Arthritis Care & Research
Vol. 69, No. 6, June 2017, pp 938–942
DOI 10.1002/acr.23017

BRIEF REPORT

Diagnostic Value and Validity of Early Spondyloarthritis Features: Results From a National Spanish Cohort

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Objective. **To evaluate the validity of different spondyloarthritis (SpA) features included in the Berlin diagnostic algorithm and the Assessment of SpondyloArthritis international Society (ASAS) classification criteria in an early SpA cohort.**

Methods. **This was a longitudinal multicenter study including patients from the ESPeranza program cohort who were suspected to have SpA. Subjects were ≤45 years old, and SpA symptom duration was 3–24 months. Patients with axial SpA symptoms were selected and categorized according to diagnosis (yes/no) of axial SpA. Descriptive analysis was performed, and the sensitivity, specificity, predictive value, and likelihood ratio (LR) of each feature were calculated.**

Results. **Of 775 patients suspected to have SpA, 665 had predominantly axial symptoms and 516 of these patients were diagnosed with axial SpA. The most useful SpA features were sacroiliitis on magnetic resonance imaging (positive LR 6.6) or radiograph (positive LR 31.1) and peripheral arthritis (positive LR 8.9). The features with the lowest diagnostic utility were a family history of SpA (positive LR 1.5) and good response to nonsteroidal antiinflammatory drugs (positive LR 1.6). Inflammatory back pain (IBP; according to ASAS criteria) was described in only 27% of SpA patients, with a positive LR of 2.3. HLA–B27 positivity was present in 245 (48%), and the positive LR was 2.8.**

Conclusion. **The diagnostic value of SpA features in patients with early axial SpA seems to be different than in patients with longstanding disease. Chronic back pain is better than IBP as an entry point to the diagnostic algorithm. Sacroiliitis on imaging is very important for early diagnosis, while the use of HLA–B27 status as a key factor is questionable.**

Introduction

Spondyloarthritis (SpA) comprises a common group of inflammatory diseases with an estimated global prevalence of 0.18–1.9% (1–3). In recent decades, it has become increasingly evident that in many patients with ankylosing spondylitis (AS), there are years between the onset of inflammatory back pain (IBP) and the appearance of radiographic sacroiliitis (4), which delays diagnosis. Early SpA patients have similar activity, and even worse functioning (5), which creates a significant socioeconomic impact on the patient and on society (6,7). Thus, an early and reliable diagnosis is a very important objective.

The Berlin criteria is a diagnostic algorithm based on the calculation of the likelihood ratio (LR) product of currently available diagnostic features for axial SpA (8). The results from it assisted in the subsequent development of the Assessment of SpondyloArthritis international Society (ASAS) classification criteria. However, these Bayesian probabilities are calculated as median values based on several longstanding populations (9), with features different from those of an early SpA cohort (10). This approach could be improved if the probabilities were calculated in early cohorts.

The aim of this study was to evaluate the diagnostic value and validity of different SpA features in the early diagnosis of the disease. For this purpose, we used data from patients included in the early SpA ESPeranza cohort. ESPeranza is a national health care multicenter program for the early diagnosis and treatment of SpA (10). Patient characteristics were collected during the baseline visit, enabling the exploration of the Bayesian probabilities of each feature in a true early cohort.

Supported by Instituto de Salud Carlos III and FONDOS FEDER (restricted grant no. PI13/02034).

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Submitted for publication February 25, 2016; accepted in revised form August 16, 2016.

Significance & Innovations

- To our knowledge, this is the first study to evaluate the diagnostic value of different signs and symptoms included in spondyloarthritis (SpA) diagnosis/classification criteria (Assessment of SpondyloArthritis international Society, Amor, or European Spondylarthropathy Study Group) in an early SpA cohort.
- The results of this study show that the positive likelihood ratio of SpA features are different in patients with short disease duration compared to patients with longstanding disease, and this difference has clinical relevance.

