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Original Article

Internal Medicine Section

Comparison of Patients with Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis-A Cross Sectional Study

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ABSTRACT

Introduction: The Assessment of Spondylo Arthritis International Society (ASAS) classification criteria for Axial Spondyloarthropathy (axSpA) published in 2009 aimed to achieve a greater sensitivity in diagnosing patients of axial spondyloarthritis. Whether the radiographic form Ankylosing Spondylitis (AS) and the Non Radiographic Axial Spondyloarthritis (nr-axSpA) form, are subgroups or different phases of the same disease is a pertinent question because this could have affected the pharmacological management of the two subgroup. Whether a distinction between AS and nr-axSpA in clinical practice is useful, remains unknown. Therefore, the present study was undertaken with the following aim.

Aim: To investigate the differences in clinical presentation and disease activity between nr-axSpA and AS.

Materials and Methods: A cross sectional study was conducted in Division of Rheumatology, Banaras Hindu University, Varanasi, India from January 2016 to June 2017. All the patients presenting with history of chronic back pain for ≥3 months and age at onset ≤45 years after taking written informed consent were included in the study. Using the ASAS criteria, patients were then classified into two groups of 50 patients each, patients having AS (if there was sacroilitis on radiographs as defined in modified New York criteria) and nr-axSpA diagnosed using ASAS criteria. The various SpA related variables were then compared including gender, age, duration of illness, enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis, family history, Human Leucocyte Antigen (HLA) B27 positivity, baseline C-Reactive Protein (CRP), baseline Erythrocyte Sedimentation Rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI).

Results: Patients with AS, as compared with nr-axSpA had a longer disease duration {4.5(1.875-8.250) vs. 2.0(1.000-4.000); p-value 0.023} and had a significantly higher levels of objective markers of inflammation i.e., CRP {4.7(2.325-6.525) vs. 2.20(0.588-4.125); p-value<0.001)} and ESR {(41.98±16.936 vs. 34.20±14.552; p-value 0.015)}. No statistically significant difference was found in age of onset, male: female ratio, enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis, family history and HLAB27 positivity. Neither any statistically significant difference was noted between the mean BASDAI and BASFI in the two groups.

Conclusion: Other than elevated levels of markers of inflammation (CRP/ESR) and a longer disease duration in AS, most other features do not vary significantly between the two groups. Thus, the two groups might represent same disease in different phases.

Keywords: Backache, Human leucocyte antigen B-27, Sacroilitis

INTRODUCTION

Spondyloarthritis (SpA) is a family of inflammatory joint disease characterised by axial and peripheral skeleton involvement. AS is the prototype for axial skeleton involvement [1]. The modified New York criteria classification for AS used radiographic involvement of sacroiliac joint which may take upto a decade to develop from the appearance of clinical symptoms resulting in delayed diagnosis and hence increasing morbidity associated with disease. The modified New York criteria, which was used for classifying patients with AS had an inherent low sensitivity, and as such was not suitable for diagnosing early axial spondyloarthritis [2]. The ASAS classification criteria for Axial Spndyloarthropathy (ASpA) published in 2009 aimed to achieve a greater sensitivity in diagnosing patients of axial spondyloarthritis [3,4]. The inclusion of MRI and HLAB27 in ASAS classification criteria has broadened the spectrum of spondyloarthritis [4]. Whether AS and nr-axSpA are subgroup of same disease or different entity needs to be known as it could affect the treatment of these two subgroup of patients. Whether a distinction between AS and nr-axSpA in clinical practice is useful, remains unknown. There have been very few studies from India comparing the two classes (AS vs. nr-axSpA), so the present study was done with aims to delineate, the differences between the baseline characteristics and disease activity of these two subgroups.

MATERIALS AND METHODS

A cross sectional study was conducted in Division of Rheumatology, SS Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi a Tertiary Centre in Eastern Uttar Pradesh, India from January 2016 to June 2017. All patients gave informed consent and Ethical Approval was taken by Institute Ethics Committee (No, Dean/2015-16/EC/110).

