Prevalence of Ankylosing Spondylitis and Other Spondyloarthropathies Among Patients with Inflammatory Bowel Disease: A Population Study (The IBSEN Study)

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ABSTRACT. ***Objective.*** To study the occurrence of spondyloarthropathies (SpA) in patients with inflammatory bowel disease (IBD) seen 6 years after IBD diagnosis.

Methods. In a population based cohort of 654 patients with IBD, 521 patients (80%) were investigated, which included a complete rheumatological examination. Radiographs of the sacroiliac joints and lumbar spine were performed in 406 of these patients (78%). The development of SpA was analyzed with regard to the presence of HLA-B27, duration of IBD symptoms, and the extent of intestinal inflammation.

Results. The occurrence of ankylosing spondylitis (AS) was 2.6% in ulcerative colitis and 6% in Crohn's disease ($p = 0.08$), yielding an overall prevalence of 3.7% in IBD. No correlation between localization or extent of the intestinal inflammation and presence of AS was found. HLA-B27 was present in 73% of cases with AS. The overall prevalence of SpA was 22%. Inflammatory back pain without AS (IBP) was found in 18% of the patients. Typical features of SpA were rare, while fibromyalgia was common in IBP, indicating that IBP is not a precursor or manifestation of SpA in patients with IBD. The prevalence of radiological sacroiliitis without clinical features of SpA was 2.0%.

Conclusion. AS occurred frequently in patients with newly diagnosed IBD. IBP did not seem to predispose to AS or other forms of SpA. The overall prevalence of SpA was 22%, whereas the prevalence of asymptomatic radiological sacroiliitis was low. (J Rheumatol 2002;29:511–5)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
INFLAMMATORY BOWEL DISEASE
ULCERATIVE COLITIS
INFLAMMATORY BACK PAIN
RADIOLOGICAL SACROILIITIS
CROHN'S DISEASE

Inflammatory bowel diseases (IBD), represented by ulcerative colitis (UC) and Crohn's disease (CD), are often accompanied by extraintestinal manifestations of which rheumatic complications appear particularly prevalent. The prevalence of spondyloarthropathies (SpA) in IBD has, however, rarely been evaluated by population based studies. Further, in surveys based on patients attending hospitals, only parts of the SpA spectrum have been investigated. Rather few studies have used routine radiography of the sacroiliac (SI) joints, and the majority of studies were reported prior to the development of current diagnostic and classification criteria[1].

Thus, reports on SpA in IBD are difficult to compare, and their estimated prevalences in an unselected population of patients with IBD remain uncertain. It was therefore of interest to study the occurrence of ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, and undifferentiated SpA in a population based cohort of patients with IBD seen 6 years after diagnosis of IBD. Additionally, the prevalence of radiological sacroiliitis without AS (RSI) and the prevalence of inflammatory back pain (IBP) were estimated. The development of SpA was analyzed with regard to the presence of HLA-B27, duration of IBD symptoms, and the distribution of the intestinal inflammation.

MATERIALS AND METHODS

Study population. All newly diagnosed cases of IBD or possible IBD between January 1, 1990, and December 31, 1993, in 4 well defined areas in southeastern Norway (counties of Oslo, Østfold, Telemark, and Aust-Agder) were recorded by the local departments of gastroenterology.

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To ensure complete ascertainment, all the 1236 general practitioners and clinicians at the 14 hospitals of the 4 participating counties received information about symptoms consistent with IBD, and were invited to refer all potential cases of UC or CD to the local gastroenterological outpatient clinic. The information was given prior to the start of the study by 3 written reminders. In addition, information about the study was presented at local meetings, and as well practicing gastroenterologists, internists, surgeons, and pediatricians were informed of the study. The total study population was 966,427 on January 1, 1992.

