A study of clinical, radiological features and HLA-B27 serology of axial spondyloarthropathy with comparison of radiographic and non-radiographic disease

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ABSTRACT

Background: Axial spondyloarthropathy is a type of disease which affects the axial skeleton affecting productive years. Methods: This was a cross-sectional, observational study in which 28 consecutive patients more than 16 years of age, fulfilling the Assessment of SpondyloArthritits International Society (ASAS) criteria for axial spondyloarthropathy were included. They were further sub-grouped into radiographic and non-radiographic axial spondyloarthropathy. Clinical features, joint involvement, measurements, HLA-B27 serology, and disease activity were evaluated. Data was entered into Microsoft Excel, and SPSS (Statistical Package for Social Sciences) software 2.0 was used for analyzing the data. Results: Mean age was 28.5 ± 6.3 years. 85.7% were males. Inflammatory low back pain was the most common clinical feature at presentation (89.2%). Enthesitis was the most common extra-articular feature seen in 35.7% of patients. 42.8% were non-radiographic axial spondyloarthropathies. 85.7% of patients were HLA-B27 positive. 50% of patients had bone marrow edema on MRI, and only one patient had ankylosis indicating predominantly early disease. 50%–70% of our patients had high disease activity and 89.3% were responding well to non-steroidal anti-inflammatory drugs (NSAIDs). There was no significant difference between the radiographic axial spondyloarthropathy group and the non-radiographic group except for elevated C-reactive protein (CRP). Conclusion: Ankylosing spondylitis in western India occurs mostly in the age group of 20–30 years, suggesting affection of productive age group. There was a delay of diagnosis for approximately three years from the onset of symptoms. There was a positive association with HLA-B27 in majority of the patients. Most of our patients had early disease based on radiological findings, suggesting that there was room for therapeutic intervention before irreversible ankylosis had set in.

Keywords: Ankylosis, axial spondyloarthritis, HLA-B27, non-radiographic, radiographic, sacroiliitis

Introduction

Spondyloarthritis (SpA) are a collection of overlapping illnesses with comparable clinical characteristics, underlying pathogenic mechanisms, and genetic correlations. These include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), enteropathic arthritis, and undifferentiated arthritis.[1] Spondyloarthritis is usually seen in the second or third decade of life, usually in 0.3% to 1.9% of the general population.[2,3]

Axial SpA (axSpA) mainly affects the axial skeleton. These patients also have extra-articular symptoms such as enthesitis, dactylitis, uveitis, and inflammatory bowel disease (IBD). They may have lower limb large joint oligoarthritis. SpA patients have a genetic propensity for the disease in the form of a positive human
leukocyte antigen B27 (HLA-B27) and a negative rheumatoid factor.[1]

The morbidity of axial SpA is considerable. As it affects the productive age group, the loss of work days and societal costs are quite high. The cardinal symptom of the disease is insidious inflammatory low back pain (IBP) which increases on rest, is more nocturnal, and better on exercise. It can be misdiagnosed by primary care physicians as mechanical or degenerative disease. There is considerable delay in diagnosis at this level.[9] The reason for the delay could be due to lack of rapport with patients, inadequate history about the low back pain, lack of follow up with the patients and shortage of rheumatologists.[9]

Axial SpA is further categorized into radiographic (r-axSpA) and non-radiographic (nr-axSpA). Nr-axSpA has no evidence of sacroiliac joint destruction on conventional radiographs. Nr-axSpA can progress to AS in some cases (AS or r-axSpA).[9] Studies have shown that approximately 10% of patients with nr-axSpA progress to r-axSpA within two years and 26%–60% progress within 10–15 years after the onset of symptoms.[9] In literature, nr-axSpA has more female preponderance. The disease activity and functional deficits are comparable to those seen in r-axSPA patients.[9]

The hallmarks of sacroiliac (SI) joint involvement in AS on conventional radiographs are erosions and ankylosis which occur early on the iliac side of the SI joint. Syndesmophytes are characteristic of spinal pathology in AS. Ankylosis and new bone formation occur as the condition advances and give rise to “bamboo spine”. MRI is the most sensitive imaging modality for individuals with IBP.[7]

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), and Bath Ankylosing Spondylitis Functional Index (BASFI) are used for calculating the disease activity and functional disability in patients of Axial SpA. According to COPCORD survey, the prevalence of seronegative SpA was 0.25% of population.[9] There is paucity of literature on axial SpA and groups of nr- and r-axSpA from Maharashtra. The present study was carried out to elucidate clinical, radiological features, and HLA-B27 seropositivity of axial spondylarthritis with a comparison of features between nr- and r-axSpA in patients aged more than 16 years in a tertiary care hospital in Maharashtra.

