy is Associated with a Relatively Higher Risk of Symptomatic Disease in Patients with COVID-19

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Abstract

Objectives: Patients with Coronavirus Disease 2019 (COVID-19) can present with a broad spectrum of symptomatology. However, the impact of surgical history on the course of this disease has not been extensively investigated. This study aimed to interrogate the effect of tonsillectomy in the symptomatology and other clinical parameters of the patients with COVID-19.

Methods: Data of the patients admitted to our institution between May and July 2020 due to COVID-19 were reviewed. Patients were divided into two groups regarding the presence of tonsillectomy in their surgical history. These groups were compared concerning demographic data, symptomatology, hospital stay duration, and referral to the intensive care unit.

Conclusion: The comparative analysis revealed that the risk of symptomatic disease was significantly higher in COVID-19 patients with tonsillectomy history. However, the history of tonsillectomy did not impact other parameters.

Keywords: Tonsillectomy; COVID-19; Coronavirus; Symptom

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus disease 2019 (COVID-19) was identified for the first time in the Hubei province of China and spread around the world [1]. The first COVID-19 case was diagnosed on the 11th of March 2020 in Turkey and spread across the country.

Coronaviruses are enveloped RNA viruses with crown-like spikes ranging from 60 nm to 140 nm in length on their surface under the electron microscope [2]. Most coronaviruses cause mild respiratory tract infections in human beings.

The COVID-19 spreads by air droplets [2]. After it enters to the body by the respiratory route, it replicates in the upper respiratory tract (i.e., nasopharynx and oropharynx) and mostly leads to high fever, sore throat, myalgia, and fatigue [3]. The viral replication reaches a peak on the fifth day of infection [4].

The Waldeyer ring is located in the nasopharynx and oropharynx, where SARS-CoV-2 attaches itself and starts to replicate in the palatine, lingual and tubal tonsils [5]. The unique location of tonsils in the pharynx and palate renders direct contact of the defense cells with the pathogens and leads to immediate activation of the immune system. The Mucosa-Associated Lymphoid Tissue (MALT) of the palatine tonsils takes role in the immune activation against both air-borne and orally ingested antigens. This activation occurs by specific antibodies and B or T cells. Thus, both humoral and cellular immune functions are involved in the anti-viral immunity against air-borne viral infections, including SARS-CoV-2 [5-7].

Although tonsillectomy is the most frequent surgical procedure performed during childhood, its impact on the immune system has been debated among clinicians [8-10]. Some authors reported that tonsillectomy led to immune impairment due to a reduction in CD10 expression and B cell population [11]. Also, it was reported that adenoidectomy and tonsillectomy procedures performed during childhood caused an increase in the risk of respiratory, allergic, and contagious diseases during the subsequent years of life [8].

This study aimed to investigate the incidence of tonsillectomy in patients with COVID-19 and

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the progress of this disease in patients with tonsillectomy history.

Materials and Methods

Patients diagnosed with COVID-19 and admitted to Health Sciences University, Sanliurfa Mehmet Akif Inan Training and Research Hospital *via* Polymerase Chain Reaction (PCR) test between May 2020 and July 2020 constituted the target population of this study. The study was approved by the Ethical Review Committee of Harran University (29.06.2020/12-23). Data including age, gender, height, weight, Body Mass Index (BMI), symptom status (i.e., asymptomatic patients who were tested after close contact with another patient with COVID-19 or symptomatic patients who presented due to COVID-19 related complaints), chief complaint, and physical examination findings were all recorded. Study patients were categorized based on their BMIs as normal weight, overweight and obese according to World Health Organization (WHO) classification [10].

Also, patients were interrogated regarding comorbidities such as hypertension, cardiac diseases, thromboembolic events, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and past surgical history. Patients were divided into two groups based on their past surgical history of tonsillectomy.

