Studying patients with inflammatory back pain and arthritis of the lower limbs clinically and by magnetic resonance imaging: many, but not all patients with sacroiliitis have spondyloarthropathy

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Abstract

Objective. Clinical and magnetic resonance imaging (MRI) data of 170 consecutive patients with inflammatory back pain (IBP) and/or oligoarthritis of the lower limbs were evaluated in a retrospective study. The aim was to determine the frequency of sacroiliitis and spondyloarthropathy (SpA) in this population, and to assess the significance of HLA B27 measurements for diagnosis in early disease.

Methods. Pelvic X-rays were performed in all IBP patients and dynamic MRI of the sacroiliac joints in patients with IBP who had indefinite results on sacroiliac X-rays (n = 32).

Results. European Spondyloarthropathy Study Group criteria for SpA were fulfilled by 106/170 patients (62.4%); eight additional patients had symptoms suggestive of SpA (4.7%). The most frequent SpA subset was undifferentiated SpA (uSpA), diagnosed in 46/106 patients (43.4%). Sacroiliitis was detected by MRI in 21/32 patients with IBP and unclear X-rays (65.6%). Of those, 14 were diagnosed as SpA and seven females with moderate unilateral sacroiliitis, but no features of SpA, also not on follow-up (at least 1 yr), were classified as undifferentiated sacroiliitis (US). Ten of the 14 SpA (71.4%) and none of the seven US patients were HLA B27 positive.

Conclusion. HLA B27 positivity in IBP patients with MRI-proven sacroiliitis positively predicts SpA. uSpA is a frequent SpA subset. There are HLA B27-negative non-SpA patients with moderate unilateral sacroiliitis whom we propose to be classified as US.

The European Spondyloarthropathy Study Group (ESSG) classification criteria [1] for spondyloarthropathies (SpA) have introduced inflammatory back pain (IBP) [2] and asymmetrical peripheral oligoarthritis of the lower limbs (PALL) as leading clinical symptoms. This study was undertaken to analyse the clinical spectrum of patients presenting with such symptoms to a rheumatological out-patient clinic and to investigate the relative frequency of the SpA subgroups. To clarify the origin of IBP, also in early cases, dynamic magnetic resonance imaging (MRI) of the sacroiliac joints was used to detect sacroiliitis as recently reported [3].

Patients and methods

A total of 170 consecutive patients who presented to the university out-patient clinic with IBP and/or PALL were included in the study. The patients were followed up for at least 1 yr. Only the final diagnoses are referred to. The following criteria for classification were used:

- ESSG criteria for SpA [1].
- Modified New York criteria for ankylosing spondylitis (AS) [4].
- Clinical criteria for IBP [5].
- Clinical criteria for reactive arthritis (ReA) [6].
- Criteria for the diagnosis of psoriatic arthritis (PsA) [7].
- A diagnosis of undifferentiated SpA (uSpA) was made when the ESSG criteria were met, but no AS, ReA,
PsA or arthritis associated with inflammatory bowel disease (AIBD) could be differentiated.

- Patients were grouped as probable SpA (pSpA) if the ESSG criteria were formally not fulfilled, but there were other symptoms suggestive of SpA, such as uveitis, a possible but uncertain history of symptoms or a combination of the main symptoms.
- Patients were categorized as undifferentiated sacroilitis (US) if they had evidence of sacroilitis obtained by MRI, but no indication of SpA or other underlying diseases.
- A diagnosis of undifferentiated oligoarthritis (UOA) was made if oligoarthritis of the lower limbs, but no evidence of any other defined rheumatic disease, was present [8].

Another 22 patients with mechanical low back pain who did not fulfill the clinical criteria for IBP [5] were excluded.

