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ORIGINAL ARTICLE

Comparison of patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) from a single rheumatology clinic in New Delhi

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Abstract

Aim: Comparison of ankylosing spondylitis (AS) with non-radiographic axial spondyloarthritis (nr-axSpA) classified with the recent ASsessment of spondyloArthritis International Society (ASAS) criteria.

Patients & Methods: This study included 288 patients clinically diagnosed as having spondyloarthritis (SpA) where a satisfactory radiograph of sacroiliac (S-I) joints was available. The AS and the nr-axSpA groups were compared for the various SpA-related variables.

Results: Of 288 axSpA patients, there were 187 with AS. Of the remaining 101 patients without radiographic sacroiliitis, S-I joint magnetic resonance imaging (MRI) was available in 72; 54 of them showed active sacroiliitis thus classified as nr-axSpA according to the ASAS criteria. The remaining 18 patients with normal MRI and the other 29 patients without MRI of the S-I joints (total 47 patients), were classified as nr-axSpA using the 'clinical arm' of the ASAS criteria. On comparing the 187 AS with 101 patients in the nr-axSpA group, the AS group showed significantly more males, longer disease duration, more axial symptoms at disease onset, higher Bath Ankylosing Spondylitis Metrology Index and more syndesmophytes. Biologicals were offered significantly more often to the AS group but methotrexate as monotherapy or in combination with other disease-modifying antirheumatic drugs was offered more often in nr-axSpA group. There was no statistically significant difference between AS and nr-axSpA in other SpA parameters.

Conclusion: The differences brought out between AS and nr-axSpA groups show that they may not be the same disease. A prospective long-term follow-up of large cohorts may help in clarifying if nr-axSpA is simply an early stage in the spectrum of SpA evolving into AS over time or is there inherent difference between them.

Key words: ankylosing spondylitis, Assessment of Ankylosing Spondylitis International Society criteria, axial-spondyloarthritis, modified New York criteria, non-radiographic spondyloarthritis.

INTRODUCTION

There are several earlier reports on spondyloarthritis (SpA) from South Asia. The subject has been reviewed recently by one of the authors (ANM).[1] Older papers from the 1970s used the Rome classification criteria for ankylosing spondylitis (AS).[2] In later reports, until as recently as 2009, modified New York (mNY) criteria[3] were used for the classification of AS.[4,5] Since the publication of recently described ASsessment of spondyloArthritis International Society (ASAS) criteria in 2009 for the classification of axial SpA (ax-SpA),[6] there have not been any publications from India on the subject of AS or SpA to the best of our knowledge. The present study describes findings on patients classifiable as having AS with mNY criteria as compared with those classifiable

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as non-radiographic axial spondyloarthritis (nr-axSpA) with the more recent ASAS criteria. The objective of this study was to understand if these two categories are similar or distinct diseases.

PATIENTS AND METHODS

Institutional Ethics Committee approval was taken for extracting patient data under strict confidentiality. The study included patients seen in a single private rheumatology clinic of one of the authors (ANM). In this clinic patients' records are entered in electronic medical record software specifically designed for rheumatology.[7] Data extraction was carried out using 'structured query language' (SQL). Records of patients with the diagnosis of AS (International Classification of Diseases [ICD]-10 code M45.-) or SpA (ICD-10 code M46.-), from October 2000 till the end of July 2014 were extracted. Patients below 16 years of age, those with diagnosed inflammatory bowel disease or psoriatic arthritis or psoriasis (present or past), those with overlap with any other inflammatory rheumatological disease or other bone diseases and malignancy were also excluded.

The various available SpA parameters included gender, smoking status, age at onset of symptoms, age at presentation to the clinic, delay in diagnosis, symptoms at onset, disease pattern at presentation, family history, extra-articular manifestations, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI),[8–10] Maastricht Ankylosing Spondylitis Enthesitis Index (MASES),[11] Ankylosing Spondylitis Disease Activity Score (ASDAS),[12] human leukocyte antigen (HLA)-B27 status, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), radiographic sacroiliitis, sacroiliitis only on magnetic resonance imaging (MRI) short tau inversion recovery (STIR) sequence of sacroiliac (S-I) joints, and drugs taken prior to first presentation, including nonsteroidal anti-inflammatory drugs (NSAIDs)/coxibs, disease-modifying anti-rheumatic drugs (DMARDs) and the number of patients who were offered the biological anti-tumor necrosis factor-α (TNF α) at the first visit to the clinic.

