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REVIEW

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

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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 spondyloarthritis (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 α 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

Key messages

What is already known on this subject?

- Both the non-radiographic and the radiographic stage of axial spondyloarthritis can be recognised by the axial spondyloarthritis and ankylosing spondylitis (ASAS) classification criteria.

What might this study add?

- This review shows differences and similarities of the two subgroups of axial spondyloarthritis, confirming that these subgroups are parts of the same disease and do not represent two different and distinct diseases.

How might this impact on clinical practice?

- Patients recognised as having axial spondyloarthritis present with the same clinical characteristics and the same burden of disease and also have the same response to anti-inflammatory medication.

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.²⁻³ The majority of patients diagnosed as axial SpA (axSpA) also show objective signs of inflammation on imaging such as sacroiliitis and spondylitis⁴ 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.⁵⁻⁷

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,⁹ in which conventional radiographs of the sacroiliac joints showing more or less definite structural changes was most critical. Thereafter, another two sets of criteria^{10–11} 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,¹² 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.^{13–14} 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.¹⁵

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,^{16–17} one national study (German SpA Inception Cohort (GESPIC)¹⁸), where additional information on patients with radiographic axSpA with shorter (≤ 5 years) and longer (> 5 years) disease duration was also provided, and one international study that was mainly conducted to prove the efficacy of a new type of tumour necrosis factor α blocker.¹⁹

Prevalence and incidence of nr-axSpA and radiographic axSpA

There are limited data on the incidence, prevalence and proportion of patients classified or diagnosed as nr-axSpA and radiographic axSpA in the population or among patients who present to the GP or the rheumatologist.^{15–20–24} While the prevalence of IBP has been shown to be about 6% in the USA, the prevalence of axSpA is a lot lower. When including all forms of SpA, it may well be $> 1\%$. When looking at the GP seeing patients with chronic back pain, a prevalence of axSpA of 5% has been reported, while the real figure may be substantially higher.²² In a recent consecutive study,¹⁷ the majority (56%) of patients presenting to our outpatient clinic with typical symptoms already had radiographic changes in the sacroiliac joints (SIJ). Similar data have been reported in another study looking at different referral strategies in patients with chronic back pain.²⁵ However, analyses from GESPIC have shown that the rate of progression from nr-axSpA to AS is about 12% after only a short period of 2 years, especially in patients with increased levels of CRP,²⁶ while similar rates of progression have also been described from other regions in the world.²⁷ In the

large Swiss cohort looking at patients with axSpA treated with TNF blockers, the proportion of patients with nr-axSpA was only around 25%.²³ 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%¹⁷ and 61.2%.¹⁹ 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%,¹⁷ 74.7% vs 82.2%¹⁸ and 74.8% vs 81.5%¹⁹ 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%¹⁷ and 5.3% vs 8.1%¹⁸ 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,²⁸), 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 study¹⁷ 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.

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

	Local cohort ¹⁴		National cohort ¹⁵		Worldwide study ¹⁴	
	nr-axSpA (n=44)	AS (n=56)	nr-axSpA (n=226)	AS (n=236)	nr-axSpA (n=157)	AS (n=178)
Mean age	39.1±9.8	41.2±10.9	36.1±10.6	35.6±10.2	37.4±11.8	41.5±11.6
HLA-B27 pos. (%)	86.4	89.1	74.4	82.2	74.8	81.5
Male (%)	31.8	76	42.9	64.0	48.3	72.5
Peripheral arthritis (%)	18.2	17.9	18.2	14.4	54.4	53.9
Enthesitis (%)	2.3	1.8	24.8	20.8	–	–
Uveitis (%)	6.8	5.4	2.2	1.7	–	–
Psoriasis (%)	9.1	10.7	5.3	8.1	–	–
IBD (%)	6.8	5.4	0.9	1.7	–	–
Mean BASDAI	3.6±1.7	4.2±2.2	3.9±2.0	4.0±2.1	6.5±1.5	6.4±1.6
Mean BASFI	2.4±2.1	3.2±2.4	2.5±2.1	3.1±2.5	4.9±2.3	5.7±2.2
Mean BASMI	–	–	1.1±1.3	2.0±1.8	3.2±1.5	4.4±1.7
Mean CRP (mg/L)	5.7±6.5	11.6±12.6	10.9±18.7	14.8±16.0	11.9 (0.1,156.2)	14.3 (0.1, 174.8)
Patient's global	4.0±2.7	4.6±2.7	4.9±2.5	5.0±2.5	–	–
NRS pain	4.0±2.1	4.72.7	4.8±2.5	5.0±2.5	–	–
Inflamed spinal lesions/patient (%)	9.1	46.4	–	–	–	–

AS, ankylosing spondylitis; BASDAI, Bath AS disease activity index; BASFAI, 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 spondyloarthritis; NRS, numeric rating scale.

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 index²⁶) and mobility (assessed by the Bath AS mobility index²⁷) 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,²⁹ 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.³⁰ 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,⁷ 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,³² 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

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.³³ 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 smoking.²⁸ 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.

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