The flexibility of the lumbar spine was measured according to Schober, a difference of <4 cm was considered pathological. The thorax excursion was measured in the fourth intercostal space, a difference of ≤3 cm was considered pathological in patients aged <40 yr with adjustment in elderly patients. Minor psoriatic lesions were always searched for by careful history and physical examination. Colonoscopy for the exclusion of chronic inflammatory bowel disease was only performed in symptomatic cases. HLA B27 was determined by the standard microlymphocytotoxicity test.

Conventional X-rays of the sacroiliac joints were carried out in all patients with IBP. Dynamic MRI of the sacroiliac joints was performed in patients with IBP without definite changes in pelvic X-rays. The technique of dynamic MRI performed after i.v. bolus injection with the contrast agent gadolinium-diethylenetriamine penta-acetic acid was recently described in detail [3]. The degree of enhancement was graded as described [3] in acute sacroilitis, moderate or severe, and chronic sacroilitis, differentiated in four stages.

**Results**

Of the 170 patients examined, 106 were classified as SpA and eight as pSpA, together 114 (67.1%). Thirty patients were categorized as UOA (17.6%) and seven as US (4.1%). The remaining 19 patients had or developed other definitive inflammatory, infectious or degenerative diseases (11.2%). The characteristics and history of the patients, including the HLA B27 results, are given in Table 1.

Among the 106 patients who fulfilled SpA criteria, uSpA was diagnosed most frequently (43.4%), followed by AS (30.2%), PsA (14.2%), ReA (9.4%) and AIBD (2.8%). Eight patients with pSpA missed ESSG criteria, but had symptoms suggestive of SpA (7.0% of all 114 possible SpA patients). IBP was reported by 101/170 patients (59.4%) and 118/170 patients had PALL (69.4%).

Of the 118 patients with peripheral arthritis, 77 had SpA (65.3%), 30 UOA (25.4%) and 11 had other definitive rheumatic diseases (9.3%). Of those, six were diagnosed as Lyme arthritis, two as sarcoidosis, two as rheumatoid arthritis and one as systemic lupus.

Of the 101 patients with IBP, 86 were diagnosed as SpA (85.1%) and seven as US (6.9%). Of the remaining eight patients, one had infectious sacroilitis due to streptococci (proven by biopsy) and another one osteoarthritis diagnosed by X-ray and MRI. In the remaining six patients with initial symptoms suggestive of IBP, non-inflammatory spinal diseases were diagnosed after physical and radiological examination (5.9%).

The results and observations of the remaining groups are given in more detail in the subsequent paragraphs. Five antinuclear antibody-positive SpA patients who had concomitant Sjögren’s syndrome are described elsewhere [9].

**Undifferentiated spondyloarthropathy**

The vast majority (n = 41) of the 46 uSpA patients had IBP (89%) and 30 had PALL (65%). The combination of IBP and PALL was most frequent (41%), followed by isolated IBP (26%) in uSpA; this was the other way round in AS. Isolated oligoarthritis without spinal manifestations was only observed in five uSpA patients (11%).

In only 2/14 uSpA patients with a short disease duration of <1 yr (14%) was isolated IBP found. This was less frequent than in uSpA with a disease duration of >1 yr (n = 27), where 10 patients had isolated IBP (37%). Limitation of lumbar spine mobility was found in 41% and limited thorax excursion in 21% of the uSpA patients, respectively.

Extra-articular symptoms were seen in 26 uSpA patients (57%). These, either reported by the patient (only accepted if the location was suggestive and swelling was documented by a physician) or observed during clinical examination, were: enthesopathy 13 patients (29%), uveitis nine patients (20%) and dactylitis four patients (9%).

**Probable SpA**

The characteristics of the eight patients who did not fulfill ESSG criteria, but who had symptoms suggestive of SpA, are given in Table 1. Six of these patients had IBP, but no second SpA-defining clinical symptom or history. IBP and oligoarthritis, arthritis of the small hand joints, arthralgias or uveitis were observed. The remaining two had enthesopathy as the major complaint at presentation, but a history of probable IBP or PALL.

