

## EXTENDED REPORTS

## Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis?

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### Abstract

**Objective**—In 1971 McEwen and colleagues suggested that the radiological changes of classic ankylosing spondylitis (AS), and the changes of the spondylitis associated with inflammatory bowel disease differ in several respects from the radiological features of psoriatic and reactive spondylitis. The findings of this study have never been confirmed. The aim of this study was to replicate the McEwen study comparing films blinded to diagnostic group.

**Methods**—The study population comprised 91 patients with classic AS, 15 patients with regional enteritis, 16 patients with ulcerative colitis, five patients with sexually acquired reactive arthritis, two with post-dysenteric arthritis, and 34 with psoriatic arthritis. Blinded reading of spinal radiographs was undertaken, scoring for severity, symmetry, paravertebral ossification, size of syndesmophytes, ligamentous calcification, squaring, discitis, pseudo-fractures, zygoapophyseal joint involvement, and complete ankylosis.

**Results**—Comparison of the four groups—classic, enteropathic, psoriatic, and reactive AS—showed differences with respect to symmetry of sacroiliitis, symmetry of lumbar spinal involvement, and frequency and size of syndesmophytes. Zygoapophyseal joint involvement was more frequent in the lumbar spine in classic and enteropathic spondylitis but no between group differences were found with respect to symphitis, squaring, apophyseal joint involvement and ligamentous calcification in the lumbar spine, and other areas.

**Conclusions**—Some of the radiological differences described by McEwen *et al*, notably the asymmetry, the less severe changes, and the distinctive syndesmophytes in psoriasis, have been confirmed. A number of hypotheses are proposed to explain these differences including biomechanical, biochemical, and genetic factors.

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In 1974 Moll and colleagues defined the concept of the seronegative spondylarthritides as a group of seronegative arthritides sharing clinical features, central to which was ankylosing spondylitis (AS).<sup>1</sup> Common features of these conditions included a seronegative, an-odular, peripheral inflammatory arthritis, mucocutaneous ulceration, psoriasiform skin lesions, ocular inflammation, familial aggregation (linked to the HLA-B27 antigen), and radiological sacroiliitis with or without AS. Included within this group of disorders were classic AS, psoriatic arthritis, reactive arthritis, inflammatory bowel disease, Whipple's disease, and Behcet's disease, although it has been argued that the latter two conditions should no longer be included in the group.<sup>2</sup>

Despite the core feature of radiological sacroiliitis, it has been argued that the radiological features of enteropathic spondylitis (the AS associated with inflammatory bowel disease, EnSp) and classic AS differ in several respects, radiologically, from the spondylitis associated with psoriasis (PsSp) and reactive arthritis (ReSp).<sup>3-5</sup> The key study underlying these assertions was published in 1971 by McEwen and colleagues<sup>6</sup> and the findings of that paper are summarised in table 1. The major differences were in the symmetry and severity of the radiological changes and in the shape and size of the syndesmophytes, although other differences such as zygoapophyseal involvement, osteitis, and ligamentous calcification were also highlighted. The McEwen study has not been repeated formally, although a limited radiological comparison of classic AS and psoriatic arthritis was undertaken by Gladman and colleagues.<sup>7</sup> However, the differences described by McEwen and colleagues have generally been accepted by the rheumatological community.<sup>8,9</sup>

The advent of new imaging techniques such as magnetic resonance imaging and spiral computed tomography offers the possibility of new approaches to defining these radiographic abnormalities but, as the findings of McEwen *et al* have never been confirmed, a straightforward replication of the original study was felt to

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Table 1 Summary of radiological differences reported by McEwen *et al*<sup>6</sup>

Feature	Ankylosing spondylitis and spondylitis of ulcerative colitis and regional enteritis	Spondylitis associated with psoriasis and reactive arthritis
Sacroiliitis	Severe and symmetrical	Sacroiliitis sometimes unilateral or bilaterally asymmetrical
Symphysis	More frequent	Less frequent
Osteoporosis	More frequent	Less frequent
Lumbar straightening	More frequent	Less frequent
Apophyseal joint involvement	More frequent	Less frequent
Squaring	More frequent	Less frequent
Syndesmophytes	More frequent, usually symmetrical	Less frequent, usually asymmetrical
Shape and size of syndesmophytes	Marginal (see text)	Usually "other than marginal" (see text)
Ligamentous ossification	More frequent	Less frequent
Progression of syndesmophytes	Lumbar to dorsal to cervical	Random progression

be necessary, comparing films blinded to diagnostic group.