During the study period, all COVID-19 PCR test positive patients were admitted regardless of the symptom status as per the Turkish Ministry of Health COVID-19 Management Protocol, which was in effect. All asymptomatic patients were treated with hydroxychloroquine sulfate, while symptomatic patients were treated by a combination of hydroxychloroquine sulfate and favipiravir as per the Turkish Ministry of Health COVID-19 Treatment Protocol. On the other hand, patients with the risk of thromboembolism were given enoxaparin sodium treatment. Patients were referred to the Intensive Care Unit (ICU) as per previously approved protocols. Duration of hospital and ICU stays were recorded for each patient. Patients with and without a history of tonsillectomy were compared regarding the above-mentioned demographic and clinical data, including ICU referrals and duration of stay in regular patient floor and ICU.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). The normality of the distributions of continuous variables was assessed by the Kolmogorov-Smirnov test. The assumption of homogeneity of variances was examined by the Levene test. Categorical data were expressed as numbers (n) and percentages (%) while quantitative data were given as means ± Standard Deviations (SD) and medians (minimum-maximum). The mean differences were compared between two independent groups were by Student's t test. The continuous variables that do not meet parametrical test assumptions were evaluated by Mann Whitney U or Kruskal Wallis tests depending on number of independent groups. Categorical data were evaluated by Pearson's χ^2 or Fisher's exact, where applicable. Spearman's rank-order correlation coefficients were calculated to examine the degrees of associations between continuous variables. Multiple logistic regression analysis was performed to determine the predictors affecting referral to ICU, multiple linear regression analyses were applied for determining the predictors affecting the durations of hospital and intensive care unit stays. Since there was non-normal distribution, logarithmic transformation was used for both durations of hospital and ICU stays in linear regression analyses. Odds ratios, coefficients of regression, and 95% confidence intervals were also calculated for each independent variable. The p value was considered significant when it was less than 0.05.

Results

Demographic and clinical data of the study patients and relevant statistical data are shown in Table 1. Comparisons of these data among patients with and without a history of tonsillectomy are exhibited in Table 2. There was no statistically significant difference between the patients with and without a history of tonsillectomy concerning age, gender, BMI, comorbidities, and duration of hospital stay (p>0.05). In patients with a history of tonsillectomy, the rate of symptomatic patients was significantly higher than those without a history of tonsillectomy (p=0.045). There were no patients with a history of tonsillectomy among the patients referred to ICU and there was no statistically significant association between these two parameters (p=0.611).

The frequency distributions of the study participants as per chief complaints are displayed in Table 3. The rates of all chief complaints were similar among the groups except for joint pain (p>0.05). The rate of joint pain was significantly higher in the patient group with history of tonsillectomy (p=0.003).

Comparison of the demographic and clinical data of the patients who were referred to ICU and who remained on a regular patient

Table 1: Demographic and clinical data of the study patients.

	n=357
Age (year)	40.0 ± 16.2
Age range (year)	16 to 85
Gender	
Male	204 (57.1%)
Female	153 (42.9%)
Body mass index (kg/m²)	26.6 ± 5.1
Classification as per body mass index	
Thin	9 (2.5%)
Normal weight	133 (37.3%)
Overweight	141 (39.5%)
First to degree obese	50 (14.0%)
Second to degree obese	19 (5.3%)
Third to degree obese	5 (1.4%)
Accompanying disease	70 (19.6%)
Hypertension	33 (9.2%)
Diabetes mellitus	21 (5.9%)
Cardiac diseases	16 (4.5%)
Chronic Obstructive Pulmonary Disease	24 (6.7%)
Behçet Disease	1 (0.3%)
Type of presentation	
Asymptomatic	108 (30.3%)
Symptomatic	249 (69.7%)
History of tonsillectomy	15 (4.2%)
Referral to İntensive Care Unit (ICU)	24 (6.7%)
Duration of ICU stay (days)	13 (5 to 32)
Duration of hospital stay (days)	6 (3 to 36)

Table 2: Comparative analysis of the patients without and with Tonsillectomy History (TH) regarding demographic and clinical data.

