



PREVALENCE OF EXTRA-ARTICULAR MANIFESTATIONS IN ADULT RHEUMATOID ARTHRITIS PATIENTS AND CORRELATION WITH DISEASE ACTIVITY AND DURATION.

General Medicine

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease involving the peripheral joints in a symmetric distribution. The extra-articular manifestations of Rheumatoid arthritis have a major role as predictors of premature mortality in patients with the disease. The objective of the study was to determine the prevalence of extra-articular manifestations in adult Rheumatoid arthritis patients and correlation with disease activity and duration. **Materials and Methods:** A cross sectional study conducted among 80 patients diagnosed with Rheumatoid arthritis, attending Rheumatology OPD, Medicine OPD and wards of Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur over a period of 2 years from October 2019 to September 2021. The diagnosis of Rheumatoid arthritis was made according to the 2010 ACR-EULAR (American college of Rheumatology/European League against Rheumatism) Classification Criteria. **Result:** The prevalence of extra-articular manifestation in Rheumatoid arthritis was found to be 78.7% in the study population. The mean age was 49.66±11.68 years and preponderance of female gender (76.2%) to rheumatoid arthritis was evident. The most common extra-articular manifestation was haematological manifestations seen in 33.8% of the study subjects. 41.3% patients had existing disease duration between one year to five years. The cases with high positive rheumatoid factor had 7 times more odds of developing extra-articular manifestations. **Conclusion:** The study concluded that increased Disease activity score 28 (DAS28), duration of disease and high positive rheumatoid factor levels were significant predictors of extra-articular manifestations in adult patients of Rheumatoid arthritis.

KEYWORDS

Rheumatoid arthritis, extra-articular manifestation, DAS 28, rheumatoid factor levels

INTRODUCTION

Rheumatoid arthritis is a chronic systemic inflammatory disease affecting women two to three times more than men.¹ The characteristic feature of Rheumatoid arthritis is a persistent inflammatory synovitis involving the peripheral joints in a symmetric distribution. The potential of synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in the joint integrity is the hallmark of the disease.² The earliest involved joints are typically the small joints of the hands and feet and early morning joint stiffness lasting more than 1 hour that eases with physical activity.³ Rheumatoid arthritis is associated with a spectrum of extra-articular manifestations more frequently seen in seropositive patients and associated with severe active disease and higher mortality.^{4,5} Associated constitutional factors are male gender, HLA-related shared epitope genes, autoantibodies such as rheumatoid factor (RF), antinuclear antibodies (ANA) and anti-cyclic citrullinated peptide antibody (anti-CCP) and environmental factors such as smoking.⁶ Due to the systemic inflammatory process, the incidence of mortality in Rheumatoid arthritis is increased by four-fold compared with the general population.⁶ This study was conducted with the objective to study the prevalence of extra-articular manifestations and correlation with disease activity in patients of Rheumatoid Arthritis in North-eastern part of India.

MATERIALS AND METHOD

Study design:

A cross sectional study was done in Rheumatology Outpatient Department, Medicine Outpatient Department and inpatient wards of Department of Medicine, Regional Institute of Medical Sciences Imphal. The study period was for 2 years from October 2019 to September 2021. The objective of the study was to determine the prevalence of extra-articular manifestations in adult Rheumatoid arthritis patients and its correlation with disease activity and duration.

Inclusion criteria:

Patients aged above 18 years who gave consent for participation in the study and diagnosed with Rheumatoid arthritis according to the 2010 ACR-EULAR (American college of Rheumatology/European League against Rheumatism) Classification Criteria.

Exclusion criteria:

Patients diagnosed with Rheumatoid arthritis but not willing to participate in the study.

Independent variables: Age, Gender, Occupation

Dependent variables:

Extra Articular manifestations of Rheumatoid arthritis, Eye manifestations, Rheumatoid nodules, Pulmonary disease, Cardiac disease, Renal disease, Haematologic manifestations, Felty's Syndrome, Vasculitis.