**Sacroilitis detected by dynamic MRI**

Altogether, 55 patients with IBP were examined by dynamic MRI: 40 SpA and 15 non-SpA. Acute and/or chronic sacroilitis demonstrated by dynamic MRI was found in 43 patients (78.2%): in 36/40 SpA patients (90.0%) and 9/15 non-SpA patients (60.0%). MRI-positive sacroilitis was found in 14/14 AS patients, in 17/20 uSpA patients and in 4/5 with probable SpA. The
Diagnoses and characteristics of the patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>(n)</th>
<th>Sex ratio (m/f)</th>
<th>Mean age (yr, range)</th>
<th>Mean disease duration* (yr, range)</th>
<th>HLA B27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>uSpA</td>
<td>46</td>
<td>1.0</td>
<td>39.4 (21–60)</td>
<td>5.4 (0.1–18)</td>
<td>67.4</td>
</tr>
<tr>
<td>pSpA</td>
<td>8</td>
<td>0.6</td>
<td>49.2 (23–77)</td>
<td>10.1 (0.1–45)</td>
<td>75.0</td>
</tr>
<tr>
<td>UOA</td>
<td>30</td>
<td>0.9</td>
<td>40.4 (19–77)</td>
<td>2.5 (0.1–25)</td>
<td>36.7</td>
</tr>
<tr>
<td>AS</td>
<td>32</td>
<td>2.2</td>
<td>37.3 (20–70)</td>
<td>7.3 (0.2–33)</td>
<td>93.8</td>
</tr>
<tr>
<td>US</td>
<td>7</td>
<td>0.0</td>
<td>43.4 (34–53)</td>
<td>2.3 (0.5–5)</td>
<td>0.0</td>
</tr>
<tr>
<td>ReA</td>
<td>10</td>
<td>1.0</td>
<td>46.8 (29–67)</td>
<td>0.9 (0.1–2)</td>
<td>60.0</td>
</tr>
<tr>
<td>PsA</td>
<td>15</td>
<td>1.5</td>
<td>47.0 (34–80)</td>
<td>2.1 (0.3–7)</td>
<td>40.0</td>
</tr>
<tr>
<td>AIBD</td>
<td>3</td>
<td>2.0</td>
<td>35.5 (19–52)</td>
<td>8.1 (0.3–18)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

uSpA, undifferentiated spondyloarthropathy; ReA, reactive arthritis; pSpA, probable spondyloarthropathy; PsA, psoriatic arthritis; UOA, undifferentiated oligoarthritis; AIBD, arthritis associated with inflammatory bowel disease; AS, ankylosing spondylitis; US, undifferentiated sacroiliitis.

*Time from first symptoms to the first visit.

same was true for seven US patients and one with bacterial sacroiliitis. HLA B27 was positive in 28/43 MRI-positive patients (65.1%), all these 28 had a diagnosis of SpA.

The indications for MRI were normal or unclear findings on conventional pelvic X-rays in 32 cases. Definite acute or chronic sacroiliitis detected by dynamic MRI was demonstrated in 21 of those 32 patients (65.6%). Eleven of these 21 were clinically classified as uSpA, two as probable SpA, one as PsA (nine HLA B27 positive) and seven were finally classified as US. An example is shown in Fig. 1. The remaining 11 patients had no sacroiliitis: three uSpA, one probable SpA (one HLA B27 positive), six with mechanical low back pain and one patient with osteoarthritis of the sacroiliac joints (all HLA B27 negative).

Thus, without knowledge of other clinical data, in a small population of 32 pre-selected patients with IBP, HLA B27 positively predicted a diagnosis of SpA in 10/14 patients with MRI-proven sacroiliitis (71.4%), while HLA B27 negativity predicted a diagnosis of a disease other than SpA in 7/7 patients (100%).

