Original Paper

Clinicopathological Evaluation of Seronegative Arthritis in a Tertiary Care Hospital of Bangladesh

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Abstract

Introduction: The seronegative arthritis is a heterogeneous group of inflammatory rheumatic diseases with predominant involvement of axial, peripheral joints and enthesitis. All of these have some distinct as well as some overlapping features, characteristic peripheral asymmetrical lower limb involvement and a negative rheumatoid factor. Involvement of joints is usually oligoarticular but rarely polyarthritis may be present. Diagnosis is usually made from clinical features rather than investigations.

Objective: To evaluate the seronegative arthritis clinico-pathologically by collecting and analyzing the relevant informations.

Materials and Methods: A descriptive cross-sectional prospective study was conducted at Combined Military Hospital, Chittagong from November 2015 to October 2016. A total 74 patients of suspected seronegative arthritis were included. Detail socio-demographic data were collected from the informant and recorded in structured case report form. Clinical examination and relevant investigations were done meticulously to confirm the aetiology of seronegative arthritis.

Results: Maximum number of patients was in the 3rd to 4th decade (62.1%), mean age of the patient was 37.4±8.7 and 38.7±8.1 years in male and female respectively. Male-female ratio was 2.65:1. Symmetrical sacroiliitis was found in 15(20.2%) patients, asymmetrical sacroiliitis in 36(48.6%) and in 23(31.2%) cases sacroiliac joint was not involved. Common aetiology for seronegative arthritis showed that, reactive arthritis recognized in majority of patients 29 (39.1%) and second most common cause was seronegative rheumatoid arthritis in 23(31%) patients.

Conclusion: The Seronegative arthritis is a social, economical and health-care burden. Patients who develop arthritis have high disability, discomfort and loss of quality of life. Seronegative arthritis is an interesting group of related conditions with overlapping features and genetic and familial association. That may alert the primary care physician to attain possible diagnosis of spondyloarthritis and to consider a rheumatological opinion.

Key-words: Seronegative arthritis, Psoriatic arthritis, Reactive arthritis, Inflammatory bowel disease-related arthritis, RF-negatigve, HLA-B27 positive.

Introduction

The term arthritis literally means joint pain associated with joint inflammation, synovial thickening and eventually joint erosions leading to a deforming and debilitating disease. The classic example which is seen in day to day practice is rheumatoid Arthritis (RA). It was recognized in the early part of the 20th century that all cases of inflammatory arthritis were not homogeneous in presentation. The introduction of the rheumatoid factor (RF) test more widely in the 1950s helped confirm that not all inflammatory arthritis were seropositive. Therefore, the term, seronegative variants of rheumatoid arthritis, was introduced[1]. In the 1960s a number of family studies led Wright and his colleagues in Leeds to coin the term 'seronegative spondarthritis' to link a number of inflammatory joint diseases, including ankylosing spondylitis, psoriatic arthritis, reactive arthritis including Reiter's disease, enteropathic arthritis (associated with inflammatory bowel disease) and anterior uveitis (iritis). Subsequent studies with the human leukocyte antigen (HLA) B27 have confirmed the genetic association[2].

The prevalence of spondyloarthritis (SpA) and/or Ankylosing spondylitis (AS) in Bangladesh[3] has been reported to be approximately four per 10,000. Globally Ankylosing spondylitis is the most common, with prevalence in the Caucasian

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population in between 0.15% and 1.8%, being higher in populations with a higher background prevalence of HLA-B27 positivity. The prevalence of psoriatic arthritis ranges from 0.02% to 0.2%, and the incidence in the normal population is 7.2 per 100,000 per year. In patients with existing psoriasis, the prevalence of psoriatic arthritis rises to 6-42%. The prevalence of reactive arthritis is dependent on the background incidence of gastrointestinal or genitourinary infections. The incidence has been stated as up to 30-40 per 100,000. Symptoms of seronegative spondyloarthritis are present in up to 50% of patients with inflammatory bowel disease[4].