Procedure:

The patients were subjected to history taking and complete physical examination with emphasis on the disease activity and duration. The diagnosis of rheumatoid arthritis was made using the 2010 ACR-EULAR (American college of Rheumatology/European League against Rheumatism) Classification Criteria. The disease severity calculation was done using the disease activity score 28 (DAS 28 score).⁷ The diagnosis of extra articular manifestations was made accordingly as Rheumatoid nodules: subcutaneous nodules with a diameter >5 mm in extensor surface of extremities and fingers. Secondary Sjögren's syndrome: presence of Rheumatoid arthritis plus xerophthalmia and/or xerostomia, both objective and subjective. Interstitial lung disease: confirmed either by restrictive pattern or decrease in transfer factor for carbon monoxide (TLCO) or carbon monoxide transfer coefficient (KCO) in pulmonary function tests or by high resolution CT scan. Felty's syndrome: Neutropenia ($<1.8 \times 10^9$ neutrophils/l) plus splenomegaly (documented by ultrasound) without another cause in a patient with Rheumatoid arthritis. The serological

test included Complete blood count, Erythrocyte Sedimentation Rate, Rheumatoid Factor, Anti-CCP, C-Reactive Protein, Liver Function Test, Blood Sugar and Urine Examination. The other diagnostic test included Chest X-Ray, Ultrasonogram abdomen, Electrocardiogram, Fundus examination, Schirmer's test, Tear break-up time and miscellaneous test as required.

Statistical analyses:

The data collected was analyzed using Statistical Package for Social Sciences software namely SPSS 23.0, Microsoft word and Excel were used to generate graphs, tables etc. Descriptive and inferential statistical analysis was used. Chi square test was used to see the association between extra-articular manifestation and disease duration. Binary logistic regression was used to analyse the association between Disease activity score 28 (DAS28) and gender, age groups, disease duration, etc. A p-value < 0.05 was considered as significant.

Ethical Clearance:

The study was carried out after obtaining ethical approval from the Research Ethics Board, Regional Institute of Medical Sciences, Imphal vide letter no. A/206/REB-Comm(SP)/RIMS/ 2015/561/ 39/2019. Through out the study privacy and confidentiality was maintained at all cost for each participant by coding of patient's data. The data collected was documented and analysed statistically to draw a useful conclusion.

RESULTS

Table 1. Baseline characteristics of the study population.

Characteristics	Frequency n(%)
Age group (in years)	
Less than 46	32(40%)
46 - 60	31 (38.7%)
More than 60	17(21.3%)
Gender	
Male	19 (23.8%)
Female	61 (76.2%)
Constitutional symptoms (fatigue,malaise)	
Present	32 (40%)
Absent	48 (60%)
Morning stiffness	
<1 hour	19 (23.8%)
>1 hour	47 (58.7%)
Absent	14 (17.5%)
Duration of disease	
<1 years	28 (35%)
1-5 years	33 (41.2%)
>5 years	19 (23.8%)
Disease activity score 28 (DAS28)	
Remission (<2.6)	9 (11.2%)
Mild (2.6-3.1)	4 (5.0%)
Moderate (3.2-5.1)	20 (25%)
Severe (>5.1)	47 (58.8%)
Deformity	
Present	11 (13.8%)
Absent	69 (86.2%)
Extra articular manifestation	
Cardiac manifestations	
Pulmonary arterial hypertension	2 (2.5%)
Pericardial effusion	1 (1.3%)
None	77 (96.2%)
Lung manifestations	
Pleural effusion	3 (3.75%)
Interstitial lung disease	3 (3.75%)
None	74 (92.5%)
Skin manifestation	
Rheumatoid nodule	6 (7.5%)
Raynaud's phenomenon	3 (3.8%)
Leg ulcers	1 (1.3%)
No manifestation	70 (87.4%)

Eye manifestation	
Dry eye	16 (20%)
Episcleritis	01 (1.3%)
None	63 (78.7%)
Haematological manifestation	
Anemia of chronic disease	15 (18.8%)
Iron deficiency anemia	05 (6.2%)
Thrombocytosis	04 (5.0%)
Thrombocytopenia	02 (2.5%)
Eosinophilia	01 (1.3%)
No manifestation	53 (66.2%)
Rheumatoid factor	
Highly positive	32 (40%)
Low positive	40 (50%)
Negative	8 (10%)
Anti-citrullinated Protein Antibody	
Highly positive	31 (38.8%)
Low positive	34 (42.4%)
Negative	15 (18.8%)

The baseline characteristics of the study population are listed in Table 1. In this study, a total of 80 patients with rheumatoid arthritis were enrolled. The mean age of the study population was 49.66±11.68 years with a preponderance for the female gender. 41.3% of the patients had disease duration between 1 year to 5 years. The prevalence of extra-articular manifestation in the study population was 78.7%, with haematological manifestations accounting for one third (33.8%) of the patients. Anti-citrullinated Protein Antibody and rheumatoid factor was positive in 81.2% and 90% of the study population respectively. In our study we noted that increased Disease activity score 28 (DAS28) score, increased duration of disease and high positive rheumatoid factor levels were found to be significant predictors of extra-articular manifestations.