Subjects and Methods

This was a cross-sectional, observational study conducted in a tertiary care centre in western India in the medicine and Rheumatology OPD and wards. Twenty-eight consecutive patients more than 16 years of age, who fulfilled the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial SpA at the time of diagnosis were included in the study, over a period of 6 months.

The ASAS criteria for axial SpA are patients with age of onset of <45 years and back pain for ≥3 months who have either sacroiliitis on imaging and more than or equal to one SpA feature or HLA-B27 positivity and more than two other SpA features.

The SpA features include IBP, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27, and elevated C-reactive protein (CRP).

Sacroiliitis on imaging can be either active or acute inflammation on MRI, highly suggestive of sacroiliitis with SpA or defining radiographic sacroiliitis according to Modified New York Criteria.

Those patients fulfilling criteria for rheumatoid arthritis or connective tissue disorder or those having degenerative or traumatic spine disease and post traumatic arthritis, those who had proven infective sacroiliitis and arthritis and those with fibromyalgia were excluded from the study.

The patients were included in the study after obtaining Institutional Ethics Committee clearance and also written and informed consent from each subject.

They were further sub-grouped into radiographic and non-radiographic SpA according to Modified New York Criteria which includes both clinical and radiological criteria. The clinical criteria were low back pain of at least three months duration improved by exercise and not relieved by rest, limitation of lumbar spine in sagittal and frontal planes, and chest expansion decreased relative to normal values for age and sex. The radiological criteria include bilateral sacroiliitis grade 2 to 4 and unilateral sacroiliitis grade 3 or 4. Diagnosis of AS is made if the patient fulfills at least one clinical and one radiological criteria.

Detailed history of low back pain was taken including IBP duration of early morning stiffness, history of spinal mobility including lateral flexion and forward flexion. Joint symptoms including pattern of joint involvement (small/large, symmetrical/asymmetrical) and presence of extra-articular features, dyspnea, chest pain and palpitations was taken.

Physical examination including general examination, systemic examination, and musculoskeletal examination was done in detail. This included swollen joints/tender joints/type of joints, range of motion in the involved joint, FABERS (Flexion, Abduction, External rotation) test, presence of dactylitis, Achilles tendon enthesitis, plantar fasciitis, psoriasis lesions, especially in hidden areas like the gluteal eft, behind the ear, and breast, nail changes were looked out for. Uveitis was examined by slit-lamp and genitourinary examinations.

Measurements like Modified Schober test (normal value more than 21 cm), Tragus to wall test (normal value less than 12 cm),
chest expansion (normal value more than 4 cm), intermalleolar distance (normal value more than 100 cm), and range of lateral flexion were assessed (normal value more than 10 cm).\textsuperscript{[9]}

Systemic examinations including cardiovascular, respiratory, per abdominal, and neurological examinations were done.

Laboratory investigations include hemogram, renal function test, liver function test, rheumatoid factor (particle enhanced immunoturbidometric method), anti-CCP (by chemoluminescence microparticle assay), erythrocyte sedimentation rate (ESR) (by automated Westergren method), CRP (quantitative) by Nephelometry method, HLA-B27 by flowcytometry (by BD FACS Canto II machine) was done. Chest X-Ray, X-Ray of all the involved joints, X-Ray pelvis with both SI joints and X-ray hips, X-ray thoraco-lumbar spine and MRI (by 1.5 TESLA AVANTO, Siemens or 3 TESLA MAGNETOM VIDA, Siemens based on requirement) of SI joints in patients with IBP were done.