	TH - (n=342)	TH + (n=15)	p value
Age (year)	40.1 ± 16.3	39.3 ± 14.2	0.853†
Gender			0.102‡
Male	199 (58.2%)	5 (33.3%)	
Female	143 (41.8%)	10(66.7%)	
Body mass index (kg/m²)	26.6 ± 5.0	26.9 ± 6.7	0.815†
Body mass index			0.734¶
<25.00 kg/m²	136 (39.8%)	6 (40.0%)	
25.00-29.99 kg/m²	134 (39.2%)	7 (46.7%)	
≥ 30.00 kg/m²	72 (21.0%)	2 (13.3%)	
Accompanying disease	66 (19.3%)	4 (26.7%)	0.506¥
Hypertension	33 (9.6%)	0 (0.0%)	0.378¥
Diabetes mellitus	18 (5.3%)	3 (20.0%)	0.051¥
Cardiac disease	15 (4.4%)	1 (6.7%)	0.504¥
Chronic obstructive pulmonary disease	24 (7.0%)	0 (0.0%)	0.611¥
Behçet Disease	1 (0.3%)	0 (0.0%)	N/A
Type of presentation			0.045¥
Asymptomatic	107 (31.3%)	1 (6.7%)	
Symptomatic	235 (68.7%)	14 (93.3%)	
Referral to İntensive Care Unit (ICU)	24 (7.0%)	0 (0.0%)	0.611¥
Duration of ICU stay (day)	13 (5 to 32)	-	N/A
Duration of hospital (day)	6 (3 to 36)	6 (5 to 18)	0.718$

† Student's t test; ‡ Continuity corrected χ^2 test; ¶ Pearson's χ^2 test; ¥ Fisher's exact test; $ Mann Whitney U test; N/A: Not applicable; ICU: Intensive Care Unit

Table 3: Distribution of the study patients as per chief complaints.

	Number of patients	Percentage
High fever	108	30.3
Cough	96	26.9
Sore throat	87	24.4
Fatigue	68	19
Headache	57	16
Diarrhea	36	10.1
Dyspnea	33	9.2
Joint pain	26	7.3
Hoarseness	4	1.1
Visual impairment	1	0.3

floor are shown in Table 4. Mean patient age and comorbidity rates were higher in the patient group referred to the ICU than the other patient group (p<0.001, p<0.05). However, there was no statistically significant association between ICU referral and patient gender, BMI, symptom status at presentation and history of tonsillectomy (p>0.05). The rate of all complaints was similar between these two groups except for dyspnea (p>0.05). The rate of dyspnea was significantly higher in patients referred to ICU than the other patients who remained on a regular patient floor (p<0.001).

We also investigated the potential predictive factors for ICU referral by multivariable logistic regression analysis (Table 5). This analysis revealed that patient age was an independent predictor of ICU referral [OR=1.079, 95% CI: 1.045 to 1.113, p<0.001]. Patient age

Table 4: Comparative analysis between study patients who stayed in the regular patient floor and who were referred to intensive care unit.

	ICU -(n=333)	ICU +(n=24)	p value
Age (year)	38.5 ± 15.1	61.2 ± 16.1	<0.001†
Gender			0.737‡
Male	189 (56.8%)	15 (62.5%)	
Female	144 (43.2%)	9 (37.5%)	
Body mass index (kg/m²)	26.5 ± 4.9	27.4 ± 7.2	0.398†
Body mass index			0.867¶
<25.00 kg/m²	133 (40.0%)	9 (37.5%)	
25.00 to 29.99 kg/m²	132 (39.6%)	9 (37.5%)	
≥ 30.00 kg/m²	68 (20.4%)	6 (25.0%)	
Accompanying disease	57 (17.1%)	13 (54.2%)	<0.001¥
Hypertension	26 (7.8%)	7 (29.2%)	0.003¥
Diabetes mellitus	15 (4.5%)	6 (25.0%)	<0.001¥
Cardiac disease	11 (3.3%)	5 (20.8%)	0.002¥
Chronic obstructive pulmonary disease	19 (5.7%)	5 (20.8%)	0.016¥
Behçet Disease	1 (0.3%)	0 (0.0%)	N/A
Type of presentation			0.204‡
Asymptomatic	104 (31.2%)	4 (16.7%)	
Symptomatic	229 (68.8%)	20 (83.3%)	
History of tonsillectomy	15 (4.5%)	0 (0.0%)	0.611¥

† Student's t test; ‡ Continuity corrected χ^2 test; ¶ Pearson's χ^2 test; ¥ Fisher's exact test; N/A: Not applicable

Table 5: Multivariable logistic regression analysis of the potential predictive factors for referral to intensive care unit.