Undifferentiated sacroiliitis

Altogether, seven patients were classified as US, all women and HLA B27 negative. They had a relatively short disease duration of 2.3 yr. The erythrocyte sedimentation rate (ESR) was slightly elevated in two patients and normal in the remainder. No indication of osteoarthritis, hyperparathyroidism, hyperuricaemia, tuberculosis or sarcoidosis was present. None of these patients developed another defined rheumatic disease on a mean follow-up of 3.6 yr (2.8–5.3).

All seven patients had moderate unilateral sacroiliitis documented by dynamic MRI according to the criteria recently proposed [3]. Enhancement of the contrast agent was <80% in all cases (mean 74 ± 23%) and the chronic changes <II in all seven patients.

Anterior uveitis

Altogether, there were 18 patients with past or present anterior uveitis (AU) among the 114 patients with SpA and probable SpA (15.8%): nine uSpA, six AS, one PsA, one AIBD and one with pSpA. All patients with AU were HLA B27 positive. In 93.3% of the cases, AU was present in addition to at least two other SpA features (of the ESSG criteria). In only one case did a diagnosis of SpA become more probable due to the presence of AU.

Late-onset spondyloarthropathy

There were 13/106 patients who had a disease onset of >50 yr, here referred to as late-onset SpA (12.3%). Of these, 6/46 were diagnosed as uSpA (13%) and five fulfilled the modified New York criteria for AS. All 13 patients had IBP, nine had peripheral arthritis, eight oligoarthritis, one polyarthritis and three only arthralgias.

Undifferentiated oligoarthritis

In 30 patients with isolated oligoarthritis, no definite rheumatic disease could be differentiated. Nine patients had monoarthritis (seven HLA B27 positive) and 21 oligoarthritis (two HLA B27 positive). The HLA B27-positive patients did not develop other signs of SpA on a 1 yr follow-up.

Discussion

This study shows that SpA could be diagnosed in two-thirds of 170 patients presenting with IBP and PALL. Although one has to recognize that the described cohort presented to a tertiary referral centre specialized in inflammatory rather than degenerative rheumatic diseases, this finding supports recent data indicating a high prevalence of SpA on a population basis [10] and also in general practitioner practices [11]. Among the SpA subsets, uSpA, a subset that has not been widely recognized until recently [12], was the most frequently diagnosed classification group. This study, in accordance with a recent report from India on ‘unclassifiable SpA’, backs the opinion that the main advantage of the ESSG criteria is the introduction of uSpA as a fifth SpA subset [13]. uSpA covers a spectrum of different overlapping SpA features, comprising patients with early onset of not yet fully developed SpA [12]. Of interest, clinically, uSpA patients presented most frequently with both IBP and PALL (40%), while isolated IBP occurred in only
Magnetic resonance image of an HLA B27-positive patient with probable spondyloarthropathy and inflammatory back pain located to the left sacroiliac joint. (a) T1-weighted turbo spin echo sequence: smooth cartilage border and normal width of both sacroiliac joints, physiological thickness of the cortical bone in the ventral part of the joint. The periarticular iliac bone marrow of the ventral part of the left sacroiliac joint shows a diffusely diminished signal intensity indicating a higher water content in this area. (b) T2*-weighted sequence: intense signalling of the sacroiliac joint cartilage which appears normal. No widening or narrowing of the joint space, no erosions. The area of low signal intensity in the T1-weighted sequence shows a slightly augmented signal in this T2*-weighted sequence. (c) Short tau inversion recovery (STIR) sequence: marked higher signal intensity in the same region in the ventral part of the left sacroiliac joint. (d) Dynamic T1-weighted gradient-echo sequence, subtraction analysis of a post-contrast image taken 6 min after i.v. application of 0.1 mmol/kg gadolinium-diethylenetriamine penta-acetic acid: the region of interest in the ventral part of the left sacroiliac joint shows a clear-cut enhanced signal indicating acute sacroiliitis. The calculated enhancement factor was 110%. Thus, the grading was 0B (no chronic changes, enhancement >70%).

