Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain?

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ABSTRACT

Background  The value of clinical items defining inflammatory back pain to identify patients with axial spondyloarthritis (SpA) in primary care is unclear.

Objective  To identify predictive clinical parameters for a diagnosis of axial SpA in patients with chronic back pain presenting in primary care.

Methods  Consecutive patients aged <45 years (n = 950) with back pain for >2 months who presented to orthopaedic surgeons (n = 143) were randomised based on four key questions for referral to rheumatologists (n = 36) for diagnosis.

Results  The rheumatologists saw 322 representative patients (mean age 36 years, 50% female, median duration of back pain 30 months), 113 patients (35%) were diagnosed as axial SpA (62% HLA B27+), 47 (15%) as ankylosing spondylitis (AS) and 66 (21%) as axial non-radiographic SpA (nrSpA). Age at onset <35 years, improvement by exercise, improvement with non-steroidal anti-inflammatory drugs, waking up in the second half of the night and alternating buttock pain were identified as most relevant for diagnosing axial SpA by multiple regression analysis. Differences between AS and nrSpA were detected. No single item was predictive, but ≥3 items proved useful for good sensitivity and specificity by receiver operating characteristic modelling.

Conclusion  This study shows that a preselection in primary care of patients with back pain based on a combination of clinical items is useful to facilitate the diagnosis of axial SpA.

The term spondyloarthritis (SpA) covers a heterogeneous group of rheumatic diseases characterised by common clinical symptoms such as inflammatory back pain (IBP) which is considered the leading symptom in patients with the condition.1 Patients with SpA have been divided into two subgroups according to the predominant symptoms,2,3 which can either be localised in the spine (axial SpA) or in the peripheral joints (peripheral SpA). Ankylosing spondylitis (AS), the prototype of axial SpA, is characterised by spinal stiffness.1 The other common differentiations used to diagnose or classify patients with SpA are the presence of a disease-defining feature such as psoriasis, inflammatory bowel disease (IBD), Crohn’s disease or ulcerative colitis) or the history of a triggering infection in the enteral or urogenital tract (reactive arthritis). In the absence of these features, the term ‘undiagnosed SpA’ (uSpA) has been used while, for patients with IBP but without structural changes in the sacroiliac joints and the spine, the term ‘non-radiographic axial SpA’ (nrSpA) is used.4 Not all patients with SpA will develop AS.5,6

A significant delay in diagnosing AS has been reported.7 Thenew Assessment of SpondyloArthritis international Society (ASAS) classification criteria2,3 are a step forward in making an earlier diagnosis of patients with axial SpA, but it is unclear whether they work in primary care. Possible screening tools for axial SpA including IBP and HLA B27 were proposed some years ago in patients with chronic back pain.8 Some of the proposed items were tested in a referral9 and a cohort study.10

The major clinical item in SpA is IBP, first defined in 1977.11,12 IBP has long been a central part of the classification criteria for AS13 and SpA.14 Novel definitions for IBP have recently been proposed.11,15,16 In a population-based study, many false positive answers to questions on IBP were found in controls.17

Chronic back pain is a common symptom of patients presenting to GPs and orthopaedic surgeons.18 The general perception and approach to the diagnosis and management of AS has been reported to be in part inconsistent in primary care.19 There is limited knowledge on the prevalence of IBP due to SpA in primary care, but one study reported a prevalence of 5% among patients with chronic back pain,20 a percentage similar to that recently reported by chiropractors.21 Of course, the prevalence of SpA in patients presenting to rheumatologists is likely to be significantly higher, reflecting the different pretest probability of SpA.22

The aim of this study was to test different IBP-related clinical items in primary care.

METHODS

This study was designed as a prospective case ascertainment trial that included a stratification step based on prespecified recognition criteria leading to a randomised selection for referral to a rheumatologist. A total of 148 orthopaedic surgeons in private practice and 36 rheumatologists took part in the study. The time frame was April 2007 to June 2009 for screening and May 2007 to May 2009 for validation.

The study plan was to identify 1000 patients in primary care with chronic back pain for >2 months and <10 years in whom back pain first occurred between the ages of 16 and 45 years, and to refer to rheumatologists about 400 patients after stratification and randomised selection performed by an independent institute based on four prespecified recognition criteria: (1) morning stiffness ≥30 min;
RESULTS

Description of patient populations studied

A total of 1074 patients were included, of whom 950 could be analysed; 670 were referred to a rheumatologist of whom 334 attended, and 322 patients with complete data were available for analysis. The rheumatological examinations were performed a median of 20 days after the initial visit to primary care.

