Original Paper

RHEUMATOID ARTHRITIS: PATTERN AND PREVALENCE OF EXTRA-ARTICULAR MANIFESTATIONS- A PROSPECTIVE STUDY

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder which affects principally the joints producing a non-suppurative, proliferative and inflammatory synovitis. It is a systemic auto immune disease of unknown etiology. The disease often progresses to destruction of the articular cartilage and ankylosis of the joints leading to crippling deformities. The extact etiology is unknown, but it is assumed to be an auto immune disease. Individuals with HLA DR1 or HLA DR4 serotypes have an increased risk for developing the disease. RA may also affect a range of extra articular tissues and organs like skin, blood vessels, nerve, muscles, eye, oral cavity, lung, heart, kidney and haematopoietic tissue. There are periods of disease flares and remissions. Patients may experience long periods without symptoms.

Objectives: The aim of the study was to find out the pattern and prevalence of extra articular manifestations of Rheumatoid Arthritis.

Materials and Methods: This prospective study was conducted on 96 consecutive patients of Rheumatoid arthritis attending at Combined Military Hospital (CMH) Dhaka between Feb 2012 to Sept 2012. Respondents presenting with fulfilled diagnostic criteria of Rheumatoid arthritis were considered for the study. They were evaluated mainly highlighting the extra articular features.

Results: The mean age of the patients was 39+6.39 years with majority (88.54%) being female. Fever, fatigue, weight loss, anaemia were present in most of the patients. Eye dryness, foreign body sensation in the eye, and photo phobia were present in 72.9%, 67.7% and 78% cases respectively. There were Rheumatoid nodules in 8.3% cases, peripheral neuropathy in 26%, Interstitial lung diseases (ILD) in 2.08% & Raynaud's phenomenon in 8.3% cases. Almost all cases had aggravated symptoms at night & on exposure to cold weather.

Conclusion: RA as a chronic systemic auto immune disease has also got extra articular symptoms beside joint symptoms. Extra articular complications are mostly due to disease process and in a few cases as a complication of medications eg. osteoporosis from corticosteroid treatment and lung fibrosis from methotrexate treatment.

Key-words: Pattern and prevalence, extra articular manifestations of Rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is considered as a systemic auto immune disease[1]. Though it principally attacks flexible (synovial) joints, but also affects other tissues and organs. Inflammation of the tissue around the joints and inflammatory arthritis is characteristic. There occurs an inflammatory response of the capsule around the joints (synovium) secondary to swelling (hyperplasia) of synovial cells, excess synovial fluid accumulation and development of fibrous tissue (pannus) in the synovium.

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Synovitis can lead to tathering of tissue with loss of free movement and erosion of the joint surface causing deformity and loss of function[2]. Ultimately there is destruction of articular cartilage and ankylosis of the joints.

Beside joint involvement there may occur subcuntaneous nodule formation, ineffective haematopoiesis, muscle wasting, diffuse inflammation in the lung parenchyma and pleura, Inflammation of the pericardium, sclera of the eye and degeneration of peripheral nerves. Though, the exact cause of rheumatoid arthritis is unknown, auto immunity plays a pivotal role in its chronicity and progression. About 1% of the world's population is afflicted by rheumatoid arthritis. Female to male ratio is 3:1. Onset is usually around the age 40 yrs, but can begin at any age and even affects children (Juvenile RA). Manifestations in RA can appear as swelling, tenderness, warmth and painful movement of joint[3].

Characteristic morning stiffness or inactivity stiffness is a common complain .in inflammatory arthritis. The joints often involved in RA include the proximal interphlangeal joints (PIP), metacarphophalangeal (MCP) joints, wrists, elbows, shoulders, knees, ankles, subtalar and metatarsophalangeal (MTP) joints[3].
Rheumatoid nodule is the most common extra articular manifestation, which is usually associated with the presence of RF i.e. auto antibodies to the Fc component of immunoglobulin[4]. Other extra articular manifestations are fatigue, wt. loss, dryness and foreign body sensation in eyes, photophobia, interstitial lung disease (ILD), pericarditis, peripheral neuropathy, Raynaud's phenomena etc. Normocytic normochromic anaemia is a common haematologic complication.