### Methods

Most of the patients were recruited from rheumatology outpatient clinics in Leeds. In 12 cases spinal radiographs and all clinical data were mailed from rheumatology colleagues in other areas: in all these cases the films were read "blind". The only entry criterion was AS diagnosed using the modified New York criteria.<sup>10</sup> Further subdivision was based on coexisting disorders. Reactive arthritis was diagnosed using the criteria of Calin *et al*.<sup>11</sup> All patients with psoriasis had seen a dermatologist and all patients with inflammatory bowel disease were under the care of a gastroenterologist: most had been examined by barium series and biopsy.

In addition to basic demographic details the following clinical data were collected: history of heel involvement, history of uveitis, lumbar flexion by the modified Schober's method,<sup>12</sup> and chest expansion measured at the level of the xiphisternum.

Recent (within 12 months) radiographs were read "blind" to diagnosis by two readers in tandem: no attempt to measure interobserver or intraobserver agreement was made. Pelvic radiographs were scored for sacroiliitis according to the New York criteria<sup>13</sup> where changes are graded from 0 (normal), 1 (doubtful), 2 (mild irregularity and sclerosis), 3 (marked erosion without ankylosis), and 4 (complete ankylosis). Sacroiliitis was graded asymmetrical if a difference of more than one grade occurred between sides. Symphysis was graded using a similar system to that for sacroiliitis. Ischial and iliac enthesitis were graded from 0–4 where a score of 4 represented florid new bone formation over the affected site. Hips were also graded 0–4 with 0–1 normal or doubtful, 2 mild loss of joint

space, 3 moderate loss of joint space with sclerosis, and 4 complete loss of joint space (arthroplasty was graded as 4).

Spine radiographs were graded for overall severity as follows: normal (0); isolated erosion of the superior anterior border of a vertebra, the eponymous Romanus lesion, (1); three or fewer syndesmophytes (2); more than three syndesmophytes (3); and complete ankylosis (4). If ankylosis of the zygoapophyseal joints occurred throughout the region the films were graded as 4 independent of the other changes. Symmetry was defined as greater than or equal to 50% matching of syndesmophytes in the anteroposterior film. Thus if only three syndesmophytes were seen and two were matched that film would be scored as symmetrical. The presence of other features was recorded as follows. Paravertebral ossification as defined and described by Bywaters and Dixon,<sup>14</sup> ligamentous calcification (usually interspinous ligament), squaring of the anterior border of the vertebra without erosion/sclerosis, discitis (narrowing of disc space with erosion, and new bone formation in adjacent vertebrae), spinal pseudarthrosis (a fracture line through a fused spine with reactive new bone formation at either side of the lesion), bamboo spine (complete ankylosis of vertebrae due to contiguous syndesmophyte formation), and ankylosis of zygoapophyseal joints. Syndesmophytes were classified as chunky or marginal based on their size and shape. Marginal syndesmophytes were defined as discrete vertically oriented areas of calcification extending from the corner of one vertebra to the next. Chunky syndesmophytes were defined as more extensive areas of calcification extending vertically from the vertebral corner—included within this group were the non-marginal and "inverted comma" syndesmophytes of McEwen *et al*.<sup>6</sup>