Statistical comparison was carried out between patients with AS and nr-ax-SpA. For comparison of data-sets with continuous variables, standard unpaired '*t*' or Mann–Whitney test were used without corrections, as appropriate. For comparison of categorical data-sets chai-square test or two-tailed Fisher's exact test were used as appropriate.

RESULTS

The electronic data base of the clinic included 347 patients with the diagnosis of axSpA. Satisfactory standard radiographs of S-I joints were available only for 288 patients. Therefore, only these patients were included in the present study. Among them there were 187 patients who showed radiographic sacroiliitis as defined by mNY criteria and thus classified as AS.[3] The second group of nr-axSpA consisted of 101 patients. Figure 1 gives the break-up of patients who had MRI, how many of them showed sacroiliitis, how many of them did not show sacroiliitis on MRI and how many did not get MRI done, therefore were classified as nr-axSpA using the 'clinical arm' of the ASAS classification criteria.[6] Accordingly there were 54 patients who showed active sacroiliitis with bone marrow edema on MRI (STIR sequence). They were classified as nr-axSpA using the 'imaging arm' of the ASAS criteria.[6] The other 18 patients who did not show sacroiliitis on MRI and the other 29 patients where MRI was not available (total of 47 patients), could only be classified as having nr-axSpA using the 'clinical arm' of the ASAS classification criteria.[6] Accordingly a total of 101 (54 + 18 + 29) patients were categorized as nr-axSpA. Thus, 187 AS patients (mNY criteria) and 101 nr-axSpA patients were available for further analysis.

Results are displayed in Table 1. As can be seen, the proportion of males, disease duration, axial symptoms at disease onset, higher BASMI and syndesmophytes were significantly more among the AS group as compared to the nr-axSpA group. There was also a trend toward longer delay in diagnosis and higher MASES in the AS group but the difference did not reach the level of statistical significance. Low-dose methotrexate (LD-MTX) monotherapy or LD-MTX in combination with other DMARDs was prescribed more often in the nr-axSpA group. TNFα was offered significantly more often in the AS group at first presentation to the clinic.

DISCUSSION

To our knowledge this is the first study from India comparing AS with nr-axSpA. Pertinent observations of the study included significantly more males, longer disease duration, more axial symptoms at disease onset, higher BASMI indicative of decreased spinal mobility and more syndesmophytes indicative of more osteoproliferation among the AS group. In addition, there was a trend for longer delay in diagnosis and higher enthesitis index in the AS group although the difference did not

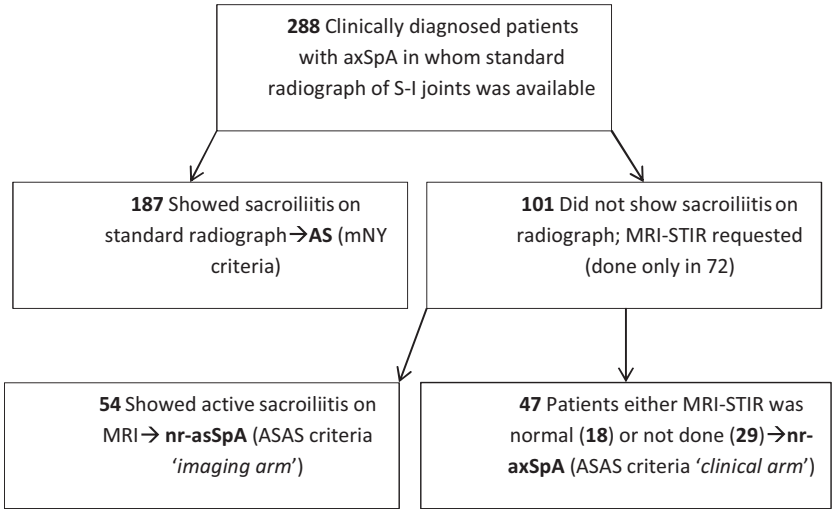

Figure 1 Break-up of the 288 clinically diagnosed axial spondyloarthritis (axSpA) patients with radiographic sacroiliitis, sacroiliitis only on magnetic resonance imaging (MRI) and those without sacroiliitis on imaging but classified as non-radiological (nr)-axSpA using the 'clinical arm' of the Assessment in Ankylosing Spondylitis International Working Group (ASAS) classification criteria.[6]