	OR	95% CI	Wald	p value
Age	1.08	1.045 to 1.113	21.89	<0.001
Male gender	1.25	0.480 to 3.277	0.213	0.644
Accompanying disease	1.9	0.700 to 5.176	1.591	0.207
Presence of symptoms	1.79	0.509 to 6.255	0.82	0.365

was positively correlated with ICU referral risk when the other factors were adjusted for the regression analysis model. On the other hand, patient gender, comorbidities and symptom status at presentation were not associated with ICU admission risk.

Patient age was also positively correlated with duration of hospital and ICU stays (p<0.001). There was a statistically significant positive correlation between BMI and duration of hospital stay (r=0.109 *vs.* p<0.001). However, there was no statistically significant correlation between BMI and duration of ICU stay (p=0.08).

Duration of hospital stay was not significantly associated with patient gender, BMI and history of tonsillectomy (p>0.05). However, the presence of comorbidities and symptoms at presentation was significantly and positively correlated with hospital stay duration (p<0.001). There was no statistically significant association between duration of ICU stay and patient gender, BMI, comorbidities and symptom status at presentation among patients referred to ICU (p>0.05).

The multivariable linear regression analysis regarding potential factors predicting duration of hospital and ICU stays is shown in Table 6. This analysis elucidated that the most potent predictive factors for estimating duration of hospital stay were patient age [B=0.009,

Table 6: Multivariable linear regression analysis for potential factors predicting durations of hospital and intensive care unit stay.

	B	95% CI	t	p value
Duration of hospital stay				
Age	0.009	0.007 to 0.012	6.629	<0.001
Female gender	0.049	-0.032 to 0.130	1.193	0.234
Body mass index	-0.01	-0.017 to -0.001	-2.125	0.034
Accompanying disease	0.053	-0.057 to 0.162	0.947	0.344
Presence of symptoms	0.111	0.024 to 0.199	2.507	0.013
Duration of ICU stay				
Age	0.021	0.011 to 0.032	4.386	<0.001
Female gender	-0.08	-0.408 to 0.244	-0.525	0.605
Body mass index	-0.01	-0.031 to 0.013	-0.887	0.385

B: Coefficient of regression; CI: Confidence İnterval; ICU: Intensive Care Unit

95% CI: 0.007 to 0.012, p<0.001], symptom status at presentation [B=0.111, 95% CI: 0.024 to 0.199 and p=0.013] and BMI [B= -0.009, 95% CI: -0.017 to -0.001, p=0.034].

Our analysis also revealed that patient age was an independent predictor of duration of ICU stay [B=0.021, 95% CI: 0.011 to 0.032, p<0.001].

Discussion

The symptomatology of COVID-19 has a broad spectrum ranging from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction [12]. The most frequent symptoms are high fever (99%), fatigue (70%), dry cough (60%), myalgia (44%), and dyspnea. Headache, drowsiness, diarrhea, nausea, and vomiting are relatively rare. It is difficult to distinguish it from other respiratory tract infections. However, in some patient groups, COVID-19 can be complicated by pneumonia, respiratory failure, and death within one week [12,13]. It was reported that 10% to 20% of the inpatients with COVID-19 were referred to ICU, 3% to 10% of these patients required intubation, and 2% to 5% died [12-14].

In line with these data, high fever (30.3%), cough (26.9%), sore throat (24.4%), and fatigue (19%) were the most common chief complaints encountered in our study. In our series, the rate of ICU referral was 7% (n=24), and 1, 96% of these patients died (n=7).

The mortality rate detected in our analysis is consistent with the literature [12-15]. However, our ICU referral rate was lower than the rates reported in the literature probably because all COVID-19 PCR test positive patients were admitted to the hospital regardless of their symptom status.

Baradaran et al. [14] reported in their systematic review that the risk of symptomatic and severe disease was significantly higher in elderly patients with COVID-19 and accompanying comorbidities. In another meta-analysis, the researchers stated that obesity was a risk factor for an unfavorable clinical course in these patients and the COVID-19 patients with higher BMI had a relatively worse prognosis [15]. In our study, the mean age of the patients referred to ICU was relatively higher and these patients had higher rates of comorbidities than the others. As such, the duration of ICU stay was positively correlated with patient age. However, we did not find a correlation between the duration of hospital stay and BMI.