Table 2 Demographic details of study group

	Ankylosing spondylitis	Enteropathic spondylitis	Psoriatic spondylitis	Reactive arthritis	$\chi^2$ (df=3)*	Significant†
Number	91	31	34	7		
Male/female	67/24	15/16	26/8	7/0	11.24	NS
Age (y) median (range)	46 (18–71)	48 (34–75)	46 (25–83)	43 (25–47)	6.58	NS
Duration disease (y) median (range)	18 (1–44)	15 (6–39)	16 (0–56)	8 (5–12)	7.15	NS
Number (%) heel involvement	12/82 (15)	3/17 (18)	4/21 (20)	1/4 (25)	‡	
Number (%) uveitis	19/83 (23)	14/21 (67)	4/23 (18)	1/5 (20)	17.75	0.004
Schober's (cm) median (range)	2 (0–7)	4 (0–7)	4.85 (1–8)	5.5 (4–7.5)	15.3	0.016
Chest expansion (cm) median (range)	3 (0–6.5)	4 (0–6)	4 (0–6)	3 (0–6)	1.36	NS
Number (%) B27 positive	31/37 (84)	8/10 (80)	4/6 (67)	2/2 (100)	‡	

\* $\chi^2$  on 2x4 tables. Kruskal-Wallis analysis of variance,  $\chi^2$  statistic for interval scale data. †p Values multiplied by 8 to allow for multiple comparisons. ‡Comparison not made because minimum expected frequency in two cells was <2.

Table 3 Sacroiliitis, symphitis, pelvic enthesitis, and hip involvement

	Ankylosing spondylitis	Enteropathic spondylitis	Psoriatic spondylitis	Reactive arthritis
Number of films available (no of cases)	91/91	31/31	34/34	7/7
Worst SI grade (number (%)) grades 3–4	84 (92)	30 (97)	28 (82)	7 (100)
Symmetry (number (%))	77 (85)	31 (100)	25 (74)	3 (43)
Symphitis (number (%)) grades 3–4	27 (31)	9 (30)	8 (25)	1 (14)
Iliac enthesitis (number (%)) grades 3–4	6 (7)	1 (4)	1 (4)	0
Ischial enthesitis (number (%)) grades 3–4	25 (30)	4 (14)	6 (22)	0
Hip involvement (number (%)) grades 3–4	22 (26)	4 (14)	7 (23)	0

Lateral heel radiographs were scored at three sites (posterior calcaneal, inferior calcaneal, and tarsal) as follows: normal (0), doubtful (1), spur less than 3 mm (2), spur 3–8 mm (3), spur greater than 8 mm (4).

#### STATISTICAL ANALYSIS

Non-parametric statistics were used throughout. As members of the ReSp group were younger and had a shorter duration of disease and, as the ReSp group was much smaller than the other three groups, statistical comparisons of spinal features specifically excluded this group of patients. In  $2 \times k$  contingency tables we followed the advice of Cochran<sup>15</sup> who recommended that the  $\chi^2$  test be used providing  $df < 30$  and minimum expected cell frequency  $\geq 2$ .

#### Results

Table 2 gives the demographic details and clinical data. Most of the patients had classic AS, as expected, so that the total figures were 91 for AS, 31 for EnSp, 34 for PsSp, and seven for ReSp. There were sex differences between the groups: the AS, PsSp, and ReSp groups were predominantly male whereas the EnSp group had an equal sex distribution. A significant difference in the amount of lumbar movement (as measured by the modified Schober's method) was found across the groups; this was largely because of the limited mobility of the AS group. Measures of chest expansion were similar.

Tables 3–6 compare the radiological features of the groups.

#### PELVIC FILMS

Severity of sacroiliac involvement, defined by the worst grade of sacroiliitis, did not differ significantly between the groups. However, the major groups (AS, EnSp, and PsSp) did differ when scored for symmetry ( $\chi^2 = 7.97$ ,  $df = 2$ ,

$p = 0.02$ ). No differences were found between the groups with respect to symphitis, iliac and ischial enthesitis, and hip involvement.

#### SPINAL FILMS

Spinal films were analysed by region. Tables 4–6 give the percentage of films in each group demonstrating the recorded features for lumbar, thoracic, and cervical spine regions. The appearances were not uniform throughout the spine. Films from patients with AS showed more severe changes, particularly in the lumbar spine, with a higher percentage of grades 3 to 4 involvement, more zygoapophyseal involvement, and more cases of complete ankylosis. Patients with EnSp also showed more severe changes in the lumbar spine. Among the major diagnostic groups (AS, EnSp, and PsSp) these differences were significant (lumbar severity:  $\chi^2 = 7.95$ ,  $df = 2$ ,  $p = 0.02$ , lumbar zygoapophyseal:  $\chi^2 = 6.93$ ,  $df = 2$ ,  $p = 0.03$ ).