Diagnostic criteria of Rheumatoid Arthritis[5] :
Diagnosis of RA is made if four or more criteria are present among the following :

- Morning stiffness (>1 hr)
- Arthritis of three or more joint areas
- Arthritis of hand joints
- Symmetrical arthritis
- Rheumatoid nodule
- Rheumatoid factor
- Radiological changes
- Duration >06 wks

New diagnostic criteria of Rheumatoid arthritis[6] : According to ACR/EULAR 2010, Diagnosis of rheumatoid arthritis is made with a point of total six or more of the following :

1. Joint involvement, designating the metacarpophalangeal joints, proximal interphalangeal joints, interphalangeal joint of the thumb, second through third metatarsophalgeal joints and wrist as small joints and elbows, hip joints and knees as large joints:

   a. Involvement of 1 large joint gives o point
   b. Involvement of 2-10 large joints give 1 point
   c. Involvement of 1-3 small joints (with or without involvement of large joints) give 2 points
   d. Involvement of 4-10 small joints (with or without involvement of large joints) give 3 points
   e. Involvement of more than 10 joints (with involvement of at least 1 small joint) give 5 points

2. Serological parameters – including the RF (rheumatoid factor) as well as ACPA (anti-citrullinated protein antibody):

   a. Negative RF and negative ACPA give 0 points
   b. Low positive RF or low positive ACPA give 2 points
   c. High positive RF or high positive ACPA give 3 points
   d. Acute phase reactants: 1 point for elevated ESR or elevated CRP value.
   e. Duration of arthritis: 1 point for symptoms lasting six weeks or longer.

Extra articular manifestations: Extra articular manifestations of RA occur in about 40% of patients either at the onset or during the course of their disease[7]. These are more common with men, smokers, severe joint diseases, high levels of inflammatory markers, presence of rheumatoid factor (RF), anti-nuclear antibodies (ANA) and the RA HLA-related shared epitope[8]. Smoking in some way drives the rheumatoid process towards extra articular involvement[9]. Extra articular RA is a serious condition and should be properly treated and monitored. These may be from rheumatoid process itself or from side effects of the medications like osteoporosis from corticosteroids or lung fibrosis from Methotrexate[10].

Incidence of such complications tend to be lower in community and population based studies than in clinic based series[11]. This study includes the common extra-articular features but also other systemic complications like normocytic normochromic anaemia, and disease associated conditions like IHD, osteoporosis, lung fibrosis. Systemic complications of RA are mostly related to vasculitis. Almost any organ can be involved[12]. Association of high titer of RF causes more extra articular complications. In the developed countries, the pattern & prevalence of extra-articular manifestations has declined in recent years, indicating that disease modifying RA treatments may be changing the natural history of the disease. But unfortunately specific therapies for extra articular features are largely disappointing or unavailable except for steroids and cyclophosphamide for vasculitis. The place for biological therapies is still not clear[10,11].

Skin manifestations: Rheumatoid nodule is the most frequent skin manifestation, usually subcutaneous and on extensor surface of the limbs mostly in RF positive patients. Leg ulcer and digital gangrene are other cutaneous manifestations of vasculitis. Small vessel vasculitis is believed to occur here[7].

Oral manifestations: Oral dryness, secondary Sjogren's syndrome etc[7].

Gastrointestinal manifestations: Mesenteric vasculitis as a part of systemic vasculitis leading to intestinal infarction is very rare. Here acute abdominal pain can lead to intestinal bleeding and perforation, where prognosis is poor. Other GIT complications are mostly iatrogenic and usually caused by medications like NSAIDs[13].