It is currently widely accepted that the symptomatology of COVID-19 patients relies on the strength of the immune system of patients [16]. This fact also explains the wide variations in the clinical manifestations of the patients. On the other hand, the impact of tonsillectomy and adenoidectomy procedures on patients' immune system was not investigated in detail. Byars et al. [8] worked on children who underwent adenoidectomy, tonsillectomy, or adenotonsillectomy [8]. They followed these patients for 10 to 30 years postoperatively. These authors concluded that children who underwent adenoidectomy and tonsillectomy had a two or three-fold increased risk of upper respiratory tract infections. They also stated that the risk of acquiring contagious diseases was increased by 17% in patients with a history of adenotonsillectomy.

Some researchers investigated the protective roles of mucosa-associated lymphoid tissue MALT and mucosal Immune globulin A (IgA) in patients with COVID-19 [17,18]. Mucosal surfaces, which represent the primary defense line, are protected against viral infections by MALT [17]. It was reported that the IgA response was induced in severe COVID-19 cases [17,18]. Since IgA is regarded as the primary effector involved in the protection of the physical barriers against viral infections, Padoan et al. [18] investigated its role in patients with COVID-19 [18]. These authors concluded that a specific IgA response was detected in the first week of infection in 75% of the patients, and it was more potent and permanent than the IgM response. In a case-control study with a long follow-up period, which included 34 patients with a history of tonsillectomy and 30 healthy controls, Radman et al. [6] denoted that the IgM, IgG, and IgA levels were significantly lower in the former group than the latter [6]. They also stated that CD4, CD8, and CD56 expressions were not significantly different in patients with tonsillectomy history than healthy controls. However, the expression of CD10, a marker of B cells, was significantly lower in patients with a history of tonsillectomy than in the controls. These findings imply that the number of B cells and the serum levels of IgM, IgG, and IgA are reduced in patients with tonsillectomy history. In line with these results, the rate of symptomatic disease was significantly higher in patients with tonsillectomy history than the others (p=0.045). Altwairqi et al. [5] reviewed ten studies regarding the impact of tonsillectomy on immune functions of children [5]. They reported that none of these studies found a significant difference in the levels of humoral immunity markers (i.e., IgA, IgG, IgM, Complements C3 and C4) measured before and after the procedure. Also, there was no significant difference between the levels of cellular immunity markers (i.e., CD3, CD8, CD16, CD19, CD25, CD56) analyzed preoperatively and postoperatively. These authors concluded that tonsillectomy had no impact on the humoral and cellular immunities of children. In line with this finding, there was no significant difference between our patients with and without a history of tonsillectomy regarding the duration of hospital stay. Besides, there were no ICU referrals in the patient group with a history of tonsillectomy, and there was no significant difference between the patients with and without a history of tonsillectomy regarding this outcome.

Polat et al. [19] worked on 775 patients and reported that the incidence of tonsillectomy was 4%, 9% in healthy patient populations [19]. Similarly, the incidence of tonsillectomy was 4%, 2% in our study population. Since the rate of symptomatic patients was significantly higher in our COVID-19 patients with the history of tonsillectomy, we hypothesize that the absence of a lymphoid organ at the primary entry site of the virus increases the risk of symptomatic disease. However, our results also show that, this risk increase does not lead to an increase in the duration of hospital stay and rate of ICU referrals.

Our study has some limitations that need to be considered while evaluating its findings. First, the sample size was relatively small. Second, patients' comorbidities were not objectively assessed by internationally accepted scales such as the Charlson comorbidity index [20]. Therefore, an objective comparison could not be made between the symptomatic and asymptomatic patients regarding their comorbidity status. Third, our study is lacking long-term follow-up data.

Conclusion

Despite these weaknesses, we conclude that the risk of developing symptoms is significantly higher in COVID-19 patients with a history of tonsillectomy than those without tonsillectomy history. However, this difference in symptomatology does not lead to a significant change in duration of hospital stay and the risk of ICU referral. Since our study lacks long-term follow-up data and the long-term consequences of symptomatic COVID-19 are uncertain, we suggest that COVID-19 patients with history of tonsillectomy should be warned about the higher risk of developing symptomatic disease.

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