Low Back Pain, Sacroiliitis, and the Relationship with HLA-B27 in Crohn's Disease

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ABSTRACT. ***Objective.*** To determine the prevalence of sacroiliitis in patients who have back pain in Crohn's disease (CD) using computed tomography (CT); and to reassess the association of sacroiliitis in CD with HLA-B27.

Methods. A total of 134 consecutive patients with CD completed a questionnaire about musculoskeletal symptoms. Those reporting low back pain were assessed, including plain radiographs and CT of the sacroiliac joints. HLA-B27 status was determined in patients with and without back pain.

Results. There were 70 (52%) patients with low back pain, of whom 31 (45%) had CT evidence of sacroiliitis. These were characterized by more frequent morning spinal stiffness and positive sacroiliac compression tests even when sacroiliitis was not suspected. Nine had previously recognized radiological and clinical ankylosing spondylitis (AS), and of these 78% were HLA-B27 positive. Of those with newly identified sacroiliitis, 14% were HLA-B27 positive. This frequency was not statistically dissimilar to the 9% HLA-B27 positivity of those without back pain.

Conclusion. Sacroiliitis defined by CT is a common cause of low back pain in CD. A relationship of sacroiliitis and HLA-B27 could be confirmed only for those with classical AS. Our results accord with the possibility that sacroiliitis in CD is an isolated phenomenon, which is unrelated to HLA-B27 and which may evolve into classical spinal ankylosis in genetically susceptible subjects. (J Rheumatol 2003;30:518–22)

Key Indexing Terms:
CROHN'S DISEASE INFLAMMATORY BOWEL DISEASE SACROILIITIS
ANKYLOSING SPONDYLITIS BACK PAIN COMPUTED TOMOGRAPHY HLA-B27

The association of arthritis with inflammatory bowel disease has been recognized for over a century[1]. However, it was not until 1964 that the link between sacroiliitis and Crohn's disease (CD) was established. Using plain radiography it was found that 18 (20%) of a series of 91 patients had radiological sacroiliitis, of whom 5 (6%) had ankylosing spondylitis[2]. Further studies using plain radiography and later, quantitative scintigraphy and computed tomography (CT) found rates of sacroiliitis varying between 11 and 35%[2-9]. These investigations examined patients without spinal pain or a combination of those with and without symptoms. It has been suggested that a higher prevalence rate of sacroiliitis in CD might be found among those with axial pain[8]. Wright and Watkinson[5] found that the prevalence of sacroiliitis was twice as high in patients with ulcerative colitis complaining of back pain compared with those who had none.

Several studies examined the association of sacroiliitis and HLA-B27 in CD[6,10-15]. No association was reported in studies using both plain radiography[10] and scintigraphy[6]. The modern imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) are considered superior to ordinary radiographic and isotope methods for detecting early sacroiliitis[16-19].

Our study attempted to redetermine the frequency of sacroiliitis among patients with CD complaining of low back pain utilizing the more sensitive imaging method of CT scanning. In addition, we reassessed the association of HLA-B27 with sacroiliitis as defined by CT scanning.

MATERIALS AND METHODS

Patients. A total of 134 consecutive patients with CD established by endoscopic and/or radiological criteria were recruited from the inflammatory bowel disease clinic at Guy's Hospital. Approval for the study was obtained from the local ethics committee and written informed consent was given by all subjects.

Clinical. Patients were asked to fill in a questionnaire about any musculoskeletal symptoms. Those reporting current or recurrent low back pain episodes lasting longer than 2 weeks were offered a full clinical evaluation. The duration of low back pain and of bowel symptoms, the presence and early morning duration of low back stiffness, any history of uveitis or erythema nodosum, clinical assessment of sacroiliac joints[20], and measurement of chest expansion, left lateral flexion and lumbosacral flexion using the modified Schober index[21] were documented. Chest expansion was measured with a

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tape measure beneath the nipples and lateral spinal flexion by measuring the distance moved by finger tips down the lateral side of the left leg.