Cardiac Complications: Pericarditis is the most common cardiac complication[14]. Autopsy studies revealed evidence of pericardial inflammation in half of the Patients. It is also common in RF positive patients with nodules. Pericardial fluid study shows changes similar to rheumatoid pleural effusions. The risk for myocardial infarction in female RA patients is twice than that of women without RA and it is much more in long standing disease. Myocarditis, endocarditis, myocardial fibrosis leading to conduction abnormalities are common. There occurs rheumatoid nodules in heart valves from endocarditis and can lead to valve dysfunctions. Congestive heart failure is also more frequent in RA patients[15].

Pulmonary Complications: Pleural effusions are common but usually asymptomatic. Autopsy showed such complications in 50% cases, though very less is clinically evident (10%)[16]. Usually associated with pericarditis and in both the situation there is exudative effusion. Pulmonary nodules are found in RF positive patients and are asymptomatic in most of the situations. The nodules sometimes cavitate and cause pleural effusion. Histopathological examination of the nodules shows central area of necrosis rimmed by corona of pallisading fibroblasts that is surrounded by a collagenous capsule with peri vascular collection of chronic Inflammatory cells[17]. They are sub cutaneous and usually on extensor surfaces of limbs. Interstitial lung disease (ILD) is found in some cases of RA. Diffuse lung fibrosis in RA is found more in RF positive patients with nodule. Pulmonary fibrosis in RA has a poor prognosis[18].

Renal Complications: Amyloidosis is found in patients with nephrotic syndrome. Renal complications are usually iatrognic[19].

Neurological manifestations: There occurs small vessel vasculitis of the vasa vasorum of the nerve as well as ischaemic neuropathy and demyelination. Sensori motor neuropathy or mononeuritis multiplex and peripheral neuropathy are common from this mechanism. Nerves can become pinched at wrist causing carpal tunnel syndrome. In severe disease atlanto axial subluxation (C1-C2) can lead to cervical myelopathy[7].

Haematologic manifestations: Anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia and haematological malignancies are common[19]. Anaemia is usually anaemia of chronic disorder. It may be due to bone marrow suppression, GIT bleeding, ineffective haematopoiesis, drug effect or nutritional. Eosinophilia may be from disease activity e.g.vasculitis or drug hypersensitivity. Sometimes lymphadenopathy occurs which shows benign follicular hyperplasia in pathological examination[20].

Materials and Methods

It is a descriptive study, designed to assess pattern and prevalence of extra articular manifestations of RA in patients attending Combined Military Hospital (CMH) Dhaka. The study was carried out on patients of RA between Feb 2012 to Sept 2012. Convenient sampling was done to select the respondents for interview. Keeping compliance with Helsinki declaration for Research Involving Human subject 1964, data were collected on Key variables of interest from the respondents using a structured questionnaire. Respondents presenting with symmetrical painful swelling of small and large joints with duration more than 06 wks and having morning stiffness were included in the study. They were evaluated especially for their extra articular manifestations.

Result

Among 96, 74 (77%) patients were of below 40 years old. Twenty (20.83%) were between 40-50 years and 4 (4.16%) were >50 years. Mean age of the patient was 39.46±6.39 years and age range was between 29 and 60 years.

Eighty five (88.5%) of the patient were female and 11 (11.45%) were male (Table-I).

Table-I: Distribution of patients by age and sex (n=96)

Baseline Characteristics	Frequency	Percentage(%)
Age(years)		
<30	02	2.0
30-40	72	72.0
40-50	20	20.8
>50	04	4.16
Sex		
Female	85	88.54
Male	11	11.45

In terms of occupation about 75(78.12%) were house wife, 15(15.62%) in other diverse jobs and 6(6.2%) were service holder. Out of 96, 85 (88.5%) of the patients were of average socio-economic status, 9 (9.3%) were well-off and 02 (2.0%) were poor (Table-II).