By contrast, comparable data suggest that the term "seronegative rheumatoid arthritis" has been used over the years to label patients who may not have rheumatoid disease. Many of these people have spondylarthritis or an arthropathy which cannot be classified. The term seronegative rheumatoid arthritis was given in 1958, when Ropes and colleagues published the 11 provisional criteria for the diagnosis of rheumatoid arthritis. Usually seronegative patient can fulfill at most the first five criteria (morning stiffness, pain in one joint, swelling in one joint, swelling in another joint and symmetry of joint involvement). These criteria are sufficient for the diagnosis of "definite rheumatoid arthritis" but are not at all specific for rheumatoid disease[5].

Patients who do not have detectable rheumatoid factor (RF) are said to be 'seronegative' (SNA). Patients with seronegative rheumatoid arthritis are thought to have a more benign course and less destructive disease. Spondylo-arthropathies are diseases not associated with increased RF[6]. On pathological point of view the synovitis is non-specific and apart from the absence of granulomas, is often indistinguishable from rheumatoid synovitis. However, a distinctive feature is the marked degree of extrasynovial inflammation, especially of the enthesis but also affecting capsule, periarticular periosteum, cartilage and subchondral bone. The inflammation tends to resolve with extensive fibrosis and the resulting scar tissue is prone to calcify and ossify. This may characteristically lead to joint fusion. The periarticular osteitis and periostitis may result in bony spurs that bridge adjacent vertebral bodies (syndesmophytes) or protrude at sites of ligament attachment (e.g. calcaneal or olecranon 'spurs'). Large central cartilaginous joints (sacroiliac, intervertebral, symphysis pubis) are particularly involved, but even when synovial joints are affected (often spinal apophyseal joints, hips, knees, shoulders), extrasynovial inflammation is still prominent[7].

Common aetiology of seronegative arthritis is seronegative rheumatoid arthritis, the spondyloarthritides, crystalline arthropathies, infectious diseases, neoplastic/ paraneoplastic arthritis, inflammatory/ connective tissue disease. The spondyloarthritides are group of disorders which encompass ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic arthritis, juvenile onset spondyloarthritis and undifferentiated spondyloarthropathy[1]. Seronegative arthritis differentiated into inflammatory versus non-inflammatory. Inflammatory arthritides, like RA, are characterised by marked morning stiffness (>30 minutes), pain which improves on gently moving the joint and elevated ESR/CRP. Non-inflammatory arthritides are characterised by mild morning stiffness (<30 minutes), pain which worsens on joint movement, and normal acute phase response[8]. Clinically, Seronegative spondyloarthropathies (SpA) should be suspected whenever a young patient (< 40 years) presents with inflammatory low back pain, and asymmetrical below waist oligoarthritis, that is, asymmetric involvement of knees or ankles. The majority of cases are associated with HLA-B27. However, it needs to be kept in mind that nearly 5-6% of the healthy north Indian population is HLA-B27 positive[8].

It is good practice to measure both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in any patient with back pain. ESR increased during active phase, RF factor is negative, HLA B27 present in 20-95% of cases[2,9]. Plain radiographs may be helpful in detecting erosions or specific signs of a disease process. The hallmark of spondyloarthropathy is spine involvement. Syndesmophyte formation and signs of sacroiliitis may be seen. In patients with psoriatic arthritis, radiographs may detect marginal erosions, which are generally indistinguishable from those of rheumatoid arthritis. However, they tend to have an asymmetric distribution affecting the carpus, metacarpophalengeal and interphalangeal joints. The upper extremity is involved more often than lower extremities. In lower extremities, interphalangeal joint erosions are common. Periosteal new bone formation, distal interphalengeal joint erosion or pencil-in-cup deformities may also be observed. If axial spondyloarthropathy is suspected and sacroiliac joint x-rays are negative, MRI of the sacrum may be utilized to detect active inflammation, tissue metaplasia and erosions at the ilium[10].

SpA group of conditions is common in rheumatology clinics in South Asian countries, but authentic data on epidemiology are scarce. Poverty is a major challenge in treating these diseases in South Asia; with poor health insurance coverage, only a few patients are able to afford biological treatment[11]. Under-treatment or maltreatment

increased the morbidity and burden of disease. Therefore present study was conducted to evaluate the spectrum of clinical presentation, risk factors, aetiology and demographic association which helps us to early and accurate management of cases.