Endoscopy was chosen as the main instrument for diagnosis and for determining the distribution of disease in colon. A total of 618 cases diagnosed as UC and indeterminate colitis and 225 cases of CD were diagnosed[2,3]. The annual incidence during the 4 year study period showed only minimal variations, to a certain extent indicating completeness of ascertainment. In a followup between one and 2 years later, the diagnoses of intestinal diseases were reevaluated. Due to deaths, the number of patients available for followup was 830, of whom 814 (98%) were reevaluated. Four percent were excluded, as the diagnosis of IBD could not be confirmed[4].

In a systematic followup 5 years after inclusion, all cases were reviewed by gastroenterologists, and patients without confirmed diagnosis of UC or CD were excluded along with patients who had died (189 patients)[5]. The remaining patients were invited to a structured interview and clinical examination by a rheumatologist (ØP). Out of a total number of 654 patients (454 with UC and 200 with CD), 521 patients (80%) responded to the invitation and underwent a clinical examination.

In 406 of the patients clinically investigated (78%), radiography of the thoracolumbar spine and the SI joints was performed. All radiographs were initially evaluated by radiologists at the local hospitals. In cases of possible or definite inflammatory changes of the SI joints (31 cases), radiographs were reevaluated independently by another radiologist and a rheumatologist. To estimate a possible rate of false negative interpretation of radiographs, a random sample of 100 radiographs initially determined as normal were reevaluated by 2 rheumatologists and one radiologist. The radiologist and one of the rheumatologists were not informed of the patients' extraintestinal symptoms. Final grading was reached by consensus. The patients who underwent both clinical and radiological examinations and those clinically investigated only, were similar with respect to sex, age distribution, and extent of intestinal inflammation (data not shown).

Diagnostic criteria and grading classification of intestinal disease. Uniform methods and diagnostic criteria were applied. The initial classification of UC and CD required symptoms consistent with IBD for more than 4 weeks, excluding infections and other acute or chronic non-IBD.

Diagnosis of UC was based on presence of at least 3 of the following criteria: (1) a history of diarrhea and/or blood/pus in stool; (2) macroscopic appearance by endoscopy with continuous mucosal inflammation affecting the rectum in continuity with some or all of the colon; (3) microscopic features on biopsy compatible with UC; and (4) no suspicion of CD at small bowel radiography or ileoscopy or in biopsy[2].

Diagnosis of CD was based on established criteria[6] as follows: (1) typical clinical features including abdominal pain, diarrhea, and weight loss; (2) macroscopic appearance at surgery or endoscopy; segmental, discontinuous and/or patchy lesions with or without rectal involvement, discrete or aphthous ulcerations, fissuring and penetrating lesions, cobblestone or strictures; (3) radiological evidence of stenosis in the small bowel, segmental colitis, or findings of fistulae; and (4) histologic evidence of transmural inflammation or epithelial granulomas with giant cells. Two or more of these criteria were required for the diagnosis of CD.

The extent and localization of colonic disease were based on endoscopic findings with characteristic histological signs of inflammation. Proctitis was defined as mucosal changes in the rectum up to 15 cm from the anus, left side colitis up to the splenic flexure, and inflammation beyond the splenic flexure was classified as extensive colitis. When the extent of disease changed during followup, the maximum extent of bowel involvement was recorded. The patients with CD were classified according to the Vienna classification[7]. Localization and extent of the intestinal disease among patients investigated by a rheumatologist have been published[8] and did not differ from those of the total group.

Diagnostic criteria of SpA, inflammatory back pain, dactylitis, enthesopathy, uveitis, and peripheral arthritis. The diagnosis of AS strictly followed the modified New York criteria of 1984[9]. Measurements of spinal and thoracic mobility were performed in all cases and standard methods were applied[10]. IBP was diagnosed according to criteria proposed by Calin and coworkers[11]. Undifferentiated SpA was defined according to the European Spondylarthropathy Study Group criteria[12].