All the patients with history of chronic back pain for ≥3 months and age at onset ≤45 years were included in the study. Patients having chronic back pain duration <3 months, age of onset >45 years, past or present biologic therapy and pregnant women were excluded from the study. The patients satisfying the inclusion and exclusion criteria who presented to the institute during the study duration were included in study. Using the ASAS criteria, patients were then classified into two groups of 50 patients each of patients having AS (if there was sacroilitis on radiographs as defined in modified New York criteria) and nr-axSpA.

The various SpA related variables were then compared including Gender, Age, Duration of illness, enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis, family history, HLAB27, baseline CRP, baseline ESR, BASDAI, and BASFI.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software (Version 16.0) for windows. For comparing two groups of mean unpaired Student's t-test and for median Mann-Whitney U test were used. For categorical variable chi-square test and Fisher's-Exact test was used. A p-value <0.05 is considered as statistically significant.

RESULTS

The mean age of patients with nr-axSpA and AS was 28.56±8.685 and 28.66±7.566 respectively with males being 88% in nr-axSpA and 96% in AS subgroup. Patients with AS, as compared with nr-axSpA had a longer disease duration {4.5(1.875-8.250) vs. 2.0(1.000-4.000); p-value 0.023} and had a significantly higher levels of objective markers of inflammation i.e., CRP {4.7(2.325-6.525) vs. 2.20(0.588-4.125); p-value<0.001)} and ESR {(41.98±16.936 vs. 34.20±14.552; p-value 0.015)}. MRI was suggestive of sacroilitis in 46 patients in nr-axSpA group. Four patients had normal MRI of sacroiliac joints with HLA B27 positivity with two SpA features.

The two subgroups did not show statistically significant difference in age of onset, male: female ratio, enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis, family history, HLA B27, mean BASDAI and BASFI indices [Table/Fig-1].

Variables	nr-axSpA (n=50)	AS (n=50)	p-value
Males#	44(88%)	48 (96%)	0.140
Age(years) $	28.56±8.685	28.66±7.566	0.951
Disease duration* (median years)	2.0 (1.000-4.000)	4.5 (1.875-8.250)	0.023
Enthesitis#	15 (30%)	12 (24%)	0.499
Dactylitis#	4 (8%)	5 (10%)	0.727
Uveitis#	3 (6%)	4 (8%)	0.695
Peripheral arthritis#	20 (40%)	25 (50%)	0.315
Psoriasis#	1 (2%)	0 (0%)	1.000
Family history#	11 (22%)	5 (10%)	0.102
HLAB27#	49 (98%)	45 (90%)	0.092
CRP(mg/dL)* {Median (IQR)}	2.20 (0.588-4.125)	4.70 (2.325-6.525)	<0.001
ESR (mm 1st hour)$ Mean±SD	34.20±14.552	41.98±16.936	0.015
BASDAI$	3.812±1.2880	4.116±1.1685	0.219
BASFI$	2.27±0.98	2.42±1.02	0.467

[Table/Fig-1]: Comparison of various parameters between AS and nr-axSpA patients.
AS: Ankylosing Spondylitis; nr-axspa: Non radiographic axial spondyloarthritis; HLA: Human leukocyte antigen; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional Index; SD: Standard deviation; IQR: Interquartile range
*Significant p-value <0.05
For comparing two groups of mean unpaired Student's t-test ($), for median Mann-Whitney U test (*) and for categorical variable chi-square test and Fisher's-exact test was used (#).

DISCUSSION

In the study, we found out that most of the SpA related features do not vary significantly in the AS and nr-axSpA group. The total duration of disease in AS patients was significantly higher than nr-axSpA group. Baseline CRP and ESR were also higher in AS group.

To the best of our knowledge, there have been two studies from India comparing the two classes (AS vs. nr-axSpA). First study by Malviya AN et al., showed that patients with AS had a longer disease duration, more with male preponderance with more axial symptoms at disease onset; however, there was no significant difference between CRP and ESR [5]. This was different from the present result in that there was no male preponderance in AS group in the present study and a higher baseline CRP and ESR in AS patients. However, we also found that longer disease duration in AS group as compared with nr-axSpA group.