Materials and Methods

A descriptive cross-sectional study was conducted in a tertiary care hospital of Bangladesh from November 2015 to October 2016. Total 74 patients of suspected seronegative arthritis were included. Sample was selected by purposive sampling technique. Information was obtained from history and clinical examination to make a clinical diagnosis. Investigations were tailored to the need of the individual case. Data were collected from the informant and recorded in structured case report form. Clinical examination and relevant investigations were done meticulously. All collected questionnaire checked very carefully to identify the error in the data. Data processing work consisted of registration schedules, editing computerization, preparation of dummy table, analyzing and matching of data. Data were processed and analyzed with the help of computer program SPSS and Microsoft excel. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram and charts.

Results

A total of 74 seronegative arthritis patients were included for study. In this study, age of the study population ranged from 14 to 71 years and mean age was 37.4±8.7 and 38.7±8.1 years in male and female respectively (Table-I). Frequency of disease was predominant at early to middle age in both sexes, but more male affected at early age. Maximum incidence was observed in the 3rd to 4th decade (62.1%). Out of 74 cases 53(71.6%) cases were male and 21(28.3%) were female. Male to female ratio was 2.52:1.

Table-I: Demographic profile of the patients (n=74)

Age in Years	Frequency		Total (%)
	Male (n=53)	*Female (n=21)*	
16-30	11(20.7)	4(19.0)	15(20.2)
31-50	33(6.2)	13(61.9)	46(62.1)
51-70	6(11.3)	3(5.6)	9(12.1)
>70	3(1.5)	1(0.5)	4(5.4)
Mean ± SD	37.4±8.7	38.7±8.1	74(100)
M:F	2.52:1		

Most common clinical presentations of the patients with seronegative arthritis were back and/or joint pain (100.0%), followed by fatigue (78.3%), Morning stiffness lasting longer than 30 minutes (75.6%), and Joint swelling and redness (71.6%) (Table-II).

Table-II: Clinical manifestation of disease among respondents (n=74)

Clinical manifestation	Frequency	%
Back and/or joint pain	74	100.0
Fatigue	58	78.3
Morning stiffness lasting longer than 30 minutes	56	75.6
Joint swelling and redness	53	71.6
Fever	24	32.4
Symmetrical symptoms and in multiple joints	26	35.1
Skin or mouth ulcers	17	22.9
Sores on the skin	11	14.8
Diarrhoea	12	16
Dactylitis	32	43.2
Uveitis	29	39.1
Enthesitis	34	45.9
H/O urethritis or cervicitis	13	40.5

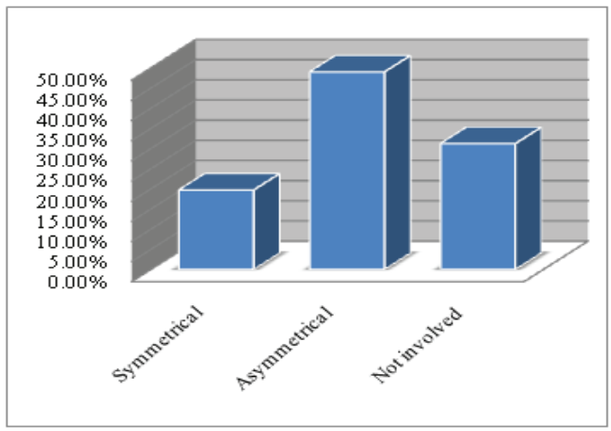

Fig-1: Sacroiliitis or Spine involvement (n=74)

Symmetrical sacroiliitis was found in 15(20.2%) patients, asymmetrical sacroiliitis in 36(48.6%) cases and 23(31.2%) cases did not have either sacroilitis or spine involvement.

Elevated ESR/CRP was observed in all patients, Rheumatoid factor (RF) negative in all patients. HLA-B27 was significant in 60.8% of patients and bulky marginal syndesmophytes were seen in 41.8% patients (Table-III).