Patients and methods

Population and data collection. Baseline data from patients recruited within the ESPeranza program were used for this study. A detailed description of the ESPeranza program has been published previously (10). In brief, this was a Spanish national health program in which patients with suspected SpA were referred from general practitioners to 25 SpA units over 3 years. The referral criteria have been previously published (10). In summary, patients met the following criteria: age <45 years; symptom duration 3–24 months; and at least one of the following: IBP (defined as 2 of the following: insidious onset, spinal morning stiffness for ≥30 minutes, and improvement with exercise but not with rest), asymmetrical arthritis (especially in the lower extremities), and the presence of spinal pain (at any level) or joint pain plus at least 1 of the following: psoriasis, inflammatory bowel disease (IBD), anterior uveitis, radiographic sacroiliitis, HLA–B27 positivity, or a family history of spondylitis, psoriasis, IBD, or anterior uveitis (10).

In the ESPeranza program, IBP was predefined as 2 of the following: insidious onset, spinal morning stiffness for ≥30 minutes, and improvement with exercise but not with rest. All of them are included in the Calin criteria, and therefore it was possible to calculate how many patients fulfilled the Calin criteria. The ASAS criteria were published after the ESPeranza program was established, but all of the items on it were included and therefore it was also possible to later calculate how many patients fulfilled the ASAS criteria.

A rheumatologist confirmed the fulfillment of the referral criteria in each center. For all patients, a detailed medical history and examination were performed, and data were collected and registered in the program's platform, including sex, age, clinical SpA features (IBP characteristics, enthesitis, arthritis, dactylitis, psoriasis, IBD, diarrhea, urethritis, cervicitis, prostatitis, positive family history for SpA, or good response to nonsteroidal antiinflammatory drugs [NSAIDs]), laboratory data (C-reactive protein [CRP] level, erythrocyte sedimentation rate [ESR], and HLA–B27), and conventional radiograph and magnetic resonance imaging (MRI) of sacroiliac joints. Radiographs were scored locally according to the modified New York criteria (11). MRI was not included in the protocol as a mandatory test, but all participating centers were asked to perform an MRI if possible. However, due to differences in accessibility, an MRI was not performed for all patients. But if it was performed, the MRI was evaluated locally for the presence or absence of ASAS-defined sacroiliitis (12). Finally, based on the clinical, laboratory, and imaging information, a local rheumatologist in each clinical center with interest in the field of SpA confirmed diagnosis. The gold standard employed for this study was the diagnosis performed by the clinician in charge.

In total, 775 patients met the referral criteria. Of these patients, 665 were referred because of predominant axial SpA symptoms and were included in the study. Patients with both types of symptoms (axial and peripheral) were classified as having predominant axial symptoms. Thus, patients included in this study fulfilled the following criteria: ≤45 years old, symptom duration 3–24 months, and IBP or back pain and the presence of at least 1 of the following features: psoriasis, IBD, anterior uveitis, radiographic sacroiliitis, HLA–B27 positivity, or a family history of SpA (10). As mentioned previously, these patients could have peripheral symptoms too (Figure 1). The program was designed in compliance with the Helsinki Declaration, and all of the procedures were approved by the Ethical Committee of the Hospital Reina Sofía in Córdoba. All patients gave informed consent.

Statistical analysis. For descriptive purposes, the results are shown as relative frequencies (percentages) for categorical variables and as means ± SDs for continuous variables. Chi-square and Student's *t*-tests were employed to compare variables between groups. To determine diagnostic utility, the sensitivity, specificity, positive predictive value, negative predictive value, positive LR, and negative LR of each feature for SpA (according to the rheumatologist) were calculated.

Results

In total, 516 patients were diagnosed as having SpA, and 149 patients received another diagnosis. Baseline characteristics for both groups are shown in Table 1. The

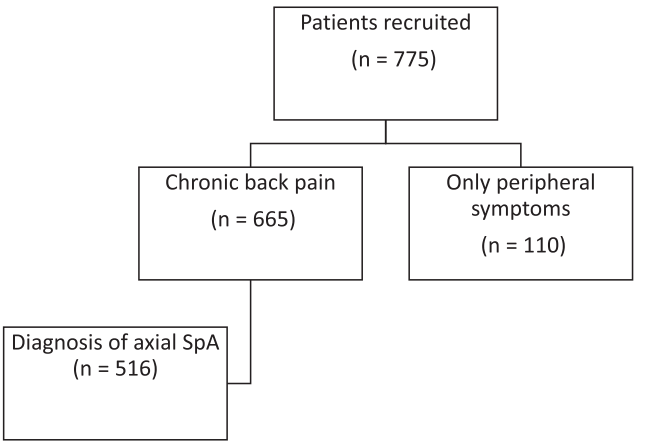

Figure 1. Flow chart of all ESPeranza program patients. SpA = spondyloarthritis.