The study from Gavali M et al., showed that patients with AS compared with nr-axSpA were older at presentation, had a longer mean time to disease diagnosis, and had a higher proportion of positive family history [6]. This was in contrast to the present result wherein the age of onset was same, and no difference in family history could be found. The parameter that is similar in this study and present study include a longer disease duration in AS group as compared to nr-axSpA group.

The MRI was done of the patients who did not show X-ray changes of Grade 2 or higher sacroiliitis. Nr-axSpA can be diagnosed even if MRI is negative, for example in HLAB27 positive individuals with two or more SpA features. It is also true that many patients whose X-rays were initially normal and yet they fulfill the ASAS criteria for axSpA, may later on develop x-ray changes. At this time they will not be categorised as nr-axSpA. Thus, MRI may be positive in both subgroups but it is X-Ray of sacroiliac joints which differentiate the two subgroups. Sacroilitis was present in 46 patients of nr-axSpA in MRI. Four patients were diagnosed to have nr-axSpA because of HLA B27 positivity and two SpA features.

Others studies outside India have been done in the present regard [Table/Fig-2]. The study by Kiltz U et al., included 56 patients with AS and 44 with nr-axSpA [7]. They reported a higher proportion of males

	Kiltz U et al., [7]	Wallis D et al., [8]	Malviya AN et al., [5]	Gavali M et al., [6]	Swedish cohort [10]	GEPSIC COHORT [9]
	nr-axSpA (n=44) AS (n=56)	nr-axSpA (n=73) AS (n=639)	nr-axSpA (n=47) AS (n=187)	nr-axSpA (n=41) AS (n=55)	nr-axSpA (n=86) AS (n=238)	nr-axSpA (n=226) AS (n=236)
Females%	nr-axSpA =68 AS=24	nr-axSpA =53 AS=24	nr-axSpA =30 AS=16	N.S	nr-axSpA =38 AS=24	nr-axSpA =57.1 AS=36
Age (years) of onset	N.S	N.S	N.S	nr-axSpA =26.5 AS=33.7	nr-axSpA =38 AS=43	N.S
Disease duration (years)	N.S	nr-axSpA =12.1 AS=17.7	nr-axSpA =5.5 AS=7.75	nr-axSpA =1.3 AS=4.4	nr-axSpA =9 AS=16	N.S
Enthesitis	N.S	N.S	N.S	N.S	N.S	N.S
Dactylitis	N.S	N.S	N.S	N.S	N.S	N.S
Uveitis	N.S	N.S	N.S	N.S	N.S	N.S
Peripheral arthritis	N.S	N.S	N.S	N.S	N.S	N.S
Psoriasis	N.S	N.S	N.S	N.S	N.S	N.S
Family history%	N.S	N.S	N.S	nr-axSpA =9.8 AS=29	-	N.S
HLAB27	N.S	N.S	N.S	N.S	N.S	N.S
CRP (mg/dL)	nr-axSpA =5.7 AS=11.6	nr-axSpA =5.2 AS=11.4	N.S	-	nr-axSpA =10 AS=23	nr-axSpA =10.9 AS=14.8
ESR (mm 1st hour)	-	nr-axSpA =9.9 AS=13.7	N.S	N.S	nr-axSpA =23 AS=28	-
BASDAI	N.S	N.S	N.S	N.S	N.S	N.S
BASFI	nr-axSpA =2.4 AS=3.2	N.S	N.S	N.S	N.S	nr-axSpA =2.5 AS=3.1

[Table/Fig-2]: Comparison between various studies related to SpA variables.
NS-Non significant (significant p-value <0.05); Mean (SD) if not otherwise stated; Variables highlighted in bold were found to be statistically significant in respective studies; (-) indicates data is not available for that variable
AS: Ankylosing spondylitis/axial spondyloarthritis; Nr-axSpA: Non radiographic axial spondyloarthritis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index

and increased inflammatory burden as indicated by more signs of inflammation and higher CRP levels in the AS group as seen in the present study too.

Another recent study by Wallis D et al., compared 639 AS patients with 73 nr-axSpA patients [8]. The results of this study showed significantly more males and more inflammation by way of higher CRP levels in the AS group. In addition, longer disease duration was also reported in the AS group.

