Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences?

X Baraliakos, J Braun

ABSTRACT

The development of the axial spondyloarthritis and ankylosing spondylitis (ASAS) classification criteria has had several implications for our understanding of the entire spectrum of spondyloarthritides (SpA). Going beyond the modified New York criteria, which concentrate on conventional radiographs of the sacroiliac joints (SIJ) for the classification of ankylosing spondylitis, the ASAS criteria add active inflammation of the SIJ as obtained by MRI and human leucocyte antigen (HLA) B27 to classify patients with chronic back pain starting at a young age as axial SpA (axSpA). AxSpA should be considered as one disease that includes AS, the radiographic form, as well as the non-radiographic (nr-axSpA) form. Similarities and differences between these subgroups have been described in 3 studies: 1 local study, 1 national study (German SpA Inception Cohort) and 1 international study mainly conducted to test the efficacy of a tumour necrosis factor \( \alpha \) blocker. Most clinical features and assessments of axSpA showed the same prevalence in patients with and without radiographic changes. However, some differences have been observed: the male:female ratio, the proportion of patients with objective signs of inflammation such as bone marrow oedema as detected by MRI, and the proportion of patients with increased levels of C reactive protein were higher in patients with AS. Importantly, these factors have also been identified as prognostic factors for more severe disease in terms of new bone formation. Thus, nr-axSpA may represent an early stage of AS but may also just be an abortive form of a disease which does cause much pain but which may also never lead to structural changes of the axial skeleton. Since the cut-off between nr-axSpA and AS is artificial and unreliable, we think that the term nr-axSpA should not be used for diagnosis but only for classification for historical reasons.

INTRODUCTION

The term spondyloarthritis (SpA) covers a partly heterogeneous group of rheumatic diseases with the prototypes ankylosing spondylitis (AS) and forms of psoriatic arthritis. Patients with SpA are genetically linked.\(^1\) They may present with characteristic clinical features such as inflammatory back pain (IBP), with peripheral symptoms such as enthesitis or arthritis, and with extra-articular manifestations such as anterior uveitis, psoriasis and chronic inflammatory bowel disease.\(^2\) The majority of patients diagnosed as axial SpA (axSpA) also show objective signs of inflammation on imaging such as sacroiliitis and spondylitis\(^3\) or on laboratory examinations such as C reactive protein (CRP) or erythrocyte sedimentation rate. Furthermore, many patients, especially those who are positive for human leucocyte antigen (HLA) B27, have a positive family history of SpA or related diseases.\(^6\)\(^7\)

The concept of spondyloarthritis had already been recognised decades ago by Moll and Wright,\(^8\) and classification of patients as...
having AS has relied on the modified New York criteria, in which conventional radiographs of the sacroiliac joints showing more or less definite structural changes was most critical. Thereafter, another two sets of criteria have been published which aimed to classify patients presenting with axial and peripheral symptoms, even without the presence of radiographic damage in the sacroiliac joints.

The era of MRI, which started 20 years ago, has contributed to a better assessment of patients with early disease stages of axSpA. The publication of new classification criteria for axSpA, which also include, in addition to conventional radiographs showing structural changes, positive findings obtained by MRI of the sacroiliac joints showing inflammation, and HLA-B27 as an entry criterion, has broadened the spectrum of SpA. This development has initiated clinical research comparing the two axSpA subgroups, non-radiographic (nr-axSpA) and radiographic (AS) axSpA. However, in daily practice, this distinction has not been considered useful with respect to the diagnosis of the patients.

The aim of this overview is to describe and discuss the similarities and differences between the two axSpA subgroups, mainly taking into account data published in three studies that have investigated cohorts from different origins: one local study, one national study (German SpA Inception Cohort (GESPIC)) and a large Swiss cohort looking at patients with axSpA treated with TNF blockers, the proportion of patients with nr-axSpA was only around 25%. Overall, the proportions of patients with nr-axSpA and radiographic axSpA seem to be largely similar, and it can be stated that both subtypes are equally relevant for the axSpA concept. Clinicians should be aware about the similarities and slight differences between the subtypes, which in part may also represent different stages of the disease and also different disease courses.