All patients were asked if psoriasis had been diagnosed by a physician. Positive answers were interpreted as a disease history of psoriasis. Peripheral arthritis was defined as at least one anamnestic or current episode of pain, swelling, and increased skin temperature in one or several joints. The diagnoses of psoriatic arthritis and reactive arthritis were based on both present and past clinical findings and followed standard diagnostic criteria[13,14]. Dactylitis was diagnosed when typical findings of sausage fingers or toes due to inflammation had been present. Enthesopathy was diagnosed when signs of inflammation of the insertion of the Achilles tendon to the bone or the plantar fascia had been present without preceding infection or trauma. Uveitis was recorded when diagnosed by an ophthalmologist. Erythema nodosum was diagnosed when tender, bluish red nodules (mainly on the extensor side of the limbs) were observed, and pyoderma gangrenosum when typical chronic ulcers with undermined necrotic bluish margins persisted for several weeks or longer. Fibromyalgia was defined according to the American College of Rheumatology criteria of 1990[15].

Grading and definition of radiological sacroiliitis. The grading of sacroiliitis followed the criteria proposed by Dale and coworkers[16]. Grade 0: normal conditions, with normal width and sharp margins of the joints; a slight sclerosis of the ileum side of the joint, i.e., osteitis condensans ilei, may be present. Grade 1: suspicious changes; the radiologist is uncertain whether there are changes described under grade 2. Grade 2: definite early changes; pseudo-widening of the joint space, and/or localized areas with erosions. Sclerosis of the bone usually on both sides of the joint space. Blurring of the joint margins often present. 2a: unilateral changes; 2b: bilateral changes. Grade 3: severe destructive changes; the erosions and often the pseudo-widening at least in one joint are more marked than in grade 2. The arthritic changes are always bilateral. Small bony bridges may be present. Grade 4: regressive changes; bilateral arthritic changes as described under grade 3, but in addition signs of narrowing of the joint space, often with bony bridges in one or both SI joints. Some regress of the sclerosis in the neighborhood of the joints. Grade 5: terminal changes; pronounced signs of bony ankylosis in both SI joints. Regress of the sclerosis in the neighborhood of the joints. Radiological sacroiliitis (RSI) was diagnosed in patients with grade 2b to 5 on plain radiographs who did not meet the criteria of AS or other SpA.

The study was approved by the Regional Ethics Committee and the Norwegian Data Registry. Confidentiality of both patient identity and records was maintained, using guidelines suggested by the National Health Department.

Statistics. Fisher's exact test, chi-square test and Student t test were used for statistical analyses and $p < 0.05$ was regarded as significant.

RESULTS

Ankylosing spondylitis. Among the 406 patients clinically and radiologically investigated, AS was found in 7 (4 men, 3 women) of 273 patients with ulcerative colitis (2.6%) and in 8 (all men) of 133 patients with Crohn's disease (6.0%). Thus, the total prevalence of AS in IBD was 3.7%. The

difference between UC and CD was not significant (p = 0.08). Onset of AS antedated symptoms of IBD in all patients with UC and in 4 (50%) of the patients with CD. The occurrence of uveitis, enthesopathy, and peripheral arthritis (Table 1) was found significantly more often in patients with AS compared to those without AS. No correlation between the distribution of the intestinal inflammation and the occurrence of AS was found. The use of prednisolone, sulfasalazine, 5-aminosalicylic acid, and azathioprine and rate of surgery were similar in the groups with and without AS (data not shown). Sacroiliitis grades 3–5 were present in 9 of the 15 patients with AS (60%), spinal radiographic changes typical of AS (squaring or syndesmophytes) were seen in 4 patients (27%), and total ankylosis of the spine (Bamboo spine) was not observed. Severe unilateral sacroiliitis was present in 2 cases (13%) among those diagnosed as AS. HLA-B27 was present in 11 of the patients (73%).

Inflammatory back pain in patients without AS. Excluding the patients with AS, a history of IBP was found in 46 of 266 (17%) patients with UC (17 men, 29 women) and in 28 of 125 (22%) patients with CD (12 men, 16 women) yielding an overall prevalence of 18% in all cases with IBD. The occurrence of uveitis, enthesopathy, and HLA-B27 was similar to that of the patients without IBP. The prevalence of fibromyalgia (15%) was, however, significantly increased compared to those without IBP (p < 0.001) (Table 1).