The inter-regional pattern of severity also differed between the four diagnostic groups but not consistently between groups; for AS the worst affected area was the lumbar spine but there was little difference between the spinal areas (lumbar 55% grades 3–4; thoracic 45%; cervical 50%). For the EnSp the worst affected area was the cervical spine but, again, the range was small (lumbar 40% grades 3–4; thoracic 31%; cervical 45%). In the PsSp group the worst affected area was easily the cervical spine (lumbar 25% grades 3–4; thoracic 36%; cervical 47%).

Syndesmophyte morphology, as recorded by the percentage of "chunky" syndesmophytes, was not significantly different between the major groups (AS, EnSp, and PsSp). However, consistent differences between the groups were found throughout the spine with respect to this feature, with the PsSp and ReSp groups having a larger percentage of "chunky" syndesmophytes. Furthermore, the degree of symmetry

Table 4 Lumbar spine involvement

	Ankylosing spondylitis	Enteropathic spondylitis	Psoriatic spondylitis	Reactive arthritis
Number of films available (no of cases)	78/91	25/31	28/34	5/7
Worst grade (number (%)) grades 3–4	43 (55)	10 (40)	7 (25)	1 (20)
Number (%) symmetry*	38/52 (73)	8/16 (50)	4/14 (29)	2/3 (67)
Paravertebral ossification (number (%))	1 (1)	1 (4)	1 (4)	0
Chunky syndesmophytes (number (%))*	12/52 (23)	3/16 (19)	5/14 (36)	1/3 (33)
Ligamentous calcification (number (%))	11 (14)	1 (4)	1 (4)	0
Squaring (number (%))	15 (19)	1 (4)	1 (4)	0
Romanus lesion (number (%))	17 (22)	0	4 (14)	3 (60)
Spinal pseudarthrosis (number (%))	2 (3)	0	1 (4)	0
Zygoapophyseal ankylosis (number (%))	16 (21)	4 (16)	0	0
Discitis (number (%))	5 (6)	2 (8)	1 (4)	0
Bamboo spine (number (%))	9 (12)	3 (12)	0	0

\*Note data on symmetry and syndesmophyte morphology only apply to severity grades 2–4: the number of available films is given by the denominator.

Table 5 Thoracic spine involvement

	Ankylosing spondylitis	Enteropathic spondylitis	Psoriatic spondylitis	Reactive arthritis
Number of films available (no of cases)	64/91	13/31	14/34	4/7
Worst grade (number (%)) grades 3–4	29 (45)	4 (31)	5 (36)	1 (25)
Number (%) symmetry*	24/40 (60)	4/5 (80)	2/6 (33)	0
Paravertebral ossification (number (%))	1 (2)	0	0	0
Chunky syndesmophytes (number (%))*	2/40 (5)	0	4/6 (67)	1/2 (50)
Ligamentous calcification (number (%))	9 (14)	0	2 (14)	0
Squaring (number (%))	7 (11)	0	0	0
Romanus lesions (number (%))	9 (14)	0	2 (14)	1 (25)
Spinal pseudarthrosis (number (%))	1 (2)	0	0	0
Zygoapophyseal ankylosis (number (%))	7 (11)	0	0	0
Discitis (number (%))	4 (6)	0	0	0
Bamboo spine (number (%))	8 (13)	2 (15)	0	0

\*Note data on symmetry and syndesmophyte morphology only apply to severity grades 2–4: the number of available films is given by the denominator.

