

A cross-sectional study of association of serostatus and extra-articular manifestations in patients with rheumatoid arthritis in a teaching hospital

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease, which mistakenly attacks the joints and induces the inflammatory changes that thicken the joints (the synovium) resulting in swelling and pain in and around the joints. It causes pain, joint deformity, and also affects the quality of life. The joint is affected symmetrically. It also can affect body systems, such as the cardiovascular, respiratory systems, or other systems, which manifest as extra-articular manifestations. Extra-articular manifestations of RA are documented less in India hence this study was undertaken to correlate RA with extra-articular manifestations as well as its relationship with serostatus in patients with extra-articular manifestations. **Materials and Methods:** Sixty patients (age between 18–60 years) attending Medicine/Rheumatology outpatient department were included in the study (12 months) who fulfilled the 2010 RA classification criteria laid down by American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) for RA. All the subjects underwent a thorough history, clinical examination, and laboratory investigations. The relevant data were analyzed with appropriate statistical methods after 12 months' duration. **Results:** Nearly 68.33% of the subjects were found to have extra-articular manifestations mostly in the age group of 31–40 years with prevalence higher in the female. In the seropositive patients, early morning stiffness (EMS) constitutes 63.82% of the total extra-articular manifestations in the patients followed by anemia (38.29%) and peripheral neuropathy (34.04%). On the other hand, in the seronegative cases, EMS (61.53%) followed by anemia (23.07), peripheral neuropathy (15.38%), and keratoconjunctivitis sicca (15.38%). Extra-articular manifestations in seropositive patients have a statistically significant relationship with the increase in the duration of the disease. **Conclusion:** Extra-articular manifestations need to be looked carefully as it is associated with more severe disease. Seropositivity and extra-articular manifestations both usually indicate that the RA is more severe and may affect the quality of life.

Keywords: Extra-articular manifestations, rheumatoid arthritis, rheumatoid factor, seronegativity, seropositivity

Background

Rheumatoid arthritis (RA) is the most common cause of inflammatory arthritis affecting around 1% of the population of

India.^[1] The incidence in women is thrice than men worldwide.^[2] It is the leading cause of pain, disability, and poor quality of life.^[3] It has a complex history and affected by age of onset, gender, genotype, phenotype, and comorbid conditions.^[4–6] It is marked by symmetric peripheral polyarthritis with synovium being the primary target.^[7] The cause of RA remains unknown but the pathological mechanism of synovial inflammation may result due to complex interplay of genetic, immunologic, and environmental factors.^[6–9]

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Received: 16-01-2020

Revised: 12-03-2020

Accepted: 30-03-2020

Published: 30-06-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_99_20

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How to cite this article: Kumar B, Das MP, Misra AK. A cross-sectional study of association of serostatus and extra-articular manifestations in patients with rheumatoid arthritis in a teaching hospital. J Family Med Prim Care 2020;9:2789-93.

RA results in a variety of extra-articular manifestations including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematological abnormalities.^[10,11] It reduces lifespan by 5–10 years depending on the age of onset.^[12] Mortality and morbidity increase more with systemic extra-articular manifestation, male gender, rheumatoid factor positivity, chronic prednisone use, low socioeconomic status, low education, and low functional capacity. The objective of the study is to find out the incidence of extra-articular manifestations in relation to serostatus and correlation between serostatus with the duration of disease.

Materials and Methods

Study design

A prospective, observational, cross-sectional study was conducted in the Department of Medicine at a tertiary care teaching hospital. The duration of the study was 12 months. Adults (18–65 years of age) attending Medicine or Rheumatology outpatient department in a tertiary care teaching hospital. During the study period, the patients were included according to the 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria. Every patient with a total point of 6 or more is unequivocally classified as a RA patient provided he/she has synovitis in at least one joint and given that there is no other diagnosis better explaining the synovitis. Four areas are covered in the diagnosis.

Inclusion criteria

1. Joint involvement: Depending on the type and number of joints up to 5 points.
2. Serological parameters including the rheumatoid factors as well as anti-citrullinated protein antibody (ACPA) up to 3 points depending on titer level.
3. Acute phase reactants have 1 point for elevated erythrocyte sedimentation rate (ESR) or elevated C-reactive protein (CRP)
4. Duration of arthritis has 1 point for symptoms lasting six weeks or longer.