Table-III: Evaluation of physical signs and investigation findings (n=74)

Variables	Frequency	%
Elevated ESR/CRP	74	100.0
Rheumatoid factor (RF)	0	0
HLA-B27	45	60.8
Aortic regurgitation	29	39.1
Bulky marginal syndesmophytes	31	41.8
Delicate marginal Syndesmophytes in lumbar spine	14	18.3
Bulky marginal syndesmophytes in cervical spine	08	10.8
Keratoderma blennorrhagica	12	16.2
Circinate balanitis	12	16.2

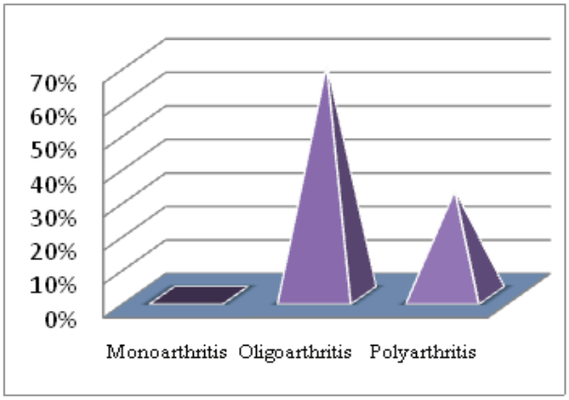

Fig-2: Spectrum of joint involvement (n=74)

The seronegative arthritis constitutes the vast majority of oligoarthritides encountered in clinical practice. In this study 51(68.9%) cases had oligoarthritis and below waist oligoarthritis (Figure-2) that is, asymmetric involvement of knees or ankles. On the other hand polyarthritis were found in 23(31.0%) patients, but none of the cases detected monoarthritis.

Clinical manifestations, physical examination and available investigation were evaluated meticulously. Clinical diagnosis of seronegative arthritis shows that, reactive arthritis recognized in majority of patients (39.4%) (Table-IV). Second most common cause of seronegative arthritis was seronegative rheumatoid arthritis, present in 23(31.0%) of patients. Other aetiologies were Ankylosing spondylitis in 12(16.2%) patients, Psoriatic arthropathy 6(8.1%) and arthritis associated with IBD 4(5.4%) patients.

Table-IV: Clinical diagnosis and evaluation of aetiology of seronegative arthritis (n=74)

Aetiology	Frequency	%
Reactive arthritis	29	39.1
Seronegative rheumatoid arthritis	23	31.0
Ankylosing spondylitis	12	16.2
Psoriatic arthropathy	06	8.1
Arthritis associated with IBD	04	5.4

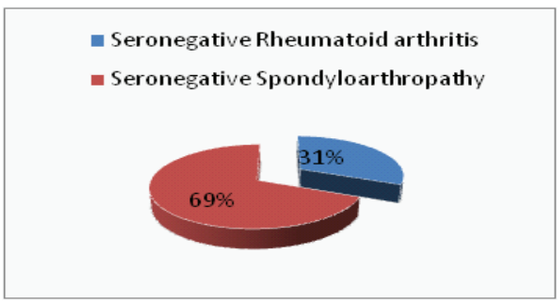

Fig-3: Overall aetiopathological distribution of disease (n=100)

Figure-3 showed that aetiopathologicaly in this study, amongst the 74 cases, 23(31%) were seronegative rheumatoid arthritis and 51(69%) cases were seronegative spondyloarthropathy.

Discussion

Symptomps suggestive of inflammatory spinal disease or asymmetrical synovitis in a patient with a history of psoriasis, iritis, inflammatory bowel disease or recent infection should alert the physician to a possible diagnosis of spondyloarthritis. There is a high incidence of HLA B27 but negative RF. Out of 74 seronegative arthritis patients, the age of the study population was ranging from 14 to 71 years and mean age was 37.4±8.7 and 38.7±8.1 years in male and female respectively. Male to female ratio was 2.52:1. Findings are consistent with the result of other studies. Common age of onset of seronegative arthritis is 20-30 years with male predominance[1]. The mean age at onset is 20 to 40 years[4].