Table 1. Baseline characteristics of 516 patients with axial SpA (77.6%) compared to 149 patients without axial SpA (22.4%)*

Chronic back pain (n = 665)	Axial SpA	No axial SpA	*P*
Mean ± SD age, years	33.1 ± 7.0	33.3 ± 7.5	0.8
Male	306 (59.3)	57 (38.3)	< 0.001
Mean ± SD symptom duration, months	12.2 ± 6.7	11.2 ± 6.2	0.1
Morning stiffness	319 (61.8)	74 (49.7)	< 0.01
ASAS inflammatory back pain	142 (27.5)	18 (12.1)	< 0.001
Calin inflammatory back pain	173 (33.5)	26 (17.4)	< 0.001
Alternating buttock pain	179 (34.7)	18 (12.1)	< 0.001
NSAID response	345 (66.9)	62 (41.6)	< 0.001
Peripheral arthritis	92 (17.8)	3 (2.0)	< 0.001
Enthesitis	96 (18.6)	11 (7.4)	< 0.001
Psoriasis	70 (13.6)	12 (8.1)	0.07
Dactylitis	26 (5.0)	0 (0)	< 0.01
Inflammatory bowel disease	24 (4.7)	2 (1.3)	0.07
Uveitis	31 (6.0)	3 (2.0)	0.051
Diarrhea, cervicitis, urethritis	14 (2.7)	0 (0)	0.04
Family history	143 (27.7)	27 (18.1)	0.02
HLA–B27 positivity	245 (48.2)	25 (17.2)	< 0.001
Elevated CRP or ESR	63 (12.2)	7 (4.7)	< 0.001
Radiographic sacroiliitis†	110 (21.8)	1 (0.7)	< 0.001
MRI sacroiliitis‡	125 (48.6)	5 (7.2)	< 0.001

* Values are the number (%) unless otherwise indicated. SpA = spondyloarthritis; ASAS = Assessment of SpondyloArthritis Society; NSAID = nonsteroidal antiinflammatory drug; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging.
† Total number = 650 (505 axial SpA group, 145 no axial SpA group).
‡ Total number = 326 (257 axial SpA group, 69 no axial SpA group).

mean ± SD age was similar in both groups (33 ± 7 years), but the frequency of males was higher in patients with axial SpA. All SpA features were more frequent in the group of patients with axial SpA, although the difference for psoriasis and IBD was not statistically significant.

Table 2 shows the diagnostic utility measure results of all SpA features. Based on these results, the most useful clinical features were the presence of sacroiliitis on the MRI (positive LR 6.6) and especially the radiograph (positive LR 31.1) and peripheral arthritis (positive LR 8.9).

Table 2. Diagnostic utility measures for each of the SpA features*

Chronic back pain (n = 665)	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
ASAS inflammatory back pain	27.5	87.9	88.8	25.9	2.27	0.82
Calin inflammatory back pain	33.5	82.6	86.9	26.4	1.93	0.81
Alternating buttock pain	34.7	87.9	90.9	28.0	2.87	0.74
NSAID response	66.9	58.4	84.8	33.7	1.61	0.57
Peripheral arthritis	17.8	98.0	96.8	25.6	8.90	0.84
Enthesitis	18.6	92.6	89.7	24.7	2.51	0.88
Psoriasis	13.6	91.9	85.4	91.9	1.68	0.94
Dactylitis	5.0	100	100	23.3	–	0.95
Inflammatory bowel disease	4.7	98.7	92.3	23.0	3.62	0.97
Uveitis	6.0	98.0	91.2	23.1	3.00	0.96
Diarrhea, cervicitis, urethritis	2.7	100	100	22.9	–	0.97
Family history	27.7	81.8	84.1	24.6	1.52	0.88
HLA–B27 positivity	48.2	82.8	90.7	31.3	2.80	0.63
Elevated CRP or ESR	12.2	95.3	90.0	23.9	2.60	0.92
Radiographic sacroiliitis†	21.8	99.3	99.1	26.7	31.1	0.79
MRI sacroiliitis‡	48.6	92.7	96.2	32.7	6.66	0.55

* SpA = spondyloarthritis; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; ASAS = Assessment of SpondyloArthritis Society; NSAID = nonsteroidal antiinflammatory drug; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging.
† Total number = 650 (505 axial SpA group, 145 no axial SpA group).
‡ Total number = 326 (257 axial SpA group, 69 no axial SpA group).