Radiological sacroiliitis in patients without AS or other SpA. Among the 406 patients evaluated by both radiographic and clinical investigation, RSI was found in 4 cases (1.0%). However, at reevaluation of the 100 radiographs initially interpreted as negative, one additional case of RSI was detected. Assuming a similar rate of RSI in the 275 radiographs not reevaluated, a total prevalence of RSI of 2.0% could be expected.

Characteristics of the 4 cases investigated are listed in Table 1. Sacroiliitis grade 3 was present in one patient (25%) and sacroiliitis grade 4–5 in none.

Psoriatic arthritis and reactive arthritis. Among those investigated clinically and radiologically, PsA was found in 3 patients (0.6%) (2 UC and one CD) and SAPHO syndrome in one patient. A history of reactive arthritis was reported by 2 patients, all men with ulcerative colitis (Table 2).

Undifferentiated spondyloarthropathy. USpA was found in 42 patients (15%) (17 men, 25 women) with UC and in 25 patients (19%) (11 men, 14 women) with CD, yielding a prevalence of 17% among the patients investigated both clinically and radiologically. The distribution of sex, age, and intestinal disease localization in these cases was similar to that of the patients without USpA. HLA-B27 was positive in 4 of 41 patients tested (9.8%) with UC and in 2 patients (8.0%) with CD, yielding a total occurrence of 9.1% in USpA. This prevalence of HLA-B27 in IBD was similar to that of patients without USpA and to those without other forms of SpA, but was significantly lower than in IBD patients with AS (p < 0.0001). Dactylitis was registered in 2 patients (one UC, one CD; 3%), uveitis in 2 patients (both UC; 3%), and enthesopathy in one patient (UC; 1.5%), also similar to those without USpA. Sacroiliitis (grade 2a) was found in one patient, while the remainder had normal radiographs of the SI joints.

DISCUSSION

We found a prevalence of AS of 3.7% in patients seen 6 years after diagnosis of IBD. Comparable data obtained by population based studies are lacking, and in the few hospital based surveys employing routine radiographs of SI joints, calculated prevalence rates of AS vary from 3.7% to 10%[17,18]. The striking variation in frequencies reported is most likely due to differences in patient selection. Thus, in spite of a rather high frequency of the disease susceptibility gene HLA-B27 (10%) in our population[19,20], the prevalence of AS in the present study was rather low. The explanation for the discrepancy is most likely caused by different study designs — this population based study conceivably covered a broader spectrum of IBD patients, and thus included both milder and more severe cases of the intestinal disease.

Table 1. Characteristics of AS, IBP without AS, and radiological sacroiliitis (RSI) in patients with IBD. All patients were investigated clinically and radiologically (n = 406).

	AS	IBP	RSI	Cases without AS IBP, or RSI	All Cases
Number (%)	15 (3.7)	74 (18) 5	4 (2.0†)	313 (77)	406 (100)
Age at onset of IBD, yrs	35 (11–57)	37 (13–71)	50 (16–62)	39 (9–74)	39 (9–74)
Age at onset of SpA, yrs	26 (14–50)	30 (14–67)	—	—	—
Uveitis (%)	4 (27)*	3 (4.1)	0	8 (2.6)	15 (3.7)
Enthesopathy (%)	5 (33)*	6 (8.1)	0	15 (4.8)	26 (6.4)
Peripheral arthritis (%)	7 (47)*	12 (16)	0	50 (16)	69 (17)
Dactylitis (%)	0	6 (8.1)	0	12 (3.5)	18 (4.4)
Fibromyalgia (%)	0	11 (15)**	0	6 (1.9)	17 (4.2)
HLA-B27+ (%)	11 (73)*	7 (9.6)**	2 (40%)	30 (9.8)**	50 (13)**

† The prevalence is adjusted for cases initially interpreted as false-negative. *p < 0.05 compared to cases without AS. ** Of the number analyzed.