According to the New York grading system, sacroiliitis was radiographically graded as grade I (suspicious), grade II (evidence of erosion and sclerosis), grade III (erosion, sclerosis, and early ankylosis), and grade IV (total ankylosis).

According to ASAS/OMERACT MRI working group, the definition of a positive MRI is if there is an active inflammatory lesion of the SI joints, bone marrow edema (BMO) on STIR or osteitis must be clearly located in typical anatomical areas (subchondral or peri-articular bone marrow) or presence of a single BMO lesion seen in at least two successive slices in the case of a solitary BMO lesion or evidence of inflammation on a single slice is sufficient in the case of several BMO lesions on a single slice or the presence of enthesitis, synovitis, or capsulitis without concurrent BMO/osteitis is insufficient to diagnose the condition. Spondylitis must be present in three or more vertebral locations.\textsuperscript{[10]}

Disease activity was measured (single point) by using the BASDAI, ASDAS-CRP and BASFI for ankylosing spondylitis.

BASDAI score of $\geq 4/10$ was considered active disease and BASFI score of $\geq 6$ indicated disability in the patient.\textsuperscript{[10]} ASDAS-CRP score of $<1.3$ denoted inactive disease, 1.3–2.0 low disease activity, 2.1–3.5 high disease activity, and $>3.5$ very high disease activity.\textsuperscript{[11]}

Data analysis

Data was entered into Microsoft Excel and SPSS (Statistical Package for Social Sciences) software 2.0 for analysis. Continuous variables were expressed in terms of mean and standard deviation (SD), and categorical variables were expressed in terms of frequency and percentage. Difference in the mean $\pm$ SD of quantitative variables between two groups (radiographic vs non-radiographic axial SpA) was analyzed using Mann–Whitney $U$ test and unpaired $t$ test. To find the association between categorical variables, Fisher’s exact test was used.

Results

A majority of the patients were males (24, 85.7%) with a male-to-female ratio of 6:1. The mean age of the patients was 28.5 ± 6.3 years with 17 patients (60.7%) in the age group of 21–30 years out of which 14 were males [Table 1]. A majority of the patients (25, 89.2%) presented with IBP followed by sacroiliac tenderness (71.4%), peripheral joint involvement (64.2%), and early morning stiffness (53.5%). Enthesitis was seen in 35.7% of patients, dactylitis in 10.7%, buttck/gluteal pain in 10.7%, and uveitis in 7.1% of patients [Table 2].

The mean duration of symptoms was 5.25 ± 6.7 years and the mean duration of the disease was 2.75 ± 3.18 years. There was a delay in the diagnosis for approximately three years in these patients. The most common peripheral joint involved at the time of the study was knee joint seen in eight patients (28.5%), followed by hip and elbow joints in 4 patients (14.2%). Ankle joint involvement was seen in three patients (10.7%), shoulder and wrist joints in two patients (7.14%), and metacarpophalangeal joints in only one patient (3.5%).

A majority of the 25 patients (89.2%) were receiving NSAIDs at the time of presentation, four were receiving Sulphasalazine, one had received hip joint intra-articular steroid injection, and three were treatment-naïve at the time of presentation. Most of the patients (89.3%) were responding to NSAIDs.

It was found that 18 patients (64.3%) had abnormal lateral flexion, 24 (85.7%) had abnormal modified Schober test,

| Table 1: Age and gender profile of study participants |
|------------------------------------------------------|
| Age group (years) | Gender | Total |
|-------------------|--------|-------|
| Female            | Male   |       |
| 16-20             | 3      | 3     |
| 21-30             | 3 (17.6%) | 14 (82.4%) | 17 |
| 31-40             | 1 (14.3%) | 14 (85.7%) | 7 |
| >40               | 1 (100%) | 1     |
| **Total**         | 4      | 24    | 28     |

| Table 2: Clinical features among study participants at presentation |
|---------------------------------------------------------------------|
| Clinical features | Frequency | Percentage (%) |
|--------------------|-----------|----------------|
| Inflammatory low back pain | 25 | 89.2 |
| Peripheral joint involvement | 18 | 64.2 |
| Sacroiliac tenderness | 20 | 71.4 |
| Early morning stiffness >30 minutes | 15 | 53.5 |
| Enthesitis | 10 | 35.7 |
| Dactylitis | 3 | 10.7 |
| Buttock/Gluteal Pain | 3 | 10.7 |
| Chronic Diarrhea | 0 | 0 |
| Uveitis | 2 | 7.1 |
| Urinary/gynecological infections | 0 | 0 |
6 (21.4%) had abnormal tragus to wall distance, 8 (28.6%) had abnormal intermalleolar distance, and 7 patients (25%) had abnormal chest expansion. As many patients were having abnormal lateral flexion and modified Schober test, it signifies the early involvement of the lumbar spine.