Table-II: Distribution of patients by other demographic characterization (n=96)

Baseline Characteristics	Frequency	Percentage(%)
Occupation		
House wife	75	78.1
Service	6	6.2
Other	15	15.6
Socio economic status		
Poor	02	2.0
Average	85	88.5
Well off	09	9.3

Among the extraarticular manifestations fatigue was present in 90 (93.7%) cases, wt. loss in 80 (83.3%) cases and fever in 70 (72.9%) cases. Photophobia, eye dryness, foreign body sensation in eye, anemia, peripheral neuropathy was present in 75 (78.1%), 70 (72.9%), 65 (67.7%), 60 (62.5%) and 25 (26.0%) cases respectively. Rheumatoid nodule, pleural effusion and Raynaud's phenomena was found in 8 (8.3%) cases. Muscle wasting was found in 7 (7.2%). ILD, lymphadenopathy and splenomegaly was found in 2 (2.08%) cases (Table-lll).

Table-III: Distribution of patients by Extra articular characters (n =96)

Extra articular manifestation	Frequency	Percentage (%)
Fatigue	90	93.7
Fever	70	72.9
Weight loss	80	83.3
Anaemia	60	62.5
Eye dryness	70	72.9
Foreign body sensation in eye	65	67.7
Photophobia	75	78.1
Peripheral neuropathy	25	26.0
Rheumatoid nodule	8	8.31
Pleural effusion	8	8.31
Raynaud's phenomena	8	8.31
Muscle wasting	7	7.2
Osteoporosis	3	3.1
ILD	2	2.08
Splenomegaly	2	2.0
Lymphadenopathy	2	2.0
Digital Ulcer	2	2.0
Lung fibrosis	1	1.0

*Total will not correspond to 100% for multiple response.

Associated disease like hypertension was found in 23 (23.9%) patients. Diabetes, Hypothyroidism, Bronchial asthma and IHD was found in 15 (15.6%), 11 (11.4%), 10 (10.4%), and 3 (3.1%) cases respectively (Table-lV).

Table-IV: Distribution of patients by associated disease (n=96)

Associated disease	Frequency	Percentage(%)
Hypertension	23	23.9
Diabetes	15	15.6
Hypothyroidism	11	11.4
Bronchial asthma	10	10.4
Ischaemic heart disease	3	3.1

Table-V: Distribution of patients by other articular manifestations (n=96)

Articular manifestation	Frequency	Percentage(%)
Symmetrical arthritis	80	83.3
Small joint arthritis	85	88.5
Morning stiffness	79	82.2
Duration of morning stiffness (min):		
<60 min	60	62.5
>60min	19	19.7
Swollen joints	45	46.8
Tender joints	69	71.8

*Total will not correspond to 100% for multiple response.

Aggravating factors like night time, the frequency was 85 (88.5%) and exposure to cold it was 80 (83.3%)

Table-VI: Distribution of patients by other Clinical characteristics (n=96)

Aggravating factor	Frequency	Percentage(%)
Night time	85	88.5
Exposure to cold	80	83.3

*Total will not correspond to 100% for multiple response.

Pain was evaluated on a 0-4 scale, where '0' means no pain and '4' means severe pain, while1, 2, 3 are in between them. Accordingly majority 66 (68.7%) patients felt mild to moderate pain, 22 (22.9%) felt moderate to severe pain and 08 (8.3%) felt severe pain. Frequency of pain was mild to moderate in 70 (72.9%), moderate to severe in 18 (18.7%) and severe in 08 (8.3%) cases. According to pain intensity on Visual Analogue Scale (pain VAS) had moderate intensity of pain (pain VAS 4-5) in 54 (56.2%), mild (pain VAS 2-3) in 13 (13.5%) cases and severe (pain VAS 6-7) in 29 (30.2%) cases (Table-Vll).

Table-VII: Objective evaluation of pain (n=96)

Pain related variables	Frequency	Percentage(%)
Pain score (0-4)		
2	66	68.7
3	22	22.9
4	08	8.3
Pain frequency score (0-4)		
2	70	72.9
3	18	18.7
4	08	8.3
Pain VAS (0-10 cm)		
2-3	13	13.5
4-5	54	56.2
6-7	29	30.2

Family history of arthritis was present in 15 (15.6%) cases (Table-Vlll).