Exclusion criteria

1. Males and females less than 18 years of age.
2. Overlapping disease, e.g. systemic lupus erythematosus.
3. Patients above 60 years of age.
4. Patients suffering from diabetes mellitus.
5. Patients having pre-existing renal disease or urinary tract infection.
6. Patients having pre-existing hypertension.
7. Patients suffering from congestive cardiac failure.
8. Patients suffering from chronic liver disease.

Sample size

As this is a preliminary study formal sample size is not calculated. Keeping in mind the availability of patients, it is decided to include 60 patients (age between 18–60 years) attending Medicine or Rheumatology out-patient department for the study duration

of 12 months after approval from Ethics committee. Written informed consent was taken from all patients. In the case of the patient being incompetent, the primary caregiver staying with the patient will be approached for the same.

All the cases were subjected to a thorough history, clinical examination, and laboratory investigations. Patient's demographic data were collected at the time of visit to the Medicine/Rheumatology outpatient department.

Socio-demographic clinical profile data

A structured proforma was used to record certain demographic variables such as age, gender, education, occupation, religion, type of family, and the income of the patient and family. Blood routine examination, random blood sugar (RBS), serum creatinine, Blood urea nitrogen (BUN), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum uric acid, ESR, CRP, fasting lipid profile, iron profile, urine routine examination, rheumatoid factor were examined in all patients. Antinuclear antibody (ANA), anti-cyclic citrullinated peptide (CCP) antibody, chest X-Ray, joint X-Ray, ECG, ultrasound W/A, computed tomography (CT) Thorax, nerve conduction velocity test, and Echocardiography (ECHO) had been done in selected patients, if clinically needed.

Assessment of disease activity and damage was done as follows

1. Tender joint count: ACR tender joint counts include an assessment of 28 joints including PIPs ($n = 10$), MCPs ($n = 10$), Wrists ($n = 2$), Elbows ($n = 2$), Shoulders ($n = 2$), and Knees ($n = 2$)
2. Swollen joint count: To check for fluctuance of the swollen joints. ACR tender joint counts include an assessment of 28 joints mentioned above.
3. Patient's assessment of pain: A horizontal visual analog scale (usually 10 cm) is used for assessment of the patient's current level of pain.
4. Patient global assessment of disease activity: It was assessed for the patient's overall prognosis regarding arthritis. It was assessed according to an acceptable method for determination by asking the question from the arthritis impact management scale (AIMS).
5. Physician global assessment of disease activity: A visual analog scale (0-10 cm) measures the physician's global assessment of current disease activity.
6. Acute phase reactant value for ESR or CRP level.

Quantification of current disease activity

Disease activity score-28 (DAS28) combines single measure into an overall, continuous measure of RA disease activity. The use of a single index has advantages because of the simultaneous interpretation of several measures of RA disease activity, which includes 28 tender joints count, 28 swollen joint counts, erythrocyte sedimentation rate and general health

assessment on a visual analog scale. It can also calculate CRP instead of ESR.

Response Scale of 28 tender joints count (28TJC) and 28 swollen joint counts (28SJC) both range from 0 to 28. ESR may range from 0 to 150 and general health (GH) ranges from 0 to 100. The range of the DAS-28 is 0–9.4. The levels of RA disease activity can be interpreted as scoring of DAS-28. High disease activity if DAS is more than 5.1, low disease activity if DAS is less than 3.2, and remission if the score is less than 2.6. The EULAR response criteria are also based on the DAS-28 and are expressed in terms of both the change and the level of the DAS.

Ethical consideration

Ethical clearance was taken from the Institutional Ethical Committee with Ethical Clearance Certificate No. MC/100/2011/Pt-11/88.

Statistical analysis

Data were compiled using Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) Version 21. Quantitative variables were expressed as numbers and percentages. Normality distribution of data was first determined by Kolmogorov–Smirnov test. As data were found to be normally distributed, the parametric analysis was used throughout the analysis. Chi-square test was used to study the correlation between extra-articular and duration of the disease. *P* values of less than 0.05 were considered statistically significant for all tests.