All cases share a common feature: that of a severe, destructive disease in seronegative RA with involvement primarily of the wrists, sub-talar and ankle joints, as well as large joints. All these patients were negative with regard to RF, aCCP and forty five cases were HLA-B27 positive but despite this, the clinical presentation (signs and symptoms) and radiographs of the sacro-iliac joints support a diagnosis of different type of seronegative spondylitis. The most common clinical presentations in this study were back and/or joint pain (100.0%), followed by fatigue (78.3%), morning stiffness lasting longer than 30 minutes (75.6%) and Joint swelling and redness (71.6%). Symmetrical sacroiliitis in 15(20.2%) patients, asymmetrical sacroiliitis in 36(48.6%) and no joints were involved in 23(31.0%) cases.

Spondyloarthropathies may sometimes be relatively mild and many patients do not seek medical advice. Common features are inflammatory back pain: lumbar or dorsal pain at night or stiffness in the morning, sacroiliitis, peripheral arthritis[4]. Seronegative arthritis may be differentiated into inflammatory versus non-inflammatory. Furthermore seronegative inflammatory arthritis may be divided into monoarthritis (single joint involvement), oligoarthritis (2, 3 or 4 joints involved) or polyarthritis (≥5 joints)[1,8]. In this study, 51(37.2%) had oligoarthritis and below waist oligoarthritis that is asymmetric involvement of knees or ankles. On the other hand polyarthritis were 23(31.9%) patients, but none of the cases detected mono arthritis.

Handa R et al demonstrated, causes of oligoarthritis are gout, juvenile idiopathic (rheumatoid) arthritis, psoriasis, seronegative spondyloarthropathies (SpA). Definitive diagnosis of gout requires crystal identification. Hyperuricaemia alone is not sufficient to make a diagnosis of gout. The seronegative spondyloarthropathies (SpA) constitute the vast majority of oligoarthritides encountered in clinical practice. Seronegative spondyloarthropathies (SpA) include ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatric spondyloarthopathy, inflammatory bowel disease (Enteropathic spondyloarthopathy), juvenile spondyloarthropathy and unclassifiable or undifferentiated spondyloarthropathy[1,8]. This study was almost near to their observation.

The European Spondylarthropathy Study Group criteria for spondylarthropathy revealed that, Inflammatory spinal pain, or synovitis (asymmetric, predominantly in the lower extremities) and one or more of the following; Family history: A first-degree or second-degree relative with ankylosing spondylitis, psoriasis, acute iritis, reactive arthritis or inflammatory bowel disease. Past or present psoriasis, ulcerative colitis or Crohn's disease, pain alternating between the two buttocks, spontaneous pain or tenderness on examination of the site of insertion of the Achilles tendon or plantar fascia (enthesitis). Episode of diarrhoea occurring within one month before onset of arthritis. Non-gonococcal urethritis or cervicitis occurring within one month before onset of arthritis. Bilateral grade 2-4 sacroiliitis or unilateral grade 3 or 4 sacroiliitis. Grade 0 is normal, 1 possible, 2 minimal, 3 moderate and 4 completely fused (ankylosed)[12].

Clinical manifestations, physical examination and available investigations were evaluated meticulously. Clinical diagnosis of seronegative arthritis shows that Reactive arthritis recognized in majority of patients (39.1%). Second most common cause of seronegative arthritis was seronegative rheumatoid arthritis, present in 23(31.0%) cases. Other aetiologies were Ankylosing spondylitis 16.2% of patients, Psoriatic arthropathy 8.1% and arthritis associated with IBD 5.4% patients. On broad aetiological distribution, sero-negative arthritis are two different conditions: seronegative rheumatoid arthritis and seronegative spondyloarthropathy. The term refers to inflammatory diseases where there is inflammation and swelling, but RF is absent. Amongst the 74 cases, 31% were seronegative RA.

Conclusion

The clinical and socioeconomic burden of musculoskeletal (MSK) disorders is as high in Bangladeshi rural and urban communities as in populations in other countries. Male and younger ages are affected more frequently. If can be detected early before development of Sacroiliitis, the more destructive disease can be prevented. Proper identification of risk factors, evaluation of clinical manifestations, drug treatment like NSAID's, Steroids, Biologics, Physiotherapy and exercises can reduce the burden of seronegative arthritis.

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