

An often overlooked joint in rheumatoid arthritis: cricoarytenoid joint.

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Abstract

Purpose: The aim of this study was to assess the prevalence of laryngeal involvement in RA patients, and thus, to increase the awareness of this condition among rheumatologists and otolaryngologists.

Method: A total of 82 subjects with non-smoker, consisting of 42 patients with RA and 40 non-RA patients in the control group, were enrolled in this study. The laryngeal symptoms such as dysphonia, vocal fatigue, foreign body sensation, coughing, dryness, dyspnea, and stridor were assessed in all patients. These patients were screened for laryngeal abnormalities using flexible Nasopharyngolaryngoscope (NFL).

Results: The mean age was 51.7 ± 10.5 years in RA group and 53.8 ± 10.1 years in control group. Concerning laryngeal symptoms, 61.9% patients reported at least one symptom in RA group, 37.5% in the control group. There was a statistically significant difference in the prevalence of coughing, dryness, foreign body sensation and dsypnea among patients with RA versus controls (respectively 42.9% vs. 17.5%, 31% vs. 2.5%, 28.6% vs. 7.5%, 9.5% vs. 0%). The prevalence of NFL alterations was 57.1% in RA patients and 30% in the control group. In RA group, the arytenoid and interarytenoid inflammation were higher compared with control (respectively 50% vs. 12.5%, 54.8% vs. 22.5%).

Discussion: The laryngeal involvement in RA is very common and critical because it can lead to life-threatening conditions such as airway obstruction. Therefore, early diagnosis has utmost important. We suggest that both the rheumatologists and the otolaryngologists should certainly evaluate the laryngeal symptoms, and moreover, they should get their patients laryngoscopic examinations are made periodically.

Keywords: Rheumatoid arthritis, Larynx, Cricoarytenoid joint, Laryngoscope, Dysphonia.

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Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that leads to extra articular involvement [1]. Laryngeal manifestations of RA were firstly described in cadavers at 1880's by Kenzie [2]. The first studies began in 1960 with randomly selected patients who underwent clinical and laryngoscopic assessment [3,4]. Laryngeal involvement of RA is critical because it can lead to life-threatening conditions such as airway obstruction [5-7]. The cricoarytenoid joint is the most frequently affected laryngeal area in RA [8]. Other laryngeal manifestations in RA are rheumatoid nodules in the vocal cords, secondary Sjogren's syndrome and amyloidosis [1,9]. The symptoms of the laryngeal involvement in RA can be listed as a sensation of a foreign body, vocal fatigue, dysphonia, cough, and dyspnea as it can also be asymptomatic [10].

The diagnosis of laryngeal involvement depends on clinical suspicion and is confirmed by laryngoscopic examination.

Laryngoscopy may reveal mucosal edema and diffuse or localized inflammation. Cricoarytenoid arthritis, interarytenoid fibrosis, fixation or impaired mobility of the vocal cords and nodule formation are also other laryngoscopy findings that can be observed in laryngeal involvement [1,10].

The laryngeal manifestations of RA, known for many years, have been overlooked in everyday clinical practice. The aim of this study was to assess the prevalence of laryngeal involvement in RA patients, and thus, to increase the awareness of this condition among rheumatologists and otolaryngologists.

Materials and Method

Method

A total of 82 subjects, consisting of 42 patients with RA in the study group and 40 non-RA patients in the control group, were enrolled in this study. The patients, who were diagnosed with

RA according to the American College of Rheumatology (ACR) criteria of 2010, were included in the study group [11]. The control group was composed of patients with gonarthrosis, coxarthrosis, and lumbar spondylosis, along with or without the laryngeal complaints. However, the patients with the diagnosis or suspicion of RA were excluded from the control group. Patients were excluded if they had undergone previous laryngeal surgery, had been actively smoking or had been suffering from cognitive impairment. The Ethics Committee of the University approved the study protocol, and the study was conducted in accordance with the Declaration of Helsinki.

Demographic data such as gender, age, and education level, together with the medications used, including disease-modifying drugs (DMARDs) and proton pump inhibitors (PPI) were recorded. In the study group, parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) were evaluated. The disease activity was assessed with disease activity score by using 28-joint Disease Activity Score (DAS-28). The patients were divided into three groups according to DAS28 scores as follows: mild (DAS28 \leq 3.2), moderate (3.2 < DAS28 \leq 5.1), and severe (DAS28 > 5.1). The laryngeal symptoms such as dysphonia, vocal fatigue, foreign body sensation, coughing, dryness, dyspnea, and stridor were assessed in all patients. Reflux symptoms were evaluated by using the Reflux Symptom Index (RSI) [12]. Patients were instructed to fill out the 9-item RSI on a rating scale ranging from 0 to 5, where 0 means no problems and 5 means a severe problem.

The laryngeal examination was performed by a flexible nasopharyngolaryngoscope (NFL) (Karl Storz, Germany) to detect arytenoid and interarytenoid inflammation, the mobility of the vocal cords, interarytenoid fibrosis, or the presence of laryngeal rheumatoid nodules. NFL is a minimally invasive clinical tool that allows the evaluation of the larynx [10].

SPSS-18 was used for statistical analyses. The results were expressed as mean \pm Standard Deviation (SD). Categorical data were analysed with the Chi-squared test. Correlations between the variables were estimated by Spearman's correlation coefficient method. For group comparison, we used t-test for continuous variables if normally distributed and Mann-Whitney U test if not normally distributed and chi-square test for categorical variables. All P values refer to two-sided tests; P values less than 0.05 were considered as significant.

Results

37 (88.1%) and 30 (90.0%) patients were female in RA group and control group, respectively. Mean age was found as 51.7 \pm 10.5 in the RA group, and 53.8 \pm 10.1 in the control group ($p > 0.05$). PPI use was present in 14 (33.3%) and 12 (30%) patients in RA group and control group, respectively ($p > 0.05$). RSI was calculated as 2.05 \pm 2.7 (range 0-15) in the RA group and 1.15 \pm 1.7 (range 0-6) in the control group ($p > 0.05$). The general characteristics of patients in RA group were

summarized in Table 1. The mean DAS-28 value was 3.41 \pm 0.9. The state of disease activity was remission state in 8.4% of patients, whereas it was mild, moderate and severe in 10.8%, 27.7%, and 3.6%, respectively. Laryngeal symptoms were present in 26 (61.9%) patients in RA group and 15 (37.5%) patients in the control group ($p < 0.05$). One patient in the RA group had the 6 of the symptoms (dysphonia, vocal fatigue, foreign body sensation, coughing, dryness and dyspnea) and one patient in the control group had 3 symptoms. Stridor wasn't reported in either group. The distribution of symptoms was shown in Table 2.

Table 1. Baseline characteristics of patients with Rheumatoid arthritis.

RA (n:42)	Mean \pm SD	N	%
Duration of disease (years)	6.2 \pm 6.3	-	-
RF	141.4 \pm 178.3	34	81.0
Anti-CCP	96.6 \pm 79.0	38	90.5
ESR	44.24 \pm 22.1	-	-
CRP	10.8 \pm 11.1	-	-
DAS-28	3.41 \pm 0.9	-	-
MTX	-	20	73.8
MTX+other DMARD	synthetic -	9	21.4
Other synthetic DMARD excluding MTX	-	8	19.0
Biological DMARD	-	5	11.9
Steroid usage	-	19	45.2

RF: Rheumatoid Factor; anti-CCP: anti-Cyclic Citrullinated Peptide; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protein; DAS-28: Disease Activity Score of 28 joints; MTX: Methotrexate; DMARD: Disease Modifying Drug.

The prevalence of NFL alterations was 57.1% in RA patients and 30% in the control group ($p < 0.05$). Only one patient with RA revealed a rheumatoid nodule. The patient was positive in terms of RF (Rheumatoid Factor) and anti-CCP (anti cyclicitruillated peptide) and was receiving methotrexate treatment. Four of the 16 patients who were asymptomatic were detected to have findings of NFL. The results of NFL were shown in Table 2.

Table 2. Laryngeal manifestations of rheumatoid arthritis.

Symptoms	Rheumatoid arthritis		Control		p
	n	%	n	%	
Dysphonia	15	35.7	10	25	**
Coughing	18	42.9	7	17.5	*
Dryness	13	31	1	2.5	*

Foreign body sensation	12	28.6	3	7.5	*
Vocal fatigue	4	9.5	4	10	**
Dyspnea	4	9.5	-	-	*
Findings of NFL					
Arytenoid inflammation	21	50	5	12.5	*
Interarytenoid inflammation	23	54.8	9	22.5	*
Abnormal vocal mobility	1	2.4	1	1	**
Interarytenoid fibrosis	1	2.4	2	5	**
NFL:Nasopharyngolaryngoscope; *: p<0.05, **: p>0.05.					

Laryngeal findings were significantly correlated with the symptoms (p<0.05). Laryngeal manifestations were not found as correlated with duration and activity of the disease, RF, and anti-CCP (p>0.05). RSI was correlated with NFL findings in the control group (p<0.05), but not in RA group (p>0.05).

Discussion

The laryngeal involvement in RA is a well-known entity for many years. However, its prevalence shows variations between 27% to 80.9% among studies [8-10,13-16]. In this study also, laryngeal symptoms were determined to be present in 61.9% of the patients. Different results of the studies may be due to methodological variables. For example, smoking patients were not excluded from the study or non-specific symptoms for laryngeal arthritis were taken into consideration during evaluation [9,10]. As well as the diversity of the results may be related to the laryngeal symptoms being present in a broad spectrum, from asymptomatic to dyspnea, during the clinical course of RA.

Most patients with laryngeal involvement have minor symptoms. The symptoms at onset are usually dysphonia, vocal fatigue, and foreign body sensation in the throat [9]. Dryness of the mouth, cough, dyspnea, and stridor might develop afterwards [17]. Rarely, it might lead to life-threatening airway obstruction [5]. In our cases, foreign body sensation, dryness, dyspnea, and cough were more frequent when compared to healthy subjects. But vocal fatigue and dysphonia which are the common symptoms were reported by patients from both groups at a similar rate. These symptoms may also occur due to reflux. For this reason, this result could be due to the lack of significant difference between the two groups in terms of RSI. Dyspnea which is significant findings of airway obstruction was detected only 4 cases (9.5%), in RA group. This ratio is lower than in previous studies [9,18]. Dyspnea is also the most common symptom of lung disease in RA [19]. Therefore the presence of dyspnea is considered pulmonary involvement in RA or pulmonary disease such as asthma or chronic obstructive pulmonary disease. However dyspnea is also evidence the laryngeal involvement of RA and the laryngoscopic evaluation should be performed in the presence. Stridor develops due to bilateral vocal cord paralysis and is usually manifested in severe cases [6]. In our cases, we did not encounter stridor. Dyspnea and stridor are very

significant findings indicating an airway obstruction particularly [5]. Therefore, in their presence, a detailed evaluation should be made.

The laryngeal involvement in RA can be subclinical [20]. Indeed, laryngeal involvement was detected in 4 of 16 patients who were asymptomatic in this study. Beinenstock determined laryngeal findings as similar to our results [3]. Grossmann reported that laryngeal involvement was present in 5 of 11 RA patients at post-mortem examination, and only 2 of them were symptomatic [21]. Miyahara stated that the laryngeal arthritis was aggravated and postoperative stridor developed following the surgery for wrist arthrodesis in a patient with RA [22]. Therefore, they suggested that the laryngeal evaluation should certainly be made in RA patients who are planned to undergo surgery, even though they are asymptomatic. The diagnosis of laryngeal involvement is not difficult, but it should be kept in mind that the symptoms might be obscured.

NFL is a non-invasive and valuable method for laryngeal evaluation [13,23]. In the acute phase, redness and swelling are usually observed in the arytenoid and interarytenoid areas in laryngoscopy. Vocal cords may be normal or oedematous. In the chronic phase, the findings are thickening of the arytenoid mucosa, narrowing of the glottic space, and various degrees of arytenoid fixation [10,13,24]. As the result of the laryngoscopic evaluation of our patients, particularly arytenoid and interarytenoid inflammation were observed more frequently in RA patients than the control group. Abnormal vocal cord movements and interarytenoid fibrosis were found in only one patient, individually. This situation is the indicator of our laryngeal findings being more likely the manifestations of the acute phase. However, it should be kept in mind that the laryngeal evaluation might reveal normal results in the very early period of the disease [8]. In this study, laryngoscopic findings were detected 57.1% of the cases with RA and this ratio was significantly higher than healthy group. The prevalence of laryngeal involvement in RA is highly variable between 26% to 72.3 [9,10,13, 25,26] in clinical studies and 45 % to 88% in post-mortem studies [7,9,17]. The difference in results is due to changes in the study design. Gomez-Puerta identified laryngoscopic findings in 67% of the cases; however, they did not use a control group [10]. While Beirith identified laryngoscopic findings in 72.3% of their cases, they found that this ratio was 65% in their control group. These high ratios, determined in both groups, might be related to nonspecific findings for RA, such as laryngitis, been taken into consideration during the evaluation. In addition, smoking patients were not excluded from the study, unlike as [9]. However, there is a correlation between smoking with laryngeal symptoms, especially dysphonia and laryngoscopic findings [26]. Therefore, the assessment of only non-smoker patients is very important as in our study.

Rheumatoid nodules are common extra-articular findings occurring in 20% RA patients. They are mostly found subcutaneously, but may occasionally develop in internal organ such as larynx [1,8]. Rheumatoid nodule might be formed due to the disease itself or the methotrexate usage and are found

mainly in seropositive RA [2,27,28]. In our study, the rheumatoid nodule was determined in only one patient. This case was a seropositive patient on methotrexate treatment and had complaints of dyspnea, foreign body sensation, dryness, and cough. Sjogren's syndrome is the other laryngeal finding that can be encountered in RA. The dryness and foreign body sensation are the most frequent symptoms in Sjogren's syndrome as in our RA patients [9,10]. Therefore we thought that a secondary Sjogren's syndrome might have contributed in these symptoms. Amyloidosis secondary to RA is also a rare cause of laryngeal manifestation [1].

Reflux is frequently encountered in RA patients due to the administered medications [30]. It might also cause various laryngeal problems. In this study, RSI was not found to be different in RA patients when compared to the control group, and no correlation was determined between RSI and laryngoscopic findings. This situation is an indicator of that the laryngeal problems did not have any relation with reflux. In the studies in which relation was found to be present between relations was found to be present between laryngeal symptoms and reflux, the findings not specific for RA were generally taken into consideration during evaluation [9]. We determined a significant correlation between RSI and laryngeal findings in our control group. Therefore, we considered that the laryngeal pathologies identified in the control group might have been related to reflux.

Although laryngeal involvement has been described to be more likely present in RA patients with disease duration longer than ten years in the literature, the long duration of the disease is not a risk factor regarding the laryngeal involvement [9]. In our study, the disease duration was not found to be correlated with the laryngeal involvement as in the previously conducted studies [3,6]. No correlations were found to be present between the NFL findings and disease activity, CRP, and anti-CCP, similar to the study carried out by Gómez-Puerta [10]. Briefly stated, there is no parameter that may cause us to suspect laryngeal involvement in RA.

Since the laryngeal symptoms may be quite variable in RA, they might easily be overlooked. Cases or case series who were admitted with acute airway obstruction have been reported in the literature [5-7]. Therefore, making the diagnosis before the laryngeal involvement becomes chronic and leads to life-threatening conditions such as airway obstruction has utmost importance. The essential issue in diagnosis is being suspicious and identifying the pathology by a simple laryngoscopic evaluation. In clinical practice, the other joints are brought to the forefront, and the laryngeal evaluation is usually ignored in RA patients. As a conclusion, we suggest that both the rheumatologists and the otolaryngologists should certainly evaluate the laryngeal symptoms, and moreover, they should get their patients laryngoscopic examinations are made periodically.

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