Table 2. Logistic regression analysis for various variables and Extra-articular manifestations

Variables	Odds Ratio	95% CI	p-value
Age Groups (in years)			
<46	1 (Reference)		
46-60	1.569	0.580-4.246	0.375
>60	3.683	0.986-13.765	0.053
Gender			
Male	1 (Reference)	0.345-2.777	0.968
Female	0.979		
DAS-28 Score			
Remission	1 (Reference)		
Mild	2.667	0.123-57.620	0.532
Moderate	9.778	1.023-93.496	<0.05*
Severe	18.857	2.151-165.291	<0.05*
Disease Duration (in years)			
<1 year	1 (Reference)		
1-5 years	3.150	1.103-8.993	<0.05*
>5 years	6.750	1.755-25.956	<0.05*
Rheumatoid Factor			
Negative	1 (Reference)		
High Positive	7.667	1.298-45.289	<0.05*
Low Positive	3.316	0.596-18.451	0.171

*Significant

On logistic regression analysis as listed in table 2, extra-articular manifestation with gender and age groups were not found to be statistically significant. Those who had severe and moderate score in DAS-28 had 18 times and 9 times more odds of developing extra-articular manifestation. Patients who had longer disease duration (>5 years and 1-5 years) had 6 times and 3 times more odds of developing extra-articular manifestation. Cases with high positive rheumatoid factor had 7 times more odds of developing extra-articular manifestations.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic,

autoimmune disease with an undefined etiology. The studies done on extra-articular Rheumatoid arthritis manifestations have emphasized their major role as predictors of premature mortality in patients with Rheumatoid arthritis.⁸ In our study among 80 patients of Rheumatoid arthritis the prevalence of extra-articular manifestation was 78.7%.⁹ The lack of consensus on the disease definitions of extra-articular manifestations may be the reason of discrepancy in the prevalence rate.¹⁰ In our study of Rheumatoid arthritis patients of age range from 20 years to 77 years, the mean age was 49.66±11.68 years. The majority of the patients belonged to the category of less than 46 years of age, indicating that rheumatoid arthritis dominantly affects the young and middle aged group. The preponderance of female gender to Rheumatoid arthritis was evident in our study.¹¹ The majority (41.2%) of the patients had disease duration between 1 year to 5 years.¹² The haematological manifestations were the most common extra-articular manifestation seen in the study where one third (33.8%) of the patients presented as anaemia of chronic disease, iron deficiency anaemia, thrombocytosis, thrombocytopenia and eosinophilia.¹² Ocular manifestations of rheumatoid arthritis presented both as sight and life threatening because of the association with systemic vasculitis.¹³ Anticitrullinated protein antibody was positive in 81.2% of the participants in both low positive levels and high positive levels. The presence of anti-citrullinated protein antibody is significantly associated with ocular manifestations and it is the most prevalent biomarker in Rheumatoid arthritis patients.¹⁴ The presence of anti-citrullinated protein antibody indicates more severe disease activity in patients of Rheumatoid arthritis so it has both diagnostic and prognostic value in the detection of extra-articular manifestations.¹⁵ The presence of rheumatoid nodules as the most common cutaneous manifestation correlates with the appearance of extra-articular manifestations of Rheumatoid arthritis and indicates a poor prognosis.¹² Rheumatoid arthritis increases the predisposition to cardiovascular diseases and acute ischemic events such as acute myocardial infarction upto four times.¹⁶ Individuals with the disease has higher risk for morbidity and premature death secondary to the early development of cardiovascular and lung diseases in Rheumatoid arthritis.¹⁷

In this study, increased Disease activity score 28 (DAS28), increased duration of disease and high positive rheumatoid factor levels were found to be significant predictors of extra-articular manifestations.¹⁸ There exist a significant association between smoking, early disability, age and rheumatoid factor of overall extra-articular manifestations.³

One of the strength of our study was employing a representative sample of population with rheumatoid arthritis, although the sample size could have been larger to generalize the whole population. In our study, less than one fourth of the patients had disease duration more than five years. According to some studies, certain forms of extra-articular manifestations develop late in the disease course, thus the prevalence of extra-articular manifestations could have been underestimated in our study. Nonetheless, the overall prevalence of extra-articular manifestations in our study falls within the broad range of extra-articular manifestations incidences and prevalence reported. Lastly, since this was a cross sectional study, to explore and confirm additional potential predictors and influential factors of extra-articular manifestations, further research through longitudinal study or clinical trials is recommended.

Authors contribution:

All authors contributed to the design, data collection, interpretation, literature review and manuscript preparation and journal selection for submission.

Conflict of Interest: Nil

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