All four female patients and 15 of male patients (62.5%) in the study were anemic. The mean CRP of the patients was 9.4 ± 2.26 mg/L, and the mean ESR was 31.5 ± 12.02 mm/hr. There was a strong association of HLA-B27 in these patients which was positive in 24 patients (85.7%) [Figure 1].

On SI joint A-rays, 12 patients showed no changes, 11 (39.2%) had bilateral sacroiliitis, 3 (10.7%) had left-sided sacroiliitis, and 2 (7.14%) had right-sided sacroiliitis. According to the grading of sacroiliitis on X-ray, 12 patients (42.8%) had grade 0 sacroiliitis, 5 (17.8%) had grade 1, 7 (25%) had grade 2, 3 (10.8%) had grade 3, and only 1 patient (3.6%) had grade 4 sacroiliitis. There were 12 patients (42.8%) with no changes in the conventional radiographs and were grouped as nr-axSpA, and the rest 16 (57.2%) were grouped as r-axSpA. MRI was done in 25 patients who had IBP. A majority of the patient, that is, 14 patients (50%) had bone marrow edema, 12 (42.8%) had narrowing of sacroiliac joint, 8 (25.6%) had sclerosis, and 2 (7.1%) had ankylosis. X-ray thoracolumbar spine was done in 25 patients who had IBP. The most common X-ray finding was syndesmophytes which were seen in four patients (16%). Five patients (20%) had loss of lumbar lordosis, four (16%) had squaring of vertebrae, and bamboo spine was seen in two patients (8%). Twenty-two patients (55%) had normal spine on X-ray of thoracolumbar spine [Table 3].

Out of the total patients, 19 (67.85%) had active disease based on the BASDAI scoring, and 9 patients (32.15%) were not having active disease at the time of study; the mean BASDAI score was 4.3 ± 0.7. The mean BASFI score was 3.1 ± 1.5, and four patients (14.28%) had a BASFI score of ≥6 which indicated functional disability in these patients. According to the ASDAS-CRP score, 16 patients (57.2%) had high disease activity, 6 (21.4%) had very high disease activity, and 6 (21.4%) had low disease activity. This suggests that a majority of the patients had high disease activity but low disability at the time of the study.

On comparing the qualitative variables among radiographic and non-radiographic SpA groups, there was a significant difference in presence of sacroiliac tenderness among both groups, with it being more common in radiographic SpA (using Fisher’s exact test \((P = 0.044)\)). There was no significant difference in any other qualitative variable between two groups (using Fischer’s exact test \((P > 0.05)\) [Table 4].

The mean and median values on comparison of quantitative variables among radiographic and non-radiographic SpA groups, the CRP values were significantly higher in the radiographic

| Table 3: Radiographic findings in patients with axial SpA |
|-----------------|-----------------|-----------------|
| **X-ray of sacroiliac joints** | **Frequency** | **Percentage (%)** |
| Bilateral sacroiliitis | 11 | 39.2 |
| Left-sided sacroiliitis | 3 | 10.7 |
| Right-sided sacroiliitis | 2 | 7.14 |
| Normal | 12 | 42.8 |
| **Total** | **28** | **100** |

| **X-ray grading of sacroiliitis** | **Frequency** | **Percentage (%)** |
| Grade 0 | 12 | 42.8 |
| Grade 1 | 5 | 17.8 |
| Grade 2 | 7 | 25 |
| Grade 3 | 3 | 10.8 |
| Grade 4 | 1 | 3.6 |
| **Total** | **28** | **100.0** |