In German Spondyloarthritis Inception Cohort (GEPSIC) and Herne cohorts, the age of onset was same in AS and nr-axSpA groups; patients with AS had a longer disease duration, female representation was higher in nr-axSpA group, and proportion of patients with increased CRP was higher in AS group than nr-axSpA [9]. The results are consistent with the present study except a higher female preponderance in nr-axSpA group in GEPSIC and Herne cohorts.

In a Swedish study, 86 patients of nr-axSpA were compared with 238 patients of AS. In this study, they found a statistically significant female preponderance and lower levels of acute phase reactants in the nr-axSpA group. No difference was found in the two subgroups of AS and nr-axSpA with regards to other SpA related variables [10]. Again, this study differs from the present study in terms of female preponderance in nr-axSpA group; however this study, similar to present study, had significantly higher baseline markers of inflammation (namely ESR and CRP).

In most studies depicted in [Table/Fig-2], there was a female preponderance in the nr-axSpA group. However, we could not find a statistically significant difference in the present study. The reason could be that most of the patients in present study were from eastern part of Uttar Pradesh, India and adjacent areas of Bihar. There is a common neglect of symptoms of back pain among rural women in this part of the state because women are involved in agricultural works as well and back pain is a symptom common enough to be neglected and not further evaluated.

Another aspect of the study that requires an explanation is the raised baseline CRP and ESR levels. This parameter is consistent with all international studies but differ from Indian studies as outlined above. This probably occurs because in frank AS, there was longer disease duration than in nr-axSpA. Also, there was more obvious damage as evidenced by erosion and joint space narrowing in radiographs. Owing to this increased burden of the disease, the markers of inflammation should be higher in AS than in nr-axSpA wherein there was relatively a lesser damage and shorter disease duration. For Indian studies that otherwise have not found a significant difference between CRP and ESR levels, this could be explained as most patients in India get their reports of ESR and/or CRP from any local laboratory having little quality control. Hence, such reports are not entirely reliable and potentially could affect the final result.

If one considers nr-axSpA to be an early stage that will eventually progress to AS, the longer disease duration in AS could be explained. However, as noted above, the BASDAI and BASFI in the two groups do not vary significantly. This translates clinically into similar severity of axial symptoms in the two groups. The probable reason, as also suggested by Malviya AN et al., of why patients with AS have a longer disease duration is; because, the natural history of AS has a remitting and relapsing (flare) course, with a long symptom free period in some patients [5]. This symptom free period might be overlooked in a young person attributable to sprain. If this theory of intermittent symptom free period in AS holds true, then there should be a scarcity of such interval in nr-axSpA. This needs further studies.

The GEPSIC analyses showed that the rate of progression from nr-axSpA to AS is roughly 12% after a period of two years especially with those patients in whom baseline CRP was higher [9]. Finally certain parameters at baseline may predict the progression from the non-radiographic form to the radiographic form, and includes age of onset of symptoms, male sex, environmental factors (smoking, physical stress), genetic factors (HLA B27, certain genotypes, ERAP-1, and IL23R polymorphism), certain receptor protein biomarkers (KIR3DL1, Sclerostin, and Dkk-1), intensity of acute phase response, and presence of syndesmophyte(s) at first presentation [11,12].

LIMITATION

The study had a small sample size and absence of follow-up of patients with nr-axSpA to look for progression to the radiographic form i.e., AS. The second caveat of the present study was a failure to record the effects of pharmacological therapy on patients in the two groups. This would have been interesting to note if patients in AS group responded better to anti inflammatory therapy owing to an increased base line CRP and ESR. To clearly delineate the differences between nr-axSpA and AS a longer follow-up is essential.

CONCLUSION

The ASAS criteria for classifying patients of axSpA has a greater sensitivity, and for early diagnosis in the course of disease. These cases, wherein there was an absence of structural damage on conventional radiograph were previously misdiagnosed and treated wrongly. Progression of nr-axSpA to AS is well documented so these two may be considered different phases in the spectrum of same disease. On the other hand, structural changes in sacroiliac joints may never appear in nr-axSpA in spite of the functional limitation and disease index. Further research with large sample size is warranted to look for factors responsible for early, late, and no progression at all, from nr-axSpA to AS and in order to tell the exact prevalence of nr-axSpA.

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