All patients with back pain underwent plain anteroposterior radiographs of the pelvis and CT of the sacroiliac joints. A Philips Tomoscan AV scanner was used for CT. Imaging was performed with 5 mm contiguous slices through the sacroiliac joints; slices were obtained parallel to the sacrum. Plain radiographs and CT scans were read independently. Two independent observers — a radiologist (JH) and a rheumatologist (HJ) who were blind to the clinical and HLA status of the patients — scored all images. Each sacroiliac joint was scored according to the modified New York criteria[22]: grade 0, normal; grade 1, suspicious; grade 2, minimal abnormality with sclerosis of iliac and sacral borders with no alteration in joint width; grade 3, definite abnormality with erosions, sclerosis, and joint space widening or narrowing; grade 4, total ankylosis. The scores of the 2 observers were concordant (κ = 0.94). Any disagreement was resolved by consensus. Sacroiliitis was agreed on the basis of a score of 2 or more. Where there were differences in the score for each sacroiliac joint, the higher value was used for the analysis, but only those with evidence of bilateral sacroiliitis on CT scan were included.

Laboratory tests. Blood was taken for measurement of erythrocyte sedimentation rate (ESR) and for HLA-B typing from 122 of the 134 patients completing the questionnaire; 12 patients were lost to followup or were unable to provide a blood sample and were excluded from the analysis. Four of the 12 lost to followup had low back pain. DNA was prepared from peripheral blood of 122 patients by a standard salting-out method[23]. The detection of HLA-B*27 was performed using polymerase chain reaction with sequence-specific primers (PCR-SSP). The following 3 specific primers resulted in a product fragment size of 150/151 bases when HLA-B*27 was present (forward primer: 5' GCT ACG TGG ACG ACA CGC T 3' and reverse primers 5' CTC GGT CAG TCT GTG CCT T 3',5' TCT CGG TAA GTC TGT GCC TT 3'). We also used a forward (5' TGC CAA GTG GAG CAC CCA A 3') and a reverse (5' GCA TCT TGC TCT GTG CAG AT 3') control primer with a product size fragment of 796 bases as internal control for the PCR. PCR reaction mixtures and cycling conditions were as described[24].

Statistical analysis. Patients with and without sacroiliitis were compared using the Mann-Whitney U test for nonparametric continuous data and the Student t test for parametric continuous data; categorical data were analyzed using contingency tables and the chi-squared test for significance, or where expected observations were small with Fisher's exact test. Patients with sacroiliitis were compared to those patients with CD who had previously recognized AS using similar methods. The chi-squared test was used to compare HLA-B27 frequency between patient groups, unless low numbers required Fisher's exact test. The chi-squared test for trend was used to test for a linear trend in B27 frequency across the 3 symptomatic groups — no sacroiliitis, newly recognized sacroiliitis, and established AS.

RESULTS

Demographic details and clinical features. Of 134 consecutive patients with CD, 70 (52%) had histories of low back pain. Their median age was 42 years (interquartile range 34–53) and 33 (47%) were male. These characteristics were similar in the asymptomatic group (data not shown). Pelvic radiographs were taken of all 70 patients. Sixty-nine underwent CT scanning of the sacroiliac joints. One patient refused to participate further and was excluded from further analysis. Thirty-one (45%) had CT evidence of sacroiliitis, of whom 9 had classical radiological and clinical AS that had been previously identified. These 9 had ankylosing changes in the spine as well as varying degrees of sacroiliitis. More extensive spinal radiography was not undertaken in the remaining 22 patients with sacroiliitis on CT scans. Sixteen of the 22 with sacroiliitis on CT scan had normal or equivocal radiographs (Table 1). Grade 1 unilateral change was observed on radiograph in 3 cases, but the sacroiliac joints were normal on CT scan. Grade 2 unilateral sacroiliitis on CT scan was noted in 2 patients with normal radiographs. These were excluded from the analysis. No grade 3 or 4 unilateral change was apparent on radiograph or CT scan.

Significantly more of all the patients with sacroiliitis were male (p = 0.02; Table 2) and they had experienced back pain significantly longer than those without sacroiliitis (p = 0.018; Table 2). However there was no difference in duration of CD or in age at onset of CD. Of the patients with previously recognized classical AS, 78% were male compared with 55% of the remainder with CT identified sacroiliitis, but this difference was not statistically significant (Table 3). Those with established AS had back pain for a significantly longer time than those with newly identified sacroiliitis (Table 3), and their pain usually predated the onset of CD. The onset of back pain in patients with newly identified sacroiliitis tended to coincide with the onset of CD or to develop subsequently.