Results

In the study, the prevalence of extra-articular manifestations in the total subjects was found to be 68.33%. The age at onset ranged from 19 to 65 years with a mean age of 42.07 ± 10.6 years. The maximum incidence was between 31–40 years (38.33%). The age of onset in females ranged from 19 to 60 years with a mean age of 39.18 years and in the male, the age of onset ranged from 28 to 65 years with a mean age of 50.73 years. The incidence of RA was found more in the females (nearly three-fourth) than that in males.

In the seropositive patients, EMS (63.82%) is the most prevalent extra-articular manifestations in the patients followed by anemia (38.29%), peripheral neuropathy (34.04%), muscular hypotrophy (27.65%) followed by other extra-articular manifestations. On the other hand, in the seronegative patients, EMS (63.33%) followed by anemia (23.07%), peripheral neuropathy (15.38%), and keratoconjunctivitis sicca (15.38%) [Table 1]. Extra-articular manifestations in seropositive patients have a statistically significant relation with the increase in the duration of the disease. As the duration of the disease is increased, the number of extra-articular manifestations increases [Table 2], [Figure 1]. It was found that the duration of the disease has a positive correlation with extra-articular symptoms with more than one symptom if the duration of

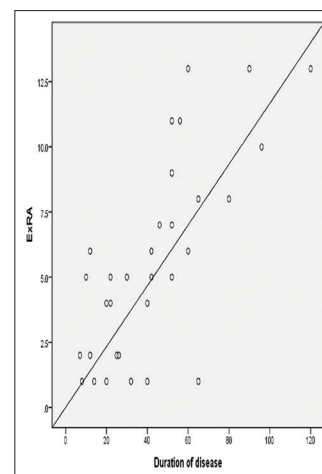


Figure 1: Correlation between number of ExRA and duration of disease (months) in SPRA. ExRA: Extra-articular manifestations of Rheumatoid Arthritis; SPRA: Seropositive Rheumatoid Arthritis

the disease was more than four years, especially in seropositive patients [Not shown in Table]. On the other hand, the correlation between duration of the disease and the number of extra-articular manifestations is not significant as the sample size is small as compared to seropositive cases [Table 2], [Figure 2].

Discussion

RA is a chronic multisystem disabling disease with various extra-articular manifestations frequently leading to physical and psychological dependence with considerable economic consequences, occurring in about 0.75% of the adult population in India. As there is a paucity of literature on the impact of extra-articular manifestations in RA in India, thus this study was undertaken to evaluate the extra-articular features and correlates with the duration of disease and serostatus.

In the study, the mean age at onset of RA was 42.07 years, which is similar to another study.^[13] In our study, it was found that females had a relatively earlier onset of the disease as compared to the male, which was in accordance with a study done in Karachi, Pakistan.^[14] Females had a higher incidence than males in the study, which was in accordance with two similar studies done in India.^[15,16] It was found that nearly 85% of females had an insidious onset.

Polyarthritides was the presenting symptom in all the cases mostly with EMS (63.3%) and deformity (16.66%), which was very similar to a study done in Kolkata, India.^[16] The mean duration was 32.7 months at presentation which is in accordance with a study done in Kathmandu, Nepal.^[17] The joint inflammation and muscle atrophy due to the disease reduces the range of motion of joints.^[18,19] Joint and tendon destruction may lead to deformities such as ulnar deviation, boutonniere, and swan-neck deformities, hammertoes and occasionally, joint ankyloses.^[3] The proposed inflammatory processes for the deformity are tenosynovitis, synovitis, synovium effusion, and synovial thickening.^[18]