reach the level of statistical significance. Considering that AS is primarily an axial disease most of these differences would have been expected. Yet, parameters of disease activity and function, as well as inflammatory markers including BASDAI, ASDAS, BASFI, ESR and CRP, did not show significant differences between these two groups (Table 1).There have been two earlier studies comparing AS with nr-axSpA. The older study by Kiltz *et al.*[13] included 56 patients with AS and 44 with nr-axSpA. It reported a higher proportion of males and increased inflammatory burden as indicated by more signs of inflammation and higher CRP levels in the AS group. The second, more recent study by Wallis *et al.*[14] compared 639 AS patients with 73 nr-axSpA patients. 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 and higher BASMI were also reported in the AS group. When compared with these two reports, our study also found significantly more males in the AS group, thus establishing male predominance among AS. Our study also found other differences as noted by Wallis *et al.* namely longer disease duration, more axial symptoms at disease onset, higher BASMI indicative of decreased spinal mobility and more syndesmophytes indicative of more osteoproliferation among the AS group. These findings would suggest that patients with AS have a phenotypic subset of SpA that has a bias for axial skeleton involvement. More males in the AS than in the nr-axSpA group could indicate that mechanism (s) causing S-I joint and axial spine damage and osteoproliferation is(are) either different between AS and nr-axSpA patients or these are more severe in AS, especially in males. More axial symptoms seen in AS patients at disease onset would be expected in a group of patients with predominantly axial disease. Higher BASMI and more syndesmophytes in this group support this impression. However, the present study differs from the two above quoted studies in not having any difference in inflammatory parameters – ASDAS, BASDAI and CRP levels that did not show any significant difference between the two groups.

Longer disease duration and possibly longer delay in diagnosis in AS require some explanation. If one considers nr-axSpA as an earlier stage in evolution of axSpA that evolves into radiographic axSpA over time, then longer disease duration could be one explanation for significantly more axial involvement in this group. However, significantly more patients in this category had axial symptoms at the disease onset, a feature that goes against the hypothesis that axial involvement is time-related and casts doubt whether these two groups of patients have the same disease. The other possibility is that episodic symptoms with long symptom-free intervals in AS may be getting ignored or being attributed to mechanical causes in a young physically active person (sprains, strains, stress in lower back) thus delaying the diagnosis. It would be interesting to study if symptoms are more persistent with little symptom-free intervals among nr-axSpA bringing them to the

Table 1 Comparison of the various variables among AS with nr-axSpA patients. Values are mean (SD) unless stated as (%) in column 1

Variables	AS = 187†	nr-axSpA = 101†	*P*
Males (%)	84.5	70.3	**0.0058**
HLA-B27 (%)	90	92	0.9288
Age of onset (years)	24.3 (8.6)	24.8 (8.2)	0.6463
Age at first visit (years)	31.07 (9.6)	30.32 (8.5)	0.5147
Disease duration (months)	93 (79.3)	67 (65)	**0.0130**
Delay in diagnosis (months)	76.24 (65.2)	62 (63.2)	0.0749
Only axial symptoms at disease onset (%)	150	52	**0.0297**
Axial disease at presentation (%)	101 (54)	44 (43.5)	0.3342
Peripheral disease also present	87 (46)	57 (56.4)	0.3969
Syndesmophytes (%)	21 (11.2)	2 (2)	**0.0061**
AAU (%)	26 (14%)	8 (8)	0.2497
Enthesitis (%)	54 (29)	33 (32.7)	0.7019
Family history (%)	127 (68)	72 (78.2)	0.8474
Smokers (%)	34 (18)	18 (17.8)	1.0
NSAIDs taken prior to first visit (%)	33 (17.1)	12 (11.8)	0.3121
SSZ monotherapy prior to first visit (%)	34 (18)	12 (11.8)	0.689
SSZ in combination with other DMARDs taken prior to first visit	33 (17.1)	24 (23.8%)	0.3657
MTX monotherapy prior to first visit	6 (3.2)	19 (18.8)	**0.0001**
MTX in combination with other DMARDs prior to first visit	7 (3.74)	18 (17.8)	**0.0004**
Glucocorticoids taken prior to first visit (%)	18 (9.6%)	8 (7.9)	0.8302
Biologicals taken prior to first visit (%)	1 (0.5)	1 (0.5)	–
TNFα offered at first visit (%)	71 (38)‡	21 (20.8)‡	**0.0297**
BASDAI			
AS *n* = 112	3.4647 (1.9)		0.9045
nr-axSpA *n* = 101	3.6561 (1.95)		
ASDAS			
AS *n* = 62	2.9 (1.2)		0.9045
nr-axSpA *n* = 56	2.9 (1)		
BASFI			
AS *n* = 111	2.8 (2.3)		0.5509
nr-axSpA *n* = 100	2.6 (2.3)		
BASMI			
AS n = 184	2.5 (1.89)		**0.009**
nr-axSpA *n* = 100	1.9 (1.6)		
MASES			
AS *n* = 106	1.05 (1.7)		0.0793
nr-axSpA *n* = 72	1.55 (2.1)		
ESR			
AS *n* = 176	42.9 (34.7)		0.4030
Nr-axSpA *n* = 95	39.27 (33.4)		
CRP			
AS *n* = 130	40 (90.7)		0.4176
nr-axSpA *n* = 76	31 (46.3)		