Table 6 Cervical spine involvement

	Ankylosing spondylitis	Enteropathi c spondylitis	Psoriatic spondylitis	Reactive arthritis
Number of films available (no of cases)	58/91	11/31	19/34	5/7
Worst grade (number (%)) grades 3–4	29 (50)	5 (45)	9 (47)	0
Number (%) symmetry*†	19/19 (100)	2/4 (50)	7/7 (100)	0
Paravertebral ossification (number (%))	1 (2)	0	2 (11)	0
Chunky syndesmophytes (number (%))*	3/34 (9)	1/6 (17)	5/12 (42)	1/1 (100)
Ligamentous calcification (number (%))	1 (2)	2 (18)	0	0
Squaring (number (%))	3 (5)	0	0	0
Romanus lesions (number (%))	1 (2)	0	0	0
Spinal pseudarthrosis (number (%))	1 (2)	1 (9)	0	0
Zygoapophyseal ankylosis (number (%))	10 (17)	0	2 (11)	0
Discitis (number (%))	0	1 (9)	0	0
Bamboo spine (number (%))	5 (9)	0	1 (5)	0

\*Note data on symmetry and syndesmophyte morphology only apply to severity grades 2–4: the number of available films is given by the denominator. †It was not possible to evaluate cervical symmetry in 23 cases because syndesmophytes were only seen on lateral radiographs.

of syndesmophytes differed: this difference was particularly apparent in the lumbar spine for groups AS, EnSp, and PsSp ( $\chi^2 = 6.4$ ,  $df=2$ ,  $p=0.04$ ).

No differences were found between the groups with respect to paravertebral ossification, ligamentous calcification, squaring, discitis, Romanus lesions, and spinal pseudarthrosis.

Radiographs of the heel were not available for all patients. Grades 3–4 plantar enthesopathy were found in the following numbers (%): AS, 8 of 40 (20%); EnSp, 0 of 5; PsSp, 1 of 7 (13%); ReSp, 0 of 2. At the Achilles tendon insertion the figures were 3 of 39 (8%), 0 of 4, 2 of 8 (25%), and 0 of 2 for AS, EnSp, PsSp, and ReSp respectively.

### Discussion

We have shown some differences between the radiological features of classic AS and the features found in enteropathic, psoriatic, and reactive AS. The differences are mainly in the severity of involvement, the symmetry of sacroiliitis and syndesmophytes, and the morphology of syndesmophytes. Our findings did not enable us to justify the grouping suggested by McEwen *et al*—that is, pairing AS/EnSp and PsSp/ReSp—except in the case of zygoapophyseal involvement of the lumbar spine. Other differences noted by McEwen, such as symphitis, squaring, and ligamentous calcification, have not been found.

The unequal numbers of patients in each group is a reflection of our clinic population rather than an attempt to overrepresent classic AS. The disproportion is in contrast with the study by McEwen *et al* where the numbers of

patients in each group was 29, 38, 39, and 34 for classic AS, EnSp, PsSp, and ReSp respectively. The disease definitions used by McEwen *et al* were not explicitly stated but clearly Reiter's disease was more common among their clinic population (New York, 1971) than Leeds, 1990–1995. Our patients with ReSp were younger with shorter duration of disease than patients in the other groups and for this reason we could not include them in the analysis between groups.

Given a similar disease duration the changes in the PsSp group were less severe overall, in agreement with McEwen *et al*. Furthermore, Gladman and colleagues noted more severe sacroiliitis, more frequent classic syndesmophytes, and less cervical spine involvement in AS compared with PsSp but their radiological definitions were imprecise and their cohorts not matched for age.<sup>7</sup> In this study severity of involvement was based on the number and extent of syndesmophytes and this may, in part, explain the asymmetry found in PsSp. We have previously noted, in peripheral psoriatic arthritis, that symmetry is a function of frequency of joint involvement so that the greater the number of sites involved the more chance that these sites will be matched and recorded as symmetrical.<sup>16</sup> For example, where syndesmophytes were recorded in the lumbar spine, 50% of films from PsSp patients had three or fewer syndesmophytes whereas this figure was only 19% in classic AS. In this study, therefore, asymmetry may be a function of paucity of syndesmophytes. Additionally, it is worth noting that a judgement on symmetry in the cervical spine was sometimes impossible to

make as syndesmophytes were noted only in the lateral radiographs.