**Similarities between nr-axSpA and radiographic axSpA**

**Demographics**

Except for the male:female ratio (see below), no major differences in patient demographics have been observed (table 1). The proportion of patients with symptom duration of ≥5 years was similar between two studies, with 68% and 61.2%. Almost no differences were found regarding the mean age of the patients at presentation between subgroups (table 1). Importantly, the prevalence of HLA-B27 was similar: 86.4% vs 89.1%, 74.7% vs 82.2% and 74.8% vs 81.5% for nr-axSpA and AS, respectively.

**Prevalence of clinical features of axSpA**

All studies showed that the frequency of typical clinical features and also of extra-spinal and extra-articular manifestations are similar between the two subgroups. Some variations between studies due to the geographic distribution of the examined populations were reported. For example, peripheral arthritis in general was found to be around 18% for nr-axSpA and AS in two studies, while the frequency was much higher in the third study with around 54%, again in both groups. Similar observations were also made for the prevalence of psoriasis, with 9.1% vs 10.7% and 5.3% vs 8.1% for nr-axSpA and AS, respectively, as well as for enthesitis and inflammatory bowel disease (table 1).

**Clinical assessments of disease activity**

The observations from the assessment of disease-specific questionnaires, which are also being used in daily practice, such as assessments of disease activity (Bath AS disease activity index, BASDAI, total pain and patient’s global assessment (both assessed on a numeric rating scale), were compared between patients with nr-axSpA and AS in all three studies taken into account here. Overall, no differences in the level of disease activity, pain and global assessment, as reported by the patients, were observed in any of the studies (table 1). Interestingly, one study also compared different clinical parameters in patients with nr-axSpA versus AS based on their level of disease activity, assessed by a high (BASDAI ≥4) versus low (BASDAI <4) disease activity. Although significant differences were found in almost all assessed parameters between patients presenting with BASDAI ≥4 vs <4, again no differences were observed between nr-axSpA versus AS.
Differences between nr-axSpA and radiographic axSpA

Despite the many similarities, patients classified as nr-axSpA have also shown differences as compared with those classified as radiographic axSpA. In general, three main differentiating categories can be considered: the degree of limitation related to mobility and function, the proportion of patients with increased objective markers of inflammatory activity, and the opposite male: female ratio in these subgroups.

In the GESPIC cohort, both function (assessed by the Bath AS function index (BASFI) and mobility (assessed by the Bath AS mobility index (BASMI)) were significantly different between patients with nr-axSpA and radiographic SpA—interestingly, with only minor differences in disease duration between the subgroups.

Although the term nr-axSpA does not necessarily imply that there are no structural changes in a patient at all (the definition just excludes structural changes in the SIJ), it can be assumed that there are no major structural changes in the spine of these patients. Thus, the more compromised function of patients with AS is likely to be mainly due to structural changes in the spine—even though it has been shown that function is influenced by both inflammation and new bone formation, and the degree to which one of these two factors contributes to a decrease in function is of course dependent on disease duration. This is clinically relevant since function is one of the items used to define ASAS partial remission. Finally, it is well known that patients with AS with poor function are less likely to reach partial remission. Whether this is all due to structural changes is not known, but it can be expected to be a major factor.

Furthermore, the proportion of patients with increased CRP was also different between patients being classified as nr-axSpA and AS in all three studies, with 29.5% vs 69.1%, 17 29.8% vs 51.9%18 and 63.3% vs 73.3,19 respectively. In addition, the inflammatory activity as assessed by the amount of inflammatory spinal lesions per patient was assessed in our study. Overall, a significantly higher amount of inflamed lesions per patient was found in the subgroup with established AS, as compared with the subgroup of patients that was classified as nr-axSpA.