Table 1: Extra-articular manifestation of RA with regard to sero-status

EA Features	SPRA		SNRA		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Anemia	18	38.29%	3	23.07%	21	35%
Fever	10	21.27%	0	0.0%	10	16.66%
Fatigue	11	23.40%	1	7.69%	12	20%
Deformity	8	17.02%	1	7.69%	9	15%
Rheumatoid Nodule	9	19.14%	1	7.69%	10	16.66%
Muscular Hypotrophy	13	27.65%	1	7.69%	14	23.33%
Osteoporosis	10	21.27%	1	7.69%	11	18.33%
EMS	30	63.82%	8	61.53%	38	63.33%
Felty Syndrome	0	0.0%	1	7.69%	1	1.66%
Hepatomegaly	5	10.63%	1	7.69%	6	10%
Splenomegaly	6	12.76%	0	0.0%	6	10%
Pleurisy	5	10.63%	1	7.69%	6	10%
ILD	5	10.63%	1	7.69%	6	10%
Pulmonary Fibrosis	1	2.12%	0	0.0%	1	1.66%
Pericarditis	3	6.38%	1	7.69%	4	6.66%
Cardiac Features	1	2.12%	0	0.0%	1	1.66%
Peripheral Neuropathy	16	34.04%	2	15.38%	18	30%
Cord Compression	1	2.12%	0	0.0%	1	1.66%
Episcleritis	5	10.63%	0	0.0%	5	8.33%
KCS	2	4.25%	2	15.38%	4	6.66%
SS	9	19.14%	1	7.69%	10	16.66%
Vasculitis	4	8.51%	0	0.0%	4	6.66%
Renal Cause	5	10.63%	1	7.69%	5	8.33%

EMS: Early Morning Stiffness; ILD: Interstitial lung disease; KCS: keratoconjunctivitis sicca; SS: Sjogren's syndrome

Table 2: Correlation between ExRA and duration of disease regarding sero-status.

ExRA	SPRA			SNRA			Total		
	Subjects (n)	Duration Percentage	Mean±SD	Subjects (n)	Duration Percentage	Mean±SD	Subjects (n)	Duration Percentage	Mean±SD
With									
ExRA	32	85.35	42.81±27.91	9	78.85	26.11±13.45	41	80.12	39.15±25.98
Without									
ExRA	15	14.65	22.27±11.06	4	21.15	15.75±8.18	19	19.88	20.89±10.66
	P=0.037			P=0.404			P=0.000		

ExRA: Extra-articular manifestations of Rheumatoid Arthritis; SPRA: Seropositive Rheumatoid Arthritis; SNRA: Seronegative Rheumatoid Arthritis

In our study, more than half of patients (68.33%) had one or more extra-articular manifestations with a high incidence of early morning stiffness (EMS) (63.33%) followed anemia (35%) followed by peripheral neuropathy (30%), muscular hypotrophy (23.33%), and fatigue (20%). These findings were very similar to those found in another study.^[13] Extra-articular manifestations of RA have a close association with inflammatory mediators like RF, CRF and also elevated levels of cytokines (tumour necrosis factor-alpha (TNF- α), Interleukin-1 (IL-1), and IL-6), and complement components (C1q, C3, and C4).^[19] These mediators play a direct pathogenic role in the development of these extra-articular manifestations.

In the study, nearly 78% of the patients were found to be seropositive, which was similar to multiple studies.^[15,20-22] It was found that patients with duration of disease of more than two years had more than one extra-articular manifestation, which was found statistically significant as compared to other

studies.^[13,22] It correlates well with the well-established facts that RA has a positive correlation with seropositivity due to the inflammatory pathogenesis of the diseases.^[11] This information will help to impart knowledge to the primary care physician to look for the extra-articular manifestations of RA and treat them as per their resource available in the primary care setting.

Conclusion

Extra-articular manifestations are present in a substantial number of RA patients, which is often overlooked or missed by the physician. Extra-articular manifestations are associated with more severe disease and the majority of them are more common in long-duration disease. Seropositivity also has a positive relationship with extra-articular manifestations and the presence of both usually indicates more severe disease. One of the limitations of the study was that the sample size is not large

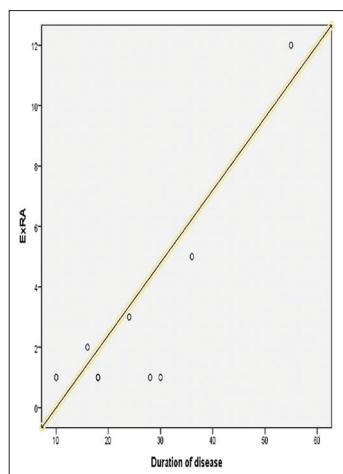


Figure 2: Correlation between number of ExRA and duration of disease (months) in SNRA. ExRA: Extra-articular manifestations of Rheumatoid Arthritis; SPRA: Seropositive Rheumatoid Arthritis

and also a large-scale study with a longer duration is needed to find out and further strengthen the correlations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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