25% in the first year, more frequently than isolated PALL (10%). Isolated IBP was observed more frequently in patients with longer disease duration (37%), possibly indicating that therapy has a better effect on PALL than on IBP. This study also shows that a significant percentage of uSpA patients (13%), similar to AS (15.6%), has a late onset of disease [14], which is important for differential diagnosis in the elderly.
However, the majority of uSpA and AS patients have an early onset. Importantly, one-third of uSpA patients may develop AS later in the disease [15].

According to the ESSG classification criteria, a definite diagnosis of SpA was made in 62% of the patients of the clinical spectrum considered in this study. Since these criteria were shown to have a sensitivity of 85%, which is even less in early disease [1], we were not surprised to identify another eight patients who formally did not fulfil the ESSG criteria, but presented with symptoms suggestive of SpA. Four of these HLA B27-positive patients had evidence of sacroiliitis provided by definite imaging. Only recently, we have shown that HLA B27-positive Berlin blood donors with IBP were 10 times more likely to have sacroiliitis and SpA than HLA B27-negative donors [10]. These data are in some accordance with earlier calculations performed for AS by Khan and Khan [16] and others [17]. In conclusion, objective evidence of sacroiliitis by MRI in HLA B27-positive patients with IBP is highly suggestive of SpA and, of importance for very early cases, this is also true if no other clinical signs of SpA are present. If our patients are representative, this will be of clinical significance in ~5–10% of all SpA patients. This statement is significantly backed by the observation that all HLA B27-positive patients with IBP and objective evidence of sacroiliitis provided by MRI did fulfill diagnostic criteria for SpA after an observation period of now 2 yr (not shown).

AU was present in 15.8% of all SpA patients and highly associated with HLA B27 [18]. The presence of AU was affirmative for a diagnosis of SpA in 17 SpA patients. In only one patient with IBP was AU indicative of SpA. Thus, AU is rarely the only symptom indicating SpA. This confirms the results of the ESSG study, in which AU was not included in the final list of diagnostic criteria. Nevertheless, recognizing AU is of clinical value in a very limited number of patients. Owing to the possible clinical similarity, sacroiliitis must be excluded in such cases. The diagnostic value for SpA of HLA B27 and AU has also been proposed by Amor et al. [19].

Taking advantage of MRI technology, we detected moderate unilateral sacroiliitis in seven patients with IBP who did not have and develop features of SpA. The term US was used to describe this cause of back pain in seven middle-aged HLA B27-negative women. IBP was only partly controlled by non-steroidal anti-inflammatory drugs and four patients received computed tomography-guided intra-articular corticosteroid treatment [20], resulting in major improvement of symptoms for several months. Thus, unilateral isolated sacroiliitis of unknown origin is a clinical entity which must be differentiated from SpA and should be considered in the differential diagnosis of IBP. Our results also document that sacroiliitis, especially unilateral, is not a totally specific feature of SpA [21]. However, it is more so than PALL, since 85% of the IBP patients had SpA compared to 65% with PALL. Nevertheless, a significant percentage of HLA B27-positive patients with oligoarthritis may develop definite SpA in the further course of the disease [22].

The latter is also relevant for the patient group classified as UOA. In this group, there are two possible indications of SpA: PALL itself and HLA B27, which was present in 30%, which is significantly higher than the HLA B27 prevalence of 9.3% in Berlin [10]. However, there are HLA B27-positive UOA patients who never develop a clinical picture of SpA [22], as was the case in the nine HLA B27-positive UOA patients in this study; their clinical pattern did not change during a short 1 yr follow-up.

In conclusion, this study confirms the usefulness of the SpA concept in clinical practice [23]. USpA is a frequent SpA subset which will have to be examined in long-term follow-up studies. Other rheumatic diseases with a similar clinical picture have to be differentiated, one of those being US. The probability of SpA is greatly increased in patients with IBP and MRI-proven sacroiliitis if HLA B27 is positive.

References

12. Zeldis H, Mau W, Khan MA. Undifferentiated spondylo-