Regarding the male:female ratio, all three studies found a higher proportion of female patients in the nr-axSpA subgroup, as observed, to an overall higher proportion of male patients in the subgroup with established AS (table 1). The male predominance in AS is due to the fact that male patients might progress faster and more frequently.31 Whether this can be explained by mechanical stress is a matter of debate.

Summary

On the basis of data from three different studies that included patients from various cohorts (local, national and international) and also from other cohorts not included in the present report, it is fair to say that patients classified as nr-axSpA according to the ASAS criteria represent an important subgroup of axSpA, but it is, nevertheless, not necessary to make the distinction between them when making a diagnosis of axSpA, because axSpA is one disease. Accordingly, patients classified as nr-axSpA have a similar clinical presentation compared to those classified as AS (radiographic axSpA). In addition, the response rates to TNF blockers were almost identical for the two axSpA subgroups.19 However, and beyond the more extensive structural

Table 1 Clinical characteristics of the three main studies compared in this report, showing similarities and differences observed between the two axSpA subtypes

|                   | Local cohort14 (n=44) | National cohort15 (n=226) | Worldwide study14 (n=157) |
|-------------------|-----------------------|---------------------------|---------------------------|
| Mean age          | 39.1±9.8              | 36.1±10.6                 | 37.4±11.8                 |
| HLA-B27 pos. (%)  | 86.4                  | 74.4                      | 74.8                      |
| Male (%)          | 31.8                  | 42.9                      | 48.3                      |
| Peripheral arthritis (%) | 18.2      | 18.2                      | 54.4                      |
| Enthesitis (%)    | 2.3                   | 24.8                      | –                         |
| Uveitis (%)       | 6.8                   | 2.2                       | –                         |
| Psoriasis (%)     | 9.1                   | 5.3                       | –                         |
| IBD (%)           | 6.8                   | 0.9                       | –                         |
| Mean BASDAI       | 3.6±1.7               | 3.9±2.0                   | 6.5±1.5                   |
| Mean BASFI        | 2.4±2.1               | 2.5±2.1                   | 4.9±2.3                   |
| Mean BASMI        | –                     | 1.1±1.3                   | 3.2±1.5                   |
| Mean CRP (mg/L)   | 5.7±6.5               | 10.9±18.7                 | 11.9 (0.1, 116.2)         |
| Patient’s global  | 4.0±2.7               | 4.9±2.5                   | –                         |
| NRS pain          | 4.0±2.1               | 4.8±2.5                   | –                         |
| Inflamed spinal lesions/patient (%) | 9.1 | 46.4 | – |

AS, ankylosing spondylitis; BASDAI, Bath AS disease activity index; BASFI, Bath AS function index; BASMI, Bath AS mobility index; CRP, C-reactive protein; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; nr-axSpA, non-radiographic axial spondyloarthritides; NRS, numeric rating scale.
changes seen on conventional radiographs of patients with AS, some differences have been identified: (1) the proportion of female patients is higher in nr-axSpA, (2) objective signs of inflammation (CRP, MRI) are observed more frequently in AS and (3) the impairment in function and mobility due to structural changes in the spine. These factors are, at least in part, related—male patients have more structural changes, which may cause more disability.31

Whether the male predominance in AS is due to more mechanical stress remains to be shown.32 Whether more mechanical stress leads to increased inflammatory activity also remains to be shown. However, all these parameters clearly contribute to a faster and more severe disease progression and to radiographic SpA, and this can even be further exaggerated by smoking26—Some patients might already develop definite structural changes in the first 3 years of the disease.7

In summary, despite the difference in the course of structural changes over time, nr-axSpA and radiographic axSpA represent stages of the same disease. However, a differentiation of these subtypes with respect to the terminology of the diagnosis in daily practice does not make sense from a clinical perspective.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES

1. Reveille JD. The genetic basis of spondyloarthropathies. Ann Rheum Dis 2011;70(Suppl 1):S44–50.
2. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379–90.
3. Douagos M, Baeten D. Spondyloarthritis. Lancet 2011;377:2127–37.
4. Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. Ann Rheum Dis 2010;69:1264–8.
5. Braun J, Baraliakos X. Imaging of axial spondyloarthritis including ankylosing spondylitis. Ann Rheum Dis 2011;70(Suppl 1):S97–103.
6. Heuft-Dorenbosch L, Landewe R, Weijers R, et al. Combining information obtained from magnetic resonance imaging and conventional radiographs to detect sacroiliitis in patients with recent onset inflammatory back pain. Ann Rheum Dis 2006;65:804–8.
7. von Olmis M, Junik AG, van der Heijde D, et al. HLA-B27 and gender independently determine the likelihood of a positive MRI of the sacroiliac joints in patients with early inflammatory back pain: a 2-year MRI follow-up study. Ann Rheum Dis 2011;70:1981–5.
8. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
9. Braun J, Bollow M, Eggens U, et al. Use of dynamic magnetic resonance imaging with fast imaging in the detection of early and advanced sacroiliitis in spondylarthropathy patients. Arthritis Rheum 1994;37:1039–45.
10. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
11. Rudwaleit M, Landewe R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.
12. Braun J, Baraliakos X, Kiltz U, et al. Classification and diagnosis of axial spondyloarthritis—what is the clinically relevant difference? J Rheumatol 2015;42:31–8.
13. Kiltz U, Baraliakos X, Karakostas P, et al. The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. Ann Rheum Dis 2012;71:1207–11.
14. Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondyloarthritis differ from patients with ankylosing spondylitis? Arthritis Care Res (Hoboken) 2012;64:1415–22.
15. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717–27.
16. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis 2014;73:39–47.
17. Weisman MH, Witter JP, Reveille JD. The prevalence of inflammatory back pain: population-based estimates from the US National Health Examination Survey, 2009–10. Ann Rheum Dis 2013;72:369–73.
18. Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondyloarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res (Hoboken) 2012;64:905–10.
19. Braun A, Saracabas E, Grifka J, et al. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? Ann Rheum Dis 2011;70:1782–7.
20. Ciurea A, Scherer A, Weber U, et al. Impaired response to treatment with tumour necrosis factor alpha inhibitors in smokers with axial spondyloarthritis. Ann Rheum Dis Published Online First 9 Feb 2015. doi:10.1136/annrheumdis-2013-205133
21. Stolwijk C, Boonen A, van Tubergen A, et al. Epidemiology of spondyloarthritis. Rheumatology 2012;51:441–76.
22. Siener J, Strinivasan S, Zamani O, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann Rheum Dis 2013;72:1621–7.
23. Podobryn D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliac joint progression over 2 years in patients with axSpA. Ann Rheum Dis 2011;70:1369–74.
24. Burgos-Vargas R, Vazquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. Arthritis Rheum 1995;38:835–44.
25. Garrett S, Jenkins T, Kenn E, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
26. Calin A, Garrett S, White lock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
27. Jenkinson TR, Mallorie PA, Whitelock HC, et al. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694–8.
28. Podobryn D, Haibel H, Listing J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the German SPOnDylarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72:1430–6.
29. Machado P, Landewe R, Braun J, et al. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:1465–70.
30. Anderson JJ, Baron G, van der Heijde D, et al. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876–86.
31. Baraliakos X, Listing J, van der Reeke A, et al. The natural course of radiographic progression in ankylosing spondylitis: differences between genders and appearance of characteristic radiographic features. Curr Rheumatol Rep 2011;13:383–7.
32. Braun J, Baraliakos X, Kiltz U. Non-radiographic axial spondyloarthritis: a classification or a diagnosis? Clin Exp Rheumatol 2015, in press.
33. Ward MM, Reveille JD, Leach TJ, et al. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. Arthritis Rheum 2008;59:822–32.