The cross sectional nature of this study precluded any meaningful conclusions about the onset and progression of the radiological changes. McEwen *et al* were less inhibited by the design of their study, using cohorts of patients based on disease duration. On this basis they concluded that in AS/EnSp the spondylitis presents with early, progressive, symmetrical sacroiliac involvement and extends progressively from the lumbar into the dorsal and finally the cervical spine. In contrast, PsSp/ReSp demonstrated frequent asymmetrical and occasionally unilateral sacroiliitis progressing in random fashion throughout the spine. We were unable to confirm this pattern.

The morphology of syndesmophytes needs further clarification and new imaging techniques may permit better anatomical description of these abnormalities. Digital radiographs will allow quantification of the area of the syndesmophytes; we have used this technique in conventional radiographs using planimetry but it is sometimes difficult to define the (normal) margins of the vertebral body. The use of three dimensional techniques such as spiral computed tomography will encounter similar difficulties but three dimensional images would improve visualisation of the syndesmophyte morphology.

Classic marginal syndesmophytes, which represent calcification in the outer fibres of the annulus fibrosis of the disc, are the predominant form in all of the spondylarthritides. Can the broader, bulky looking syndesmophytes that occur commonly, although not exclusively, in patients with PsSp correctly be called syndesmophytes? Resnick and Niwayama<sup>3</sup> describe these areas as paravertebral ossification but allow that, as they progress, they fuse with the underlying disc and bone ultimately producing appearances normally associated with diffuse idiopathic skeletal hyperostosis and, on occasions, disc degeneration. More detailed pathological data on the origin and progression of these changes are required. Peripheral psoriatic arthritis is characterised pathologically by intense osteoblastic proliferation surrounding the periosteum and it is possible that similar changes are occurring in the vertebra adjacent to the disc associated with an enthesopathy at the attachment of the annulus fibrosis, as in classic AS.<sup>17</sup> Perhaps the initiating lesion is common to all types of spondylitis but the intense osteoblastosis in PsSp and ReSp sometimes produces bulkier syndesmophytes.

An alternative explanation for the excessive new bone formation at the spinal entheses found in PsSp has been suggested by de Vlam and colleagues.<sup>18</sup> They postulate that reduced spinal mobility associated with involvement of apophyseal joints (as seen more commonly in AS) is associated with classic syndesmophyte formation, whereas if posterior spinal mobility is maintained greater tensile forces are experienced anteriorly resulting in increased inflammation/repair and consequently more bone formation. At these sites of high mechani-

cal stress transforming growth factor  $\beta$  or interleukin 6 may be the principal mediators of new bone formation in the inflammatory tissue. To examine this theory further it would be necessary to make detailed observations of syndesmophyte morphology and zygoapophyseal involvement at each vertebral level. The hypothesis does provide a plausible explanation for the observed differences in syndesmophyte morphology and might also explain the radiological changes found in diffuse idiopathic skeletal hyperostosis.

Other factors may underlie the differences noted above, particularly genetic variation. The major histocompatibility gene-HLA-B27 is pivotal to all the seronegative spondylarthritides but other genes related to both the major histocompatibility complex and elsewhere may contribute to the unique expression of each of these disorders. Both HLA-B38 and HLA-DR4 seem to be associated with psoriatic arthritis<sup>19</sup> and the role of these and other genes in reactive arthritis needs further study.

Although we have been unable to justify grouping reactive arthritis and psoriatic arthritis these conditions share other clinical features that suggest grouping them together, particularly the skin lesions (keratoderma blenorrhagica may be indistinguishable from pustular psoriasis of the foot: a similar rash is not seen in classic AS and enteropathic arthritis) the pattern of peripheral arthritis (particularly the destructive changes in distal inter-phalangeal joints) and the enthesopathy, particularly around the heel (although this feature was not prominent in this study). Furthermore, an explosive and severe form of psoriasis may follow infection with HIV, and a 10-fold increase in the prevalence of psoriatic arthritis has been reported in patients infected with HIV.<sup>20</sup> Other infective triggers may be common to both reactive and psoriatic arthritis; for example, some authors have suggested that psoriatic arthritis is a reactive arthritis to bacteria carried in psoriatic plaques.<sup>21</sup>

In summary, we have confirmed that some radiological features distinguish psoriatic, classic, and enteropathic spondylitis. The mechanisms underlying these differences remain obscure and require further clarification.

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