The Schober index was significantly reduced in all those with sacroiliitis compared to those without (p = 0.0006; Table 2). This measurement was even lower in those with previously identified AS compared to the remainder with sacroiliitis (Table 3). Early morning stiffness of more than 30 min duration and the sacroiliac compression test were significantly more likely to be positive in those with sacroiliitis than in those without (Table 2), but did not differ statistically between those with and without classical AS (Table 3). Morning spinal stiffness > 30 min and a positive sacroiliac compression test were observed significantly more often in those with newly recognized sacroiliitis than in those with no CT evidence of sacroiliitis (chi-square = 14.4, p = 0.005 and chi-square = 10.8, p = 0.001, respectively). Iritis, but not erythema nodosum, occurred more frequently in all patients with sacroiliitis compared with those who had no sacroiliac joint change (Table 2). Among those with classical AS, a history of iritis was more frequent than for others with sacroiliitis, but the difference was not statistically significant (Table 3).

The radiographic scores of those with newly identified sacroiliitis were significantly lower than those with AS (Table 3). A significant difference was also seen between the CT scores (Table 3). Those with newly recognized sacroiliitis who

Table 1 Comparison of plain radiograph and CT scores in patients with back pain (n = 69).

	CT Score				
	0	1	2	3	4
Radiographic score					
0	30	0	8	1	0
1	8	0	2	5	0
2	0	0	0	5	0
3	0	0	0	4	0
4	0	0	0	0	6

Table 2. Demographic details and clinical and laboratory features of patients with back pain. Results expressed as median (interquartile range) or number (%).

	All Sacroiliitis, n = 31	No Sacroiliitis, n = 38	p
Demographic details			
Age, yrs	45 (35–54)	42 (34–53)	NS
Sex, F:M	11:20	25:14	0.02**
Crohn's Disease duration, yrs	8.0 (5.0–14.5)	7.0 (5.5–15.5)	NS
Age at onset, yrs	30 (24–43)	30 (24–47)	NS
Back Pain duration, yrs	8.5 (5–18)	5 (2–9)	0.018*
Clinical features			
Morning spinal stiffness > 30 min (%)	27 (88)	13 (34)	0.0001***
Schober index, cm	4.5 (3.8–5.3)	5.5 (4.8–6.0)	0.0006*
Positive sacroiliac compression test (%)	20 (64)	11 (29)	0.004***
Lateral flexion, cm	15.12 (10–18.7)	19.5 (16.2–22)	0.004*
Chest expansion, cm	4.0 (3.2–5.5)	4.5 (4.0–5.5)	NS
Iritis, n (%)	9 (29)	1 (3)	0.004***
Erythema nodosum (%)	6 (19)	2 (5)	NS
Laboratory markers			
HLA-B27 positive (%)	10 (33), n = 30	0 (0), n = 36	0.0001***
ESR, mm/h	13 (4–24)	16 (8–28)	NS

*Mann-Whitney U test; **Chi-squared test; ***Fisher's exact test.

Table 3. Demographic, clinical, and laboratory features of patients with sacroiliitis. Results expressed as median (interquartile range) or number (%).

	New Sacroiliitis, n = 22	Known Ankylosing Spondylitis, n = 9	p
Demographic details			
Age, yrs	39 (31–50)	47 (39–56)	NS
Sex, F:M	9:12	2:7	NS
Crohn's disease duration, yrs	8.0 (5.5–12)	6.0 (4.5–30)	NS
Age at onset, yrs	32 (21–43)	30 (25–44)	NS
Back Pain duration, yrs	6.0 (4.0–10)	18.0 (9.5–25)	0.001*
Clinical features			
Morning spinal stiffness > 30 min (%)	18 (82)	9 (100)	NS***
Schober index, cm	5.02 (4.58–5.46)	2.67 (1.61–3.72)	0.0002*
Positive sacroiliac compression test (%)	16 (73)	4 (44)	NS
Lateral flexion, cm	18 (16.5–19.2)	8.7 (5–12.5)	0.003*
Chest expansion, cm	4.5 (4–5.5)	2 (1.2–2.7)	0.002*
Iritis, n (%)	4 (18)	5 (55)	NS
Erythema nodosum (%)	3 (13)	3 (33)	NS
Radiographic score	1 (0–2)	4 (3–4)	0.0001*
CT score	3 (2–3)	4 (3–4)	0.002*
Laboratory markers			
HLA-B27 positive (%)	3 (14), n = 21	7 (78), n = 9	0.002***
ESR, mm/h	6 (4–20)	19 (14–40)	0.0002*

*Mann-Whitney U test; ***Fisher's exact test.

had a CT score of 2 had a significantly shorter history of low back pain (median 3 yrs, IQR 1.0–6.5) compared with those who had scores of 3–4 (median 6 yrs, IQR 5.5–18.5, p = 0.0165).