The features that showed the lowest diagnostic utility were a family history of SpA (positive LR 1.5) and good response to NSAIDs (positive LR 1.6). IBP (according to ASAS criteria) had a positive LR of 2.3 and alternating buttock pain had a positive LR of 2.9.

Discussion

The early diagnosis of SpA is a challenge for physicians because back pain is frequently a problem in the general population, and radiographic sacroiliitis usually takes several years to appear. With the classic modified New York criteria, diagnosis is delayed. The Berlin diagnostic algorithm is based on the LR product of different diagnostic parameters (8,9). This product is based on a longstanding population, but its utility in early diagnosis has not been tested. We recalculated the parameters in the early SpA ESPeranza cohort, determining the LR of different features included in the Berlin criteria.

Our data show that IBP (according to ASAS criteria) was described in only 27% of SpA patients, and therefore its positive LR is 2.3. Alternating buttock pain is a slightly better criterion because it was reported in 34% of SpA patients, with a positive LR of 2.9. Good NSAID response was observed in 67% of SpA patients but also in 42% of non-SpA patients, so its positive LR was 1.6. One possible explanation for these data is that early SpA patients fail to identify inflammatory symptoms. Alternatively, AS patients may have a high pretest probability. In addition, IBP also presents as mechanical back pain. Therefore, IBP should not be considered a key symptom in the early SpA population. As observed in other cohorts of patients suspected of having axial SpA, if only IBP were considered, we would miss many patients with SpA.

In our patients, enthesitis, arthritis, and dactylitis were less frequently reported, and sensitivity was low (17%, 18%, and 5%, respectively). However, specificity remained high (98%, 92%, and 100%, respectively). The presence of arthritis was very useful for diagnosis in this cohort, with a positive LR of 8.9. Iritis was highly specific (98%) but was seen in only 31 patients (6%). Therefore, the positive LR was 3.1, which differed greatly from the positive LR of 7.3 in the Berlin group (8).

Associated diseases may also be useful for diagnosis, as IBD was diagnosed in 24 patients (5%) and had a positive LR of 3.6. Fourteen patients (3%) described previous diarrhea, cervicitis, or urethritis and were diagnosed with SpA, while no one in the non-SpA group reported these symptoms. In contrast, psoriasis was seen in 70 SpA patients (13%) but also in 12 non-SpA patients (8%), so it is not as specific, and the positive LR was 1.6.

Acute-phase reactants (CRP and ESR) were elevated in only 63 SpA patients (12%). Therefore, the sensitivity was low, and the positive LR was 2.6, which was similar to the Berlin data. HLA–B27 positivity was seen in 245 patients (48%), and the positive LR was 2.8. This is likely because our cohort included different types of SpA, not only AS, and the prevalence of HLA–B27 in south European countries is lower than in those in the north. Therefore, because a negative value does not rule out the disease, the use of HLA–B27 status as a key factor in the diagnosis of these patients is questionable.

Although the ESPeranza cohort is an early SpA group, 110 patients (21%) showed sacroiliitis on radiography at the baseline visit, with this feature being definitive for diagnosis, with a positive LR of 3.1. An MRI was performed in 257 patients with SpA and was positive according to the Outcome Measure in Rheumatology (OMERACT) criteria in 125 patients (48%), with a positive LR of 6.6. Therefore, imaging data were very useful in the diagnosis of SpA in early SpA patients, but more than 50% did not fulfill the OMERACT criteria for sacroiliitis based on MRI.

In conclusion, the diagnostic value of SpA features in the cohort of patients with early axial SpA seems to be different than in patients with longstanding axial disease, and this difference has clinical relevance. Chronic back pain is better than IBP as a starting point for the algorithm or referral criteria for early diagnosis in SpA. In some geographic areas, HLA–B27 status determination as a key criterion is questionable because it underestimates SpA diagnosis in HLA–B27–negative patients. Finally, imaging criteria are very important in early diagnosis.

ACKNOWLEDGMENTS

The authors thank all patients participating in the ESPeranza program, as well as all members of the ESPeranza Study Group.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Joven had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. de Miguel.
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