†*n* is common except in those stated otherwise. ‡Among those offered TNFα only 31 (16.5%) of 187 AS patients and 11 (10.9%) of 101 nr-axSpA patients could afford it and took only a few doses of the drug. Acute anterior uveitis (AAU), ; AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; MASES, Maastricht Ankylosing Spondylitis Enthesitis Index; MTX, methotrexate; nr-axSpA, non-radiological axial spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; sulfasalazine (SSZ),; TNF, tumor necrosis factor. Numbers in BOLD indicate statistically significant difference.

clinic much earlier in the course of the disease. To solve this puzzle, as also suggested by Deodhar *et al.*[15] a long-term follow-up of a large cohort of patients would be required. No significant difference in CRP levels between AS and nr-axSpA in our study as against others[13,14] is difficult to explain. Patients bring their investigation reports from any clinical laboratory near their residence with little quality control. Therefore, reliability of laboratory reports may be a factor.

Drugs prescribed to axSpA patients prior to their first clinic visit showed some interesting trends. Most patients were treated by orthopedicians (86%).[16] Only 45 of a total of 288 axSpA patients (15.6%) had been prescribed NSAIDs and that too only 'on demand' for pain control. It would appear that non-rheumatologists in India (mainly orthopedicians) were not aware of the disease-modifying property of continuous intake of NSAIDs/coxibs.[17] LD-MTX monotherapy or in DMARD combinations was prescribed significantly more in nr-axSpA. Possibly non-rheumatologists considered the disease to be some form of inflammatory polyarthritis akin to rheumatoid arthritis (RA) because LD-MTX is now widely recognized as the main drug for RA. Significantly more patients having being offered TNFα to AS patients at first clinic visit in the face of similar range of BASDAI and ASDAS among nr-axSpA group is difficult to explain. It could be that while prescribing TNFα the rheumatologist not only took the degree of inflammation into account but also took the amount of damage into consideration.

The present study and several other earlier studies have clearly established that the recent ASAS classification criteria are more sensitive, leading to inclusion of many patients who would not have been classified axSpA earlier. Recently several groups of workers have presented evidence that ASAS criteria are valid and may be used for classifying axSpA patients.[13,14,18–24] These workers have argued that nr-axSpA and radiographic-axSpA are within the same spectrum of axSpA diseases except that nr-axSpa is an early stage subphenotype of axSpA. Misclassification of nr-axSpA in the past could have led to inadequate treatment for such patients. In this context it needs to be emphasized that AS and nr-axSpA groups had similar disease burden as discussed above and reported by other workers as well.[25] Our group had reported that among the 'unclassifiable' SpA category described by us in 1983,[26] 68% of patients progressed toward full blown AS in 11 years.[27] This has been quoted as proof of nr-axSpA being an early subphenotype of axSpA.[28] Conversely, some have argued that being more sensitive, use of ASAS classification criteria for axSpA may include a more heterogeneous group of patients, some of whom may not have axSpA (false-positives) and thus get over-treated.[29,30] Recently, the Food and Drug Administration has also expressed concern regarding ASAS classification criteria.[15] The present study could be relevant from this standpoint.

There were several limitations in the present study. First, it is a retrospective study. The data were collected from the review of patients' charts. Second, in the absence of a predesigned, protocoled questionnaire, collected data may have limitations with inbuilt inaccuracies. This is prominently reflected in the number (n) of patients with different variables shown in Table 1. This also led to non-availability of radiographs (excluded from the study) or MRI in several patients. Also, spinal indices were measured over time by different assessors with possible inter-assessor differences. Laboratory investigations were done in a large number of different laboratories which may not have appropriate quality control; patients brought the reports from any local clinical laboratory nearest to their residence. These limitations could have affected the results. Finally, despite the issue of their classification, it is obvious that there are many similarities between these two groups of patients. They have the same degree of severity of symptoms and therefore, deserve similar treatment.

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