| **MRI of sacroiliac joint** | **Frequency** | **Percentage** |
| Bone marrow edema | 14 | 50 |
| Narrowing | 12 | 42.8 |
| Sclerosis | 8 | 25.6 |
| Ankylosis | 2 | 7.1 |

| **X-ray D-L spine findings** | **Frequency** | **Percentage** |
| Normal | 14 | 56 |
| Syndesmophytes | 4 | 16 |
| Loss of lumbar lordosis | 5 | 20 |
| Squaring of vertebra | 4 | 16 |
| Bamboo spine | 2 | 8 |

| Table 4: Comparison of qualitative variables among radiographic and non-radiographic SpA groups |
|-----------------|-----------------|-----------------|
| **Variables** | **Radiographic SpA (n=16)** | **Non-radiographic SpA (n=12)** | **P** |
| Female | 3 (75%) | 1 (25%) | 0.613 |
| Male | 13 (54.17%) | 11 (45.83%) | |
| Sacroiliac Tenderness | 14 (87.5%) | 6 (50%) | 0.044* |
| Peripheral Joint Affection | 12 (75%) | 6 (50%) | 0.333 |
| Enthesitis | 4 (25%) | 6 (50%) | 0.242 |
| Dactylitis | 1 (6.25%) | 2 (16.67%) | 0.560 |
| Uveitis | 1 (6.25%) | 1 (8.33%) | 1.0 |
| Response to NSAID | 13 (81.25%) | 12 (100%) | 0.238 |
| HLA-B27 Positive | 14 (87.5%) | 10 (83.33%) | 1.0 |
SpA group as compared to the nr-axSpA group (unpaired t test ($P < 0.05$)). There was no significant difference in mean values of any other variable between the two groups using unpaired t test ($P < 0.05$) and Mann–Whitney U test ($P < 0.05$) [Table 5].

**Discussion**

In our study a majority of the patients were males (24, 85.7%) with male-to-female ratio of 6:1. The mean age of the patients was 28.5 ± 6.3 years. In a study done by Garrido-Cumbra M et al.,[13] the mean age of the patients was 43.9 ± 12.3 years, and 61.3% were females. In a study done by Aggarwal R et al.,[13] the male-to-female ratio was 5:1.

In our study, the predominant clinical feature was IBP seen in 25 patients (89.2%). In the study done by Aggarwal R et al.,[13] the predominant clinical feature was IBP seen in 87.1% of patients.[14]

In our study, peripheral joint involvement was seen in 18 patients (64.2%). The most common peripheral joint involved at the time of the study was the knee joint, seen in 8 patients (28.5%), followed by the hip and elbow joints involvement seen in 4 patients (14.2%). In a study done by Sallam RA et al.,[14] 52% of patients had peripheral arthritis. The most common joint involved was the hip joint (65.4%), followed by the knee joint (23.1%).

In our study, the most common extra-articular feature was enthesitis seen in 10 patients (35.7%). Lee JH et al.,[18] reported 53% incidence of enthesitis among AS patients.

There was a diagnostic delay of almost three years in our study. In a study done by Aggarwal R et al.,[13] the mean delay in the diagnosis of ankylosing spondylitis was 6.9 ± 5.2 years. In a study done by Hammoudeh M et al.,[16] the mean delay of diagnosis of AS was approximately five years.

Most of the patients (89.3%) were responding to NSAIDs. In a study conducted by Stolwijk C et al.,[17] 77% of the patients were responsive to NSAIDs. Peláez-Ballestas I et al.,[18] had reported that 97% of the patients in their study were responsive to NSAID.

In our study, 18 patients (64.3%) had abnormal lateral flexion, 24 (85.7%) had abnormal modified Schober test, 6 (21.4%) had abnormal tragus to wall distance, 8 (28.6%) had abnormal intermalleolar distance, and 7 (25%) had abnormal chest expansion. In the study done by Joseph Hermann et al.,[19] abnormal modified Schober test was found in 24 patients (80%), and abnormal chest expansion was found in 6 patients (20%). In a study done by Hart FD et al.,[20] the chest expansion was decreased in 70% of the AS patients.