The relative frequency of the prespecified recognition criteria in the different subsets is shown in table 1 and the relative frequency of positive answers in table 2. Overall, there was no difference between the demographic characteristics of the patients referred to the rheumatologist and the total study population.

The characteristics of the 322 patients with complete data were: mean age 36±7.9 years, 49.4% male, mean height of men 181±7 cm, mean height of women 167±6 cm, mean weight of men 85.6±14.5 kg and mean weight of women 67±16.7 kg. The age at symptom onset was 32.2±7.4 years and the mean duration of complaints was 44.2±38.1 months.

The distribution within the age groups was 13 patients (4%) aged <20 years, 67 (21%) aged 21–30 years, 134 (42%) aged 31–40 years, 104 (32%) aged 41–50 years and 4 (1%) aged >50 years. Fifty-eight patients (18%) reported having had back pain for <6 months, 43 (13%) for 6–12 months, 51 (16%) for 12–24 months, 84 (26%) for 24–60 months and 86 (27%) for >60 months. Twenty-two (7%) reported age of onset of <20 years, 49 (15%) at age 21–25 years, 49 (15%) at age 26–30 years, 85 (26%) at age 31–35 years, 69 (21%) at age 36–40 years and 48 (15%) at age 41–45 years.

Patient diagnoses, demographics and clinical manifestations

As shown in table 3, 113 patients were diagnosed with SpA (66 with nrSpA and 47 with definite AS) and 209 patients were diagnosed as non-SpA. The majority of the latter group had non-specific lower back pain or degenerative disc disease. The mean age of the patients with SpA was 36 years. The relative distribution of the different age groups was similar among the 113 patients with SpA and the 209 non-SpA patients (9 (8%) vs 13 (6.2%) <20 years, 44 (38.9%) vs 54 (25.9%) 20–30 years, 53 (45.1%) vs 103 (49.3%) 30–40 years and 9 (8%) vs 39 (18.7%) >40 years).

The age distribution between patients with AS and nrSpA was 26 (55%) versus 27 (41%) in those aged <20–30 years and 21 (45%) versus 39 (59%) in those aged <30–45 years.

Extraspinal manifestations were reported in 23.5%, enthesitis/heel pain in 11%, arthritis/joint swelling without trauma in 7% and psoriasis in 6% of patients with SpA. A family history of AS and SpA was reported in 4% and 2% of patients, respectively.

HLA B27 results

HLA B27 was positive in 35/46 patients with AS (76.1%), in 31/60 with axial uSpA (51.7%), in 66/106 patients with axial

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### Table 2 Relative frequency of positive answers for the entry criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Screening (n=950)</th>
<th>Referral (n=670)</th>
<th>Validation (n=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1: Morning stiffness &gt;30 min</td>
<td>22.0%</td>
<td>30.8%</td>
<td>32.9%</td>
</tr>
<tr>
<td>C2: Improvement by movement not by rest</td>
<td>60.4%</td>
<td>72.4%</td>
<td>65.6%</td>
</tr>
<tr>
<td>C3: Waking up in the second half of the night because of back pain</td>
<td>38.9%</td>
<td>54.9%</td>
<td>46.4%</td>
</tr>
<tr>
<td>C4a: Improvement with NSAIDs within 48 h (in the whole cohort)</td>
<td>44.6%</td>
<td>57.0%</td>
<td>55.4%</td>
</tr>
<tr>
<td>C4b: Improvement with NSAIDs within 48 h (if taken)</td>
<td>73.6%</td>
<td>80.9%</td>
<td>76.4%</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug.
Table 3  Diagnoses of patients seen by the rheumatologist

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort referred</td>
<td>322</td>
<td>100</td>
</tr>
<tr>
<td>Axial SpA</td>
<td>113</td>
<td>35.1</td>
</tr>
<tr>
<td>Non-radiographic axial SpA</td>
<td>66</td>
<td>20.5</td>
</tr>
<tr>
<td>Undifferentiated SpA</td>
<td>55</td>
<td>16.9</td>
</tr>
<tr>
<td>SpA associated with psoriasis</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td>Reactive SpA</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>SpA associated with IBD</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>AS</td>
<td>47</td>
<td>14.6</td>
</tr>
<tr>
<td>Non-SpA back pain</td>
<td>209</td>
<td>64.9</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; non-SpA, no spondyloarthrits; SpA, spondyloarthritis.