Table 2: Occurrence of spondyloarthropathies* in ulcerative colitis (UC) and Crohn's disease (CD) in the 406 patients investigated clinically and radiologically.

	UC, n = 273 (%)	CD, n = 133 (%)	Total, n = 406 (%)
AS	7 (2.6)	8 (6.0)	15 (3.7)
Psoriatic arthritis**	3 (1.1)	1 (0.6)	4 (0.8)
Reactive arthritis	2 (0.7)	0 (0)	2 (0.5)
Undifferentiated SpA	42 (15)	25 (19)	67 (17)
SpA, total	54 (20)	34 (26)	88 (22)

*Peripheral arthritis related to IBD not included. ** One patient with SAPHO syndrome included.

The duration of the intestinal disease may also influence the prevalence of AS in IBD[21], and in a recent study, sacroiliitis was found to be more prevalent in patients with a disease duration > 10 years compared to those with a duration of 5 years[18]. Consequently, the rather short duration of IBD (6 years since diagnosis) in our study may be one explanation for the rather low prevalence rate of AS among our patients and thus partly explains the difference between the present findings and those of previous investigations[17,18]. We concluded, however, that AS occurs rather frequently in IBD, and significantly more often than the 1% prevalence of AS found in the general population[22].

We found a clear male dominance among our patients with AS (male to female 4:1), which is comparable to that of primary AS[23]. However, previous studies observed an equal sex distribution in IBD associated AS[24,25], but the small number of cases with AS does not allow any firm conclusions.

HLA-B27, peripheral arthritis, uveitis, and enthesopathy occurred significantly more often in IBD associated AS than among patients without AS and their prevalences were similar to those found in primary AS[10,26]. The grading of the sacroiliitis indicated severe changes (grade 3–5) in most of our patients. However, the spine was radiologically not involved in almost two-thirds of the patients and cases with total ankylosis of the spine (bamboo spine) were absent. Consequently, our findings may indicate that ankylosis of the spine is rare in IBD related AS, whereas extraspinal manifestations like peripheral arthritis, uveitis, and enthesopathy occur as frequently as in primary AS.

The use of clinical criteria of inflammatory back pain[11] is aimed at identifying early or mild cases of AS, and the clinical features included in the criteria represent rather typical symptoms of SpA. In our patients with IBD, 19% fulfilled such criteria without having concomitant radiological manifestations of AS. In contrast to our patients with AS, no male dominance was seen, and the frequencies of uveitis, enthesopathy, and HLA-B27 were similar to those without inflammatory back pain. Moreover, the prevalence of fibromyalgia was significantly higher among cases with IBP than among cases without IBP. Thus, in patients with IBP exclusively, the typical features of SpA and AS were not observed, suggesting that in the majority of such cases, IBP did not represent a precursor or manifestation of AS or other forms of SpA. The findings also suggest that IBP in patients with inflammatory bowel disease should not automatically be interpreted as a feature of SpA, and that fibromyalgia and other forms of chronic pain should be carefully ruled out before a diagnosis of inflammatory rheumatic disease is given.

Similarly, the findings in patients with USpA corresponded to those in patients with IBP, which may be explained by the considerable overlap between these 2 sets of criteria applied to patients with IBD.

The estimated prevalence of radiological sacroiliitis of 2.0% in our study is clearly lower than the 10–18% found in hospital based studies[18,27,28]. Differences in study design, interpretation of SI joint radiographs, methods of scoring radiographs, and rather short disease duration in our patients are possible explanations for the discrepancy.

Based on total occurrence of SpA, one in 5 patients was affected (Table 2). The occurrence of PsA, SAPHO syndrome, and reactive arthritis was rather low, and the largest subgroup was undifferentiated SpA. The high incidence of SpA in our study supports the observations[18] indicating that SpA may occur more often in patients with IBD than previously anticipated.

Interesting observations in recent years have thrown new light on the relationship between intestinal inflammation and SpA. Ileocolonoscopic studies have revealed frequent Crohn's disease-like lesions in patients with SpA[29,30]; moreover, about 6% of patients with SpA with no