In our study, 19 patients (67.8%) were anemic. In a study done by Kim KJ et al.,[21] anemia was detected in 27.9% of AS patients.

In our study, the mean BASDAI score was 4.3 ± 0.7, and the mean BASFI score was 3.1 ± 1.5. In the study done by Aggarwal R et al.,[13] the mean BASDAI score was 3.2 ± 1.8, and the mean BASFI score was 2.3 ± 2.0.

In our study, the mean CRP of the patients was 9.4 ± 2.26 mg/L and the mean ESR was 31.5 ± 12.02 mm/hr. In a study done by Alam F et al.,[22] the mean CRP was 11.4 ± 11.8 mg/L and the mean ESR was 20.3 ± 1.2 mm/hr.

In our study, HLA-B27 positivity was seen in 24 patients (85.7%). In a study done by Sheehan NJ et al.,[23] HLA-B27 positivity was seen in 90%–95% of ankylosing spondylitis patients. In the study done by Garrido-Cumbra M et al.,[13] 71.3% patients were HLA-B27 positive.

In our study, 11 patients (39.2%) had bilateral sacroiliitis on X-ray of sacroiliac joint. In the study done by Aggarwal R et al.,[13] a majority of the patients had bilateral sacroiliitis, seen in 87.1% of patients. In our study, 14 patients (50%) had bone marrow edema, 12 (42.8%) had narrowing of sacroiliac joint, 8 (25.6%) had sclerosis, 2 (7.1%) had ankylosis. In a study by Abdelsalam A et al.,[24] bone marrow edema was seen in 9.4% patients, narrowing of joint space in 11.3% patients, sclerosis in 17% patients, and ankylosis in 52.8% patients.

In our study, four patients (16%) had syndesmophytes, five (20%) had loss of lumbar lordosis, four (16%) had vertebral squaring, and two (8%) had bamboo spine. In a study done by Moshrif et al.,[25] vertebral squaring was seen in 49 patients (70%), lumbar syndesmophytes in 45 (64.3%), cervical syndesmophytes in 35 (50%), bamboo spine in 13 (18.6%) patients.

| Table 5: Comparison of quantitative variables among radiographic and non-radiographic SpA groups |
|---------------------------------------------------------------|
| **Variables** | **Radiographic SpA (n=16)** | **Non-radiographic SpA (n=12)** | **P** | **Type of test applied** |
| Age | Median or Mean + Std. Deviation | Median or Mean+Std. Deviation | | |
| Duration of disease (years) | 1 | 1 | 0.617* | Mann–Whitney test |
| Duration of illness (years) | 2 | 1 | 0.267* | Mann–Whitney test |
| BASFI score | 1 | 4.5±1.5 | 3.9±1.4 | 0.808* | Unpaired t test |
| BASDAI score | 4.7±1.4 | 4.1±0.81 | 0.062* | Unpaired t test |
| ESR | 39.6±25.2 | 35.5±15.9 | 0.232* | Unpaired t test |
| CRP | 12.86 | 7.4 | 0.015* | Mann–Whitney test |
On comparison of r-axSpA and nr-axSpA in our study, there was a significant statistical difference in the sacroiliac tenderness and raised CRP levels which were more common in r-axSpA group. In a study done by Malaviya A et al.,[20] the radiographic SpA group had more male patients with longer duration of disease, and more axial symptoms at the onset of disease. In a study done by Akashi N et al.,[21] there were more males; clinical features of enthesitis, cervical stiffness, and coxitis and ESR were seen more in the AS group when compared to nr-axSpA group.

**Conclusion**

Ankylosing spondylitis in western India occurs mostly in the age group of 20–30 years, suggesting affection of productive age group. There is a delay of diagnosis for approximately three years from the onset of symptoms. There is a positive association with HLA-B27 in the majority of patients. Most of our patients had early disease based on radiological findings, suggesting that there is room for therapeutic intervention before irreversible ankylosis sets in.

**Key take-home message:** IBP is often attributed to other factors by primary care physicians. A rapport should develop between the patients and the primary care physician. Proper history should be obtained and treating physicians should keep a follow-up with the patients.

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**Conflicts of interest**

There are no conflicts of interest.

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