Laboratory features. Among the 122 patients typed for HLA-B27, the prevalence of HLA-B27 was 12%. This was not significantly different from that of 10% among 292 healthy controls previously reported from the same laboratory[24]. Ten

(15%) of 66 with back pain were B27 positive compared with 5 (9%) of 56 without (p = NS, Fisher's exact). Of those with back pain, patients with sacroiliitis (defined as a score ≥ 2) had a significantly higher frequency of B27 compared to those without (p = 0.0001; Table 2). Those with classical AS were significantly more likely to be HLA-B27 positive than those with newly recognized sacroiliitis (Table 3). Among those with new sacroiliitis, 3 of 21 (14%) possessed HLA-B27, whereas of those with a normal CT scan none of 36 did so (p = 0.0455). The chi-square test for trend confirmed significant evidence of an increase in B27 frequency across the 3 groups with back pain, namely no sacroiliitis, isolated sacroiliitis, and classical AS (p = 0.0001).

The ESR was statistically higher in those with AS compared with isolated sacroiliitis (Table 3).

DISCUSSION

We found that half of a consecutive series of patients with CD reported low back pain, a frequency much higher than expected from population data[25]. The 45% prevalence for sacroiliitis among patients with CD reporting back pain described here is similar to a study using isotope bone scanning[6]. Other studies have deployed CT scans of the sacroiliac joints in CD and estimated prevalence rates of 29% and 32% in asymptomatic patients[7,8]. Our higher frequency probably reflects our confinement of the study to those with back pain as previously predicted[8]. It is unlikely that we overinterpreted the frequency of sacroiliitis. The increased sensitivity of CT scanning over plain radiography in investigation of sacroiliitis has been reported[7,17,18]. Iliac sclerosis and narrowing of the joint may occur in CT scans of asymptomatic individuals over age 40[26]. Grade 2 changes with involvement of the sacral border of the joint such as we described are not features of the healthy population. The majority of our positive patients had at least grade 3 changes. We did not think it was ethically justifiable to expose pain-free subjects to the radiation of CT scans and cannot therefore estimate the overall prevalence of sacroiliitis in our patients with CD. Avoidance of radiation is an obvious advantage of MRI scanning of the sacroiliac joints[27,28], but at the time of our study, experience of this technique was limited in our unit. CT images were particularly useful in cases when the plain radiograph was indeterminate or normal. This advantage has been emphasized[8] and the enhanced sensitivity of CT of the sacroiliac joints compared with radiographs has been described[16,17,29,30].

We distinguished those with known spinal involvement and classical AS from the remainder with sacroiliitis rather than separate patients on the basis of the established criteria for AS[22]. We believed that this approach would not have assisted our main enquiry, which was to define the frequency of CT demonstrable sacroiliitis. Prolonged morning stiffness and positive sacroiliac joint compression were significantly more frequent in those with previously unrecognized sacroiliitis than in those without. These classical clinical associations of inflammatory spinal disease in the patients with newly recognized sacroiliitis tend to corroborate that the CT demonstrable sacroiliitis in these patients was clinically relevant.

It is noteworthy that among those with back pain attributable to established AS, the history of spinal symptoms was longer than that of those with newly recognized sacroiliitis and often exceeded the duration of symptomatic CD. This lends support to the notion that a proportion of patients with presumed idiopathic AS actually have occult CD[31-35]. There were other differences between these 2 groups, namely that those with classical AS had less spinal flexion and chest expansion, a higher ESR, and a more frequent association with HLA-B27. We did not perform extensive radiology on the spines of all back pain patients and cannot therefore say how many with newly identified sacroiliitis had ankylosing syndesmophytes of the lumbar, dorsal, or cervical vertebrae. The shorter history of back pain and the greater spinal mobility and chest expansion in those with newly identified sacroiliitis compared to those who had classical AS may imply that some of the former had early but evolving inflammatory spinal disease. However, we suspect that many would continue to have isolated sacroiliitis in the absence of spinal ankylosis and would probably not develop classical AS. The stronger relationship of HLA-B27 with those patients who already had more extensive spinal disease supports the conclusion of earlier studies that sacroiliitis in Crohn's disease is relatively common and is mainly not associated with HLA-B27[10,13,36]. It supports the notion that classical AS is more likely to develop in Crohn's disease among those who have both sacroiliitis and HLA-B27. These observations raise challenging questions about the cause and pathology of sacroiliitis in inflammatory bowel disease and its evolutionary relationship with spinal ankylosis.

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