Table-VIII: Distribution of patients by familial tendency of arthritis

Family History	Frequency	Percentage(%)
Family History of arthritis	15	15.6%

Discussion

This descriptive study revealed mean age of the patients 39.46 years among them 72% were below 40 yrs. The youngest patient was 25 years old and oldest 60 years old. It indicates that Rheumatoid arthritis generally affects young and middle aged people.

There was a female preponderance (88.54%) and male to female ratio roughly 1:8 The mean duration of the patient was 43.38 months with lowest and highest duration were 05 and 144 months respectively.

We found the swollen joints and joint tenderness as an articular manifestation in 46.8% and 71.8% respectively. Duration of morning stiffness was <01hr in 62.5% and >1hr in 19.7%. More than three-quarter (83.3%) of the patient had symmetrical arthritis. This study correlates with the results of the study conducted by Brandtzaeg, who described that RA patients can present with swelling, tenderness, warmth and painful movement of the joints mostly involving the PIP, MCP joints, wrists, elbows, shoulders, knees, ankles in a symmetrical manner[3].

As an extra articular feature, fatigue was there in 93.3% cases, Wt. loss in 83.3% cases and, fever in 72.9%. Ophthalmic complications like eye dryness was found in 72.9%, foreign body sensation in the eye in 67.7% and photophobia in 78% caes. Ophthalmic complication in this study commensurate with the study of Cimmno et al[7]. In our study 62% patients had anaemia and 26% had peripheral neuropathy. Rheumatoid nodule, pleural effusion and Raynaud's phenomena was found in 8.3% cases. Muscle wasting, ILD, Splenomegaly, lymphadenopathy and digital ulcer were found in few cases. Kirkham et al in 2006 showed that rheumatoid nodule is the most common extra articular feature of RA. In their study rheumatoid factor (RA) was found positive in 71% cases, while we got rheumatoid factor positive in 69.75% cases[4]. Dr. Eric Matteson of American College of Rheumatology found the incidence for all extra articular manifestations of RA nearly 50% in a cohort of 463 patients with RA during 1995-2008[21]. In another study Aisha Al and Suzan M of Saudi Arabia showed that 70% of RA patients develop extra articular features[21].

This signifies that frequency of extra articular manifestation in RA differs from one country to another. In a study among Omanian patients, Al-Temimi et al showed that keratoconjunctivitis sicca is the commonest extra articular manifestation[22]. This finding highlights that extra articular features in RA has got geographic variation.

Extra articular RA is associated with significant morbidity and increased mortality compared with patients with RA in general[11]. It is more in patients with high titres of Rheumatoid factor[23]. Vasculitis as a part of systemic connective tissue disorder is the cause of most of the extra articular manifestations[24]. In the recent years extra articular manifestations has been declined significantly, probably due to use of disease modifying anti rheumatic drugs, those are changing the natural course of this disease[10].

Recent development in the understanding of disease process and invention of newer drugs are of better benefit to patients with extra articular disease[25]. Specific treatment lowers the incidence of such complications. Early diagnosis and treatment are required to decrease mortality[11].

The natural course of RA is ongoing progression and ultimate joint destruction and deformity, therefore disability & loss of functional status. There is lot of ignorance about the disease in mass people of country like us and they are little concerned about the disease in initial stages. The patients usually go to a doctor with established complications like joint deformity or acute flares of joint symptoms. With early and aggressive treatment the outlook can be very good. Patients have less favourable outlook when they have deformity, disability, ongoing uncontrolled joint inflammation, and/or disease affecting other organs of the body. Overall RA tends to be potentially more damaging when rheumatoid factor or citrulline antibody is demonstrated by blood serology. Early diagnosis or medical attention and appropriate treatment can yield much better outcome and lower the risk and severity of systemic manifestations associated with RA.

Conclusion

RA as a chronic systemic auto immune disease has also got extra articular symptoms beside joint symptoms. Extra articular manifestations are present in a substantial proportion of our patients of rheumatoid arthritis, which lead to a worse disease outcome. Extra articular complications are mostly due to disease process and in a few cases as a complication of medications eg. osteoporosis from corticosteroid treatment and lung fibrosis from methotrexate treatment.

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