SpA (62.3%) and in 22/184 patients with other causes of back pain (12%). HLA B27 was not determined in 7 patients with SpA and 25 non-SpA patients. The prevalence of HLA B27 in the German population is about 9%.17

Comparative performance of different items to predict SpA

Sensitivity, specificity and likelihood ratios of the most relevant items

The performance of the prespecified recognition criteria for the prediction of AS, nrSpA and axial SpA showed a sensitivity of 70.2%, 39.4% and 52.2%, respectively, a specificity of 74.6% and a quality of 72.7%, 57.3% and 65.7%, respectively. The positive likelihood ratio (LR+) for axial SpA was 2.8 and the negative likelihood ratio (LR−) was 0.64.

The most useful items and their combinations are shown in table 4. This table shows that single items are of limited value and that the combination of any three items does not substantially increase the likelihood of axial SpA.

While the LR+ values were all <3, the LR− of improvement by NSAIDs, age ≤35 years and ≥3 criteria fulfilled indicated possible usefulness in primary care. This was further analysed by ROC curve analyses (see below).

Regression analyses

The main results of the multivariate logistic regression analysis are shown in table 5. In general, ORs were higher for AS than for nrSpA and there were other differences between the two (see below). The OR for the whole group of patients with axial SpA was 1.2–3.6, with different levels of significance.

For axial SpA, the p values of the items age at onset ≤35 years, improvement by NSAIDs and by movement, waking up in the second half of the night and alternating buttock pain indicated a significant value for identifying patients with axial SpA in primary care, while other items known to be characteristic for SpA were not significant. For AS, the items listed for axial SpA were the same but, for nrSpA, different items (enthesitis and psoriasis) were relevant in addition to age at onset ≤35 years.

ROC curve analyses

The ROC curves were calculated on the basis of items with significant results in the regression analysis for AS, early axial SpA and the whole group of axial SpA. An example is shown in figure 1.

► For a diagnosis of axial SpA, ROC curve analysis (figure 1) showed that, if ≥4 criteria were present, the sensitivity was 47.8%, the specificity was 86.1% (area under curve (AUC) 71.3%), LR+ 3.4, LR− 0.6.

► For a diagnosis of AS, ROC curve analysis showed that, if ≥3 criteria were present, the sensitivity was 57.4%, specificity was 85.6% (AUC 75.7%), LR+ 4.0, LR− 0.5. If ≥2 criteria were present, the sensitivity was 85.1%, specificity was 46%, LR+ 1.6, LR− 0.6 (data not shown).

Thus, there were major differences between patients with AS and nrSpA.

Differences between AS and nrSpA

For a diagnosis of AS the following four parameters always proved to be relevant while this was not the case in the nrSpA group:

► Improvement of back pain in motion, not at rest.
► Waking up during the second half of the night.
► Improvement with NSAIDs within 48 h.
► Alternating buttock pain.

For the nrSpA group the following parameters were more relevant:

► Age at onset ≤35 years.
► History of enthesitis.
► History of psoriasis.

In contrast, male gender, duration of chronic back pain >30 months, a family history of SpA, a history of uveitis, a history of IBD, morning stiffness >30 min (C1) did not appear to be relevant in any model or criteria set.

The quality of the models was highest for AS, followed by axial SpA and nrSpA.

DISCUSSION

This is the first study to analyse prospectively the predictive performance of clinical items for diagnosing axial SpA in a primary care setting. In Germany, most patients with back pain will see an orthopaedic surgeon as their first contact with the health system. This does not mean that GPs and physical therapists will not also see such patients, but these healthcare professionals were not included in this study. It also needs to be stressed that we did not only include patients who visited a physician with back pain for the first time.

The results of this study show that asking single specific SpA-related questions in primary care is of no value for a diagnosis of patients with axial SpA and that specific combinations are much more useful. Furthermore, we have identified important differences between patients with established AS and those with nrSpA.

Our data confirm the results of earlier studies which also suggested that single screening parameters are of very limited value and that combinations of parameters perform better.10 It is important to stress that this dataset has been obtained in a pre-specified population of relatively young patients with chronic back pain and not in the general population. This is consistent with the major aim of the study, which was to develop a good tool to facilitate an early diagnosis of axial SpA.

The best likelihood ratio for a diagnosis of axial SpA calculated (excluding HLA B27) was obtained with the following five items: age at onset ≤35 years, waking up in the second half of the night, alternating buttock pain, improvement by NSAIDs within 48 h or no NSAID and improvement by movement not rest. It will be necessary to test this proposal prospectively to further determine its usefulness.

Some findings of this study deserve special comment. It is noteworthy that the age cut-off for SpA was lower in our study...
Table 4  Sensitivity and specificity of the main entry criteria and other SpA-specific items for AS and axial SpA in primary care

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity for axial SpA (AS) %</th>
<th>Specificity for axial SpA (AS) %</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness &gt;30 min</td>
<td>35.4 (46.8)</td>
<td>66.5 (68.0)</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Improvement by movement not by rest</td>
<td>77.9 (83.0)</td>
<td>39.7 (36.4)</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Waking up in the second half of the night because of back pain</td>
<td>58.4 (70.2)</td>
<td>57.5 (58.6)</td>
<td>1.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Improvement by NSAIDs within 48 h</td>
<td>93.8 (78.7)</td>
<td>48.0 (48.9)</td>
<td>1.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Alternating buttock pain</td>
<td>24.8 (34.0)</td>
<td>88.5 (88.5)</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>History of enthesitis</td>
<td>15.0</td>
<td>91.9</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>History of arthritis</td>
<td>10.6</td>
<td>95.7</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Age &lt;35 years</td>
<td>77.0</td>
<td>43.5</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>HLA B27 (as determined in primary care)</td>
<td>35.4</td>
<td>90.9</td>
<td>3.9</td>
<td>0.7</td>
</tr>
<tr>
<td>≥3 criteria</td>
<td>85.1</td>
<td>49.8</td>
<td>1.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis.

Table 5  Odds ratios (OR) of relevant items for a diagnosis of axial SpA: results of logistic regression analysis

<table>
<thead>
<tr>
<th>Age ≤35 years</th>
<th>AS</th>
<th>Non-radiographic axial SpA</th>
<th>Axial SpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 (p=0.03)</td>
<td>2.8 (p=0.03)</td>
<td>2.6 (95% CI 1.5 to 4.5) (p=0.0009)</td>
<td></td>
</tr>
<tr>
<td>3.3 (p=0.005)</td>
<td>2.0 (p=0.1)</td>
<td>2.7 (95% CI 1.4 to 5.5) (p=0.003)</td>
<td></td>
</tr>
<tr>
<td>2.9 (p=0.01)</td>
<td>NS</td>
<td>1.2 (95% CI 0.7 to 2.2) (p=0.004)</td>
<td></td>
</tr>
<tr>
<td>3.0 (p=0.005)</td>
<td>NS</td>
<td>1.9 (95% CI 1.1 to 3.2) (p=0.001)</td>
<td></td>
</tr>
<tr>
<td>2.0 (p=0.1)</td>
<td>1.9 (p=0.07)</td>
<td>1.9 (95% CI 1.0 to 3.4) (p=0.03)</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>3.6 (p=0.02)</td>
<td>2.1 (95% CI 0.7 to 6.4) (p=0.02)</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>2.7 (p=0.03)</td>
<td>2.3 (95% CI 1.0 to 5.1) (p=0.06)</td>
<td></td>
</tr>
<tr>
<td>7.2 (p=0.07)</td>
<td>NS</td>
<td>3.6 (95% CI 0.5 to 25.3) (p=0.2)</td>
<td></td>
</tr>
<tr>
<td>3.4 (p=0.079)</td>
<td>2.5 (p=0.1)</td>
<td>2.6 (95% CI 0.9 to 7.1) (p=0.06)</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>2.5 (p=0.1)</td>
<td>2.3 (95% CI 0.8 to 6.6) (p=0.1)</td>
<td></td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; NS, not significant; NSAID, non-steroidal anti-inflammatory agent; SpA, spondyloarthritis.

than earlier proposals for IBP.11 This makes sense since the mean age at onset of AS is 26 years.7 Currently used IBP criteria should be re-evaluated on this basis, having in mind that this will probably be mainly helpful in identifying patients with a high likelihood of developing AS, and that this may be different in patients with nrSpA including those with a slowly progressive course of disease (see below).6

On the other hand, the absence of the classic IBP criterion of morning stiffness was unexpected. Alternating buttock pain is often suggested as a possible contributor5 since, although not very sensitive, this item is rather specific and is now shown in a primary care setting. However, a combination with other items is necessary.

Waking up in the second half of the night was not part of the original criteria set for a definition of IBP11 but was introduced later.23 This item is also useful in primary care, again mainly when combined with other items.

A good response to NSAIDs24 has become increasingly established as part of the classification criteria for axial SpA,3 as confirmed in this study. The results of a recent meta-analysis on the efficacy of NSAIDs in non-specific low back pain25 support this proposal. However, as our study also shows, not all the patients had taken NSAIDs. Thus, a negative answer to the question concerning improvement by NSAIDs may simply indicate that the patient had not taken the medication. This needs to be taken into account in future studies. Improvement by movement, although not really a medical intervention, is also related to a change in patient behaviour (moving around instead of resting).

Another important finding is that the items that perform best in the prediction of axial SpA differed between established AS and nrSpA. Both enthesitis and psoriasis were found to be useful. We were surprised that enthesitis was a significant item because, although somewhat characteristic of SpA,26 it is not an easy item for patients to understand. The same is true for psoriasis, which is a rather frequent disease. The difference between AS and nrSpA may be explained by observational studies suggesting that not all patients with nrSpA develop AS.5 6 Thus, axial SpA is not only a disease continuum from early (nrSpA) to advanced disease (AS), but also a covering term for patients who might never develop structural changes in the sacroiliac joints and/or the spine. This has also been suggested by recent studies on anti-tumour necrosis factor therapy in ‘early’27 and nrSpA,28 where the mean age of the patients differed (28 and 35 years, respectively).

The design and methodology used in this study ensured that the patients seen by the rheumatologists were representative, as shown in table 1. However, the prevalence of the prespecified recognition items was slightly higher in the referral population, which may have led to more patients with SpA being seen by the rheumatologist (see below). The selection of the entry criteria was based on published criteria for IBP and expert opinion. Because of the low sensitivity of the item ‘alternating buttock pain’, we decided to use a good response to NSAIDs as a major criterion because of the expected high sensitivity, and this was clearly confirmed by the data obtained. We were surprised by the relatively bad performance of morning stiffness for >30 min which was only stated by about 22% of patients. The other two items performed as expected. As shown in table 2, we managed to include patients in the appropriate age groups, the planned gender ratio was met and the patient numbers planned were included. The majority of patients were seen within 3 weeks by the rheumatologists, but they appeared to have some problems with their capacity to see referral patients, which is why fewer than 400 patients were seen by the experts who were in charge of the diagnosis. These colleagues had been informed about the new ASAS criteria2 3 and the established AS criteria,13 but we did not systematically check whether they were correctly applied. This is a possible weakness of the study, but the
Another important new finding, we have presented these results in
the different SpA subsets studied. Since we consider this an
important new finding, we have presented these results in
detail.

What does this mean with regard to identifying patients with suspected axial SpA as early as possible? In general one would like to have a tool with very good sensitivity to identify as many patients as possible but, on the other hand, the capacity to see patients may be limited and a high specificity may be more important. We have presented our results in relation to both points of view so the rheumatologist, in cooperation with GPs or orthopaedic surgeons, can choose which way to go. Since it seems easier and more useful to stick to the criteria for axial SpA rather than to look at AS and nrSpA differently, we propose using these criteria for calculations for the selection process (figure 1). Thus, in settings with very good capacity, the preferred strategy would be to go for 2/5 criteria with a sensitivity of 96.5% and a specificity of 17%, which means that five patients with chronic back pain will have to be seen to make a diagnosis of axial SpA in one. This strategy seems to guarantee that almost all patients with axial SpA can be identified. In settings with limited capacity the strategy could be to go for 4/5 criteria, in which case almost every patient seen will have axial SpA but about half the patients will be lost. The intermediate strategy with 3/5 criteria has a sensitivity of 79% and a specificity of 47%, which means that only 20% of patients with axial SpA would be lost and a diagnosis is likely to be made in every second patient.

It remains to be seen whether strategies including HLA B27 testing in primary care will further improve the performance of the clinical parameters. This will be analysed in a separate paper.

Finally, it must be stressed that the results of this study are only valid in a primary care setting in Germany and therefore we are not discussing diagnostic or classification criteria but rather tools that can be used to preselect patients who need to be seen by the rheumatologist. The proposed strategies based on the results of this study should be further evaluated prospectively in other countries.

Acknowledgements The authors thank Professor D van der Heijde, Professor J Sieper, Dr J Listing and Dr M Vennemann for their useful comments.

Funding The study was sponsored by an unrestricted grant from Abbott, Germany. The company had no influence on the study design, results and analyses.

Competing interests None.

Ethics approval Approval of the ethical committee of the Aertztkammer Westfalen-Lippe at the University of Muenster was obtained and patients gave written informed consent before inclusion in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

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Ann Rheum Dis 2011 70: 1782-1787 originally published online August 5, 2011
doi: 10.1136/ard.2011.151167

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