Assessment of pulmonary function in rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi

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Abstract

Background: Pulmonary involvement is a frequent and among the most severe extra-articular manifestations of Rheumatoid Arthritis (RA) ranking as the second cause of mortality in this patient population. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10-20% of all mortality in RA patients. Spirometry is becoming increasingly available in Kenya and could be used in peripheral areas to screen and monitor for pulmonary function abnormalities in well characterized patient populations such as those with RA. Abnormalities detected by pulmonary function tests may precede symptoms by years and lead to early diagnosis of pulmonary fibrosis in rheumatoid arthritis and hence intervention.

***Objective*:** To determine the prevalence of pulmonary function abnormalities in rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi.

Design: Cross sectional descriptive study.

Setting: Nairobi Rheumatology Clinics in Kenyatta National Hospital, Aga Khan University Hospital and Mater Hospital.

Methods: Rheumatoid arthritis patients aged 13 to 65 years who fulfilled the study inclusion criteria were recruited. Sociodemographic characterictics and respiratory symptoms were assessed using Lung Tissue Research Consortium questionnaire (LTRC) and RA disease activity was established by Disease Activity Score (DAS28). Pulmonary function tests were then done using Spirolab 111 according to the American Thoracic Society recommendations.

Results: One hundred and sixty six RA patients were recruited; the male to female ratio was 1:9.3, with a median age of 47 years. The overall six month prevalence of pulmonary function abnormalities was 38.5% as measured by Spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was obstructive pattern at 20.4%, followed by restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. Factors that were shown to be independently associated with pulmonary function abnormalities were age and RA disease activity. Respiratory symptoms that were predictive of PFTs abnormalities were cough, increased frequency of chest colds and illnesses and phlegm.

Conclusion: High prevalence of pulmonary function abnormalities was observed. Respiratory symptoms, older age and ongoing disease activity can identify patients in greatest need of further pulmonary evaluation.

Key words : Rheumatoid Arthritis, Pulmonary function test, Nairobi Rheumatology Clinics

Introduction

Rheumatoid Arthritis (RA) is the most commonly encountered connective tissue disease. It is a chronic inflammatory and systemic disease which mostly affects the synovial joints with a prevalence ranging from 0.5% to 2%. It is a progressive autoimmune process characterized by symmetrical erosive synovitis. Although the central pathology of RA develops within the synovium of diarthrodial joints, many nonarticular organs become involved, particularly in patients with severe joint disease. The female to male ratio of RA is 2.5:1 most frequently seen in the 25-55 years age group[1]. In recent cohort studies, nearly 40% of patients with RA suffered from some type of extra-articular manifestations[2-4]. Extra-articular manifestations can be detected in almost all organ systems as cutaneous, ocular, haematological, cardiovascular and pulmonary lesions[4].

Pulmonary involvement is a frequent and among the most severe extra-articular manifestation of RA[5]. It is a leading cause of excess death in patients with RA and the second cause of death in this patient population[6,7]. Pulmonary complications are directly responsible for 10 to 20% of all mortality[8,9]. When compared with control populations, patients with RA and with a respiratory disease have an

estimated standardized mortality ratio that ranges from 2.5 to 5.0[6,9]. The majority of lung disease occurs within the first 5 years after the initial diagnosis, and may be a presenting manifestation in 9 to 20% of patients. The onset of respiratory manifestation may even precede the onset of symptoms of arthritis.

Lung disease directly associated with the underlying RA is more common, even though pulmonary infection and drug toxicity are frequent complications of RA. The lung is involved in rheumatoid disease because of the abundant vasculature and connective tissue which is involved in collagen vascular diseases. RA can affect the lung parenchyma, airways, and the pleura, with variable amounts of pathological inflammation and fibrosis. The well-characterized pulmonary disorders in RA include: RA-associated Interstitial Lung Disease (ILD), pleural effusions and pleuritis, rheumatoid nodules, Caplans syndrome, pulmonary vasculitis and pulmonary airway involvement. Bronchiectasis and an increased incidence of chest infections have also been reported[10,11].

The prevalence of a particular complication varies based on: The characteristics of the population studied, the definition of lung disease used and the sensitivity of the clinical investigations employed. However, all studies concur in that a high prevalence of abnormality can be found. Furthermore, while the prevalence of other serious extra-articular manifestations is declining, RA-associated lung disease is increasing[13] both pulmonary infection and drug-induced lung disease included[14,15]. In the USA, a study done in John Hopkins University by Pappas *et al*[16] on 159 RA patients, found a 28% prevalence of pulmonary function abnormalities on spirometry. The most common ventilatory defect was obstructive at 11.3%, restrictive pattern was observed in 7.6% and an isolated impaired diffusing capacity of carbon monoxide in 9.6%. He identified factors such as seropositivity to rheumatoid factor, high titres of Anti-cyclic citrulinated peptide antibodies and ongoing corticosteroid use and some respiratory symptoms as predictive of abnormalities on spirometry.

The aim of this study was to determine the prevalence of pulmonary function abnormalities in RA patients and certain correlates (clinical and demographic) in rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi.

Materials and Methods

This was a cross sectional descriptive study, done in three Rheumatology Clinics in Nairobi; Kenyatta National Hospital, Aga Khan University Hospital and Mater Hospital. Patients included in the study were above 13 years of age, confirmed to have RA as per ACR criteria and gave an informed consent. Those excluded were patients with documented active pulmonary lesions e.g pulmonary tuberculosis, pneumonia, asthma, COPD, patients who had documented cardiac disease and those with contraindications to spirometry. These patients were seen during the period September 2012 to February 2013. A total of 166 patients were recruited and tested for pulmonary function using spirometry according to the American Thoracic Society standards disease activity of RA was scored using (DAS 28) and respiratory symptoms evaluated by Lung Tissue Research Consortium questionnaire.

Results

Out of the 166 patients recruited, 150 (90.4%) were females and 16 (9.6%) were males with a ratio of 1: 9.3. Their ages ranged from 14 to 65 years with a mean of 47±13years. Rheumatoid factor was positive in 104 (62.7%) and negative in 62 (37.3%). The median duration of RA illness was 5 years, ranging from 4 to 10. Patients who were on DMARDs were 129 (78%), 36 (21.7%) were on steroids, while 27 (16.2%) patients were on NSAIDS. The mean DAS28 score was 3.68 ± 1.5 with a range of 1.5-7.6. Prevalence of pulmonary function abnormalities as measured by spirometry was 38.5%. The common ventilator defect was obstructive pattern at 20.4%, followed by restrictive pattern at 16.8% and then 1.2% with a mixed obstructive and restrictive ventilatory defect (Table 1).

Table 1: Prevalence of PFTs abnormalities with confidence intervals

Prevalence	No. (%)	95% CI of %	Median measurements
Normal	102 (61.4)	53.0-68.1	-
Pulmonary function abnormalities	64 (38.5)	31.9- 47.0	-
Obstructive	34 (20.4)	15.7- 28.3	FEV1/FVC 65%
Restrictive	28 (16.9)	11.4- 22.9	FVC 71%
Mixed	2 (1.2)	0.0- 2.4	-

Certain demographic and clinical factors were observed to be associated with pulmonary function abnormalities in this patient population. Those who showed abnormalities on PFT were significantly older in age; a mean age of 51 years for those who had pulmonary function abnormalities compared with 44.5 years with normal spirometry (p=0.003). Among RA features, the variables shown to be associated with pulmonary involvement were seropositivity to rheumatoid factor, 47 out of the 64 patients with PFT abnormalities had positive rheumatoid factors (p= 0.03). Fifty six patients with DAS 28 score of 3.2 to 7.6, depicting moderate to high disease activity, were observed to have abnormalities compared to 25 who had mild disease activity (p=0.001). The ESR median value of 36.1 had abnormal spirometry compared with those at 11 who had normal (p=0.001). DMARDs or steroids medications did not show any relationship to the outcome (p= 0.907, p=0.970 respectively) (Table 2).

Table 2: Comparison of patients with PFTs abnormalities and those with normal tests

Variable	PF abnormalities	Normal	OR (95% CI)	P value
Sex				
Male	5 (7.7)	12 (10.9)	0.65 (0.2-2.1)	0.495
Female	59 (92.3)	90 (89.1)	1.0	
Age	51.0 (12.6)	44.5 (14.2)	-	0.003
Duration of illness (years)	5.0 (4.0-10.0)	5.0 (3.0-10.0)	-	0.168
Rheumatoid factor				
Positive	47 (72.3)	57 (56.4)	2.0 (1.0-3.9)	0.039
Negative	18 (27.7)	44 (43.6)	1.0	
Smoking				
Yes	8 (12.3)	10 (9.9)	1.3 (0.5-3.4)	0.626
No	56 (87.7)	92 (90.1)	1.0	
Smoking history				
Yes	4 (6.2)	2 (2.0)	3.3 (0.6-18.3)	0.211
No	60 (93.8)	100 (98.0)	1.0	
Disease activity				
Moderate to high dse activity (3.2-7.6)	56 (69.2)	6 (7.0)	29.5(11.9-76.7)	<0.001
Mild to no disease activity (1.5-3.1)	25 (30.8)	79 (92.9)	1.0	
ESR	36.1 (19.8)	11.0 (9.2)	-	<0.001
Medications				
Methotrexate				0.248
Yes	34(52.3%)	62(61.4%)	0.7 (0.4-1.30)	
No	30(47.7%)	38(38.6%)		
HCQ+MTX				
Yes	10(15.6%)	15(14.7%)	1.0 (0.5-1.8)	0.907
No	54(84.4%)	87(85.2%)		
Prednisolone				
Yes	14(21.5%)	22(21.8%)	1.0 (0.5-2.1)	0.970
No	50(78.5%)	80(78.2%)		
Occupation				
Unemployed	33 (50.8)	31 (30.7)	2.4 (1.2-5.2)	0.020
Formal employment	17 (26.2)	39 (38.6)	1.0	
Business	6 (9.2)	18 (12.9)	1.1 (0.3-3.3)	0.921
Farming	8 (12.3)	14 (13.9)	1.3 (0.5-3.7)	0.609

Table 3: Associations between respiratory symptoms and pulmonary abnormalities

Variable	PFT	Normal	OR (95% CI)	P value
Cough				
Yes	36 (56.3%)	19 (18.7%)	5.6 (2.8-11.5)	<0.001
No	28 (43.7%)	83 (81.3%)	1.0	
Phlegm				
Yes	20 (31.0%)	6 (6.8%)	7.1 (2.6-18.7)	<0.001
No	44 (69.0%)	96 (93.2%)	1.0	
Wheeze				
Yes	3 (4.6%)	3 (2.9%)	1.6 (0.5-5.2)	0.352
No	61 (95.4%)	99 (97.1%)	1.0	
Breathlessness				
Yes	1 (1.5%)	3 (3.0%)	0.5 (0.1-5.0)	1.000
No	63 (98.5%)	99 (97.0%)	1.0	
Frequency of chest colds				
Less than once a year	11 (17.2%)	43 (41.2%)	1.0	
Once a year	11 (17.2%)	24 (22.7%)	1.8 (0.7-4.9)	0.234
2-4 times per year	32 (50.0%)	29 (29.9%)	4.0 (1.7-9.3)	0.001
5 or more times per year	10 (15.6%)	6 (6.2%)	6.1 (1.8-20.4)	0.004

As regards respiratory symptoms, cough was reported in 36 (56.3%) patients with abnormal spirometry compared with 19 who had normal (p= 0.001), phlegm was reported by 20 (31.0%) such patients compared with 6 patients (p= 0.001). A history of increased frequency of chest colds and chest illnesses (> 2 times in a year) was reported by 32 (50%) patients with pulmonary involvement compared with 20 who had normal test (p=0.001). Hence respiratory symptoms observed to be associated with PFTs abnormalities were cough, production of phlegm and frequency of chest colds (Table 3).

Discussion

The overall six month prevalence of pulmonary function abnormalities was 38.5% as measured by spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was obstructive pattern at 20.4%, followed by restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. When evaluation of severity was done majority of these patients had mild defects (83.3% in the obstructive pattern and 60.7% in the restrictive).

A study done by Pappas *et al*[16] in John Hopkins University in the United States of America found a prevalence of pulmonary function abnormalities at 28%, nearly a third of the patients he studied, commonest being obstructive pattern at 11.3%, followed by restrictive at 7.6%. He also identified 9.6% with an impaired DLCO. Notably is that the patients studied had a lower disease activity score at a median of 3.1 compared to our study which was at 3.68, depicting that our patients were symptomatic for RA and still had active disease. It has been shown pulmonary involvement is higher in the setting of severe RA disease.

In Africa, Amir *et al*[17] studied 36 RA Egyptian patients and 64% of them demonstrated abnormalities in their pulmonary function tests, Mixed restrictive and obstructive pattern was commonest and reported in 11(30.6%), restrictive pattern at 8(22.2%) and obstructive pattern in 4 (11.1%). The mean disease activity score in his study was 3.63, almost similar to ours, hence the high prevalence of pulmonary impairment but differed in the patterns observed. His study excluded patients who had been exposed to cigarette smoking, since smoking has been shown to be the most consistent independent risk factor predicting the development of ILD in RA in most studies[11]. This could explain the lower incidence of obstructive pattern in his study as compared to our study which included 24 patients exposed to cigarette smoking. The present study found the prevalence of obstructive ventilatory defect to be the most common at 20.4%. This was an important finding since other studies have solely set out to find the prevalence of obstructive dysfunction in small airways in RA.

In France, Thierry *et al*[18] found an obstructive pattern of lung changes in 18% of RA patients using spirometry. He found no significant difference in the proportion of airflow obstruction among smokers and non smokers suggesting a minor role of tobacco smoke in such manifestations. This was also observed in our study where exposure to cigarette smoke had no relationship with the outcome (p=0.626), though we only had a small number of our patients exposed to cigarette smoking. A case control study by Vergnenegre *et al* [19] reported a 16% prevalence of airway obstruction (verses 0% in matched controls). A recent one by Shunsuke *et al*[20] found this to be 30.3%, after excluding 18% of the patients who had abnormalities in their HRCT indicative of interstitial lung disease. However, he included a significant number of smokers.

The reason for the high prevalence of PFTs abnormalities in our study is possibly due to ongoing RA disease activity. However the study took place in sub-Saharan Africa where environmental pollution and the use of biomass as fuel is common. These are known to cause deterioration in the physiological lung function and

though not assessed in our study, may have contributed to our results.

From this study, older age was shown to be associated with pulmonary abnormalities (p = 0.010), the mean age of those affected was 51 years compared to 44 with normal tests. On the other hand, we could not get any conclusion regarding sex of the patients since we only included 16 male patients. Exposure to cigarette smoking, though depicted, showed no relationship to outcome, other factors that were shown to associate with function abnormalities were seropositivity to rheumatoid factor (p=0.039) unemployment (p=0.02), moderate to high score on disease activity (p=<0.001) and ESR (p=0.001). These potentially significant parameters were tested for possible interrelationship by logistic regression analysis. Age remained an independent factor, the older the patient the more likely she had pulmonary involvement (p=0.010). Presence of disease activity as measured by DAS 28; clinical index of joint tenderness and swelling, also remained an independent factor. Patients who had a high and moderate score were more likely to have abnormalities in their tests (P = 0.025).

These findings are comparable to Amir *et al*[17] who observed that pulmonary abnormalities by PFT or HRCT were associated with older age and the RA clinical features that proved to associate with pulmonary involvement were joint tenderness index, duration of morning stiffness, and clinical disease severity. Pappas *et al* [16] did not find any age correlation, but observed that seropositivity to rheumatoid factor, presence of high titres of anti CCP antibodies and ongoing steroid therapy were associated with abnormalities in pulmonary function and identified patients in need of further pulmonary evaluation. These could well infer that symptomatic RA disease and/or disease severity was associated with pulmonary involvement because these are serological markers of disease activity hence supporting our findings. We did not evaluate for disease severity with the use of radiological score (hand and feet X-rays) or serology markers such as anti-CCP as these studies did, instead we used the disease activity score.

As might be expected, respiratory symptoms were statistically more significant in patients with abnormal PFTs. Presence of cough in 56.9% (P=0.001), increased number of chest colds in a year (2-4 times a year) reported by 50% (p=0.001) and production of phlegm by 30.8% were found to be significant. Receiver Operator Characteristic (ROC) curve was constructed to examine the ability of pulmonary symptoms to predict PFTs abnormalities. Area under the curve values for cough was 0.70, frequency of chest colds in a year 0.67, and production of phlegm 0.63 hence these symptoms were found to be predictive.

Our findings were in contrast with Amir *et al*[17] who among respiratory symptoms, dyspnea and cough were associated with any pulmonary abnormalities. He went further to elucidate that when specific pulmonary abnormalities were considered, dyspnoea was identified as predictor for restrictive pattern and for obstructive, both cough and wheezing provided valid prediction. Pappas *et al*[16] found chronic cough was predictive of obstructive pattern, breathlessness for restrictive and chronic phlegm for impaired gas transfer.

The different environments where each study took place could explain these findings. Our study was in the African tropics where the climatic conditions, environmental pollution and presence of communicable diseases may predispose the patients to experience frequent chest colds and illnesses in a year.

Conclusion

We observed a high prevalence of pulmonary function abnormalities as measured by spirometry in this RA population. The commonest ventilator defect pattern was obstructive followed by restrictive. In terms of severity most of the ventilatory defects were mild. There was an increased frequency of reported respiratory symptoms in RA patients with abnormal tests. Rheumatoid disease activity, older age and respiratory symptoms were identified as predictors of lung impairment as determined by spirometry.

Limitations

The study had the following limitations;

(i) PFTs are not the gold standard for detecting respiratory disease. We chose to use PFTs as our marker of lung disease in this analysis as they provide a common and low-risk diagnostic modality that often precedes radiographic evaluation in clinical practice.

(ii) Recruitment of patients from a university hospital rheumatology department could introduce some bias through selection of patients with somewhat more severe articular involvement than that in the overall RA population.

Recommendations

Pulmonary involvement is an important part of the systemic affection of RA. The role of surveillance for lung disease in patients with RA is clear and necessary. Rheumatologists and internists should routinely screen patients for early detection and intervention. Respiratory symptoms, older age and ongoing disease activity can identify patients in greatest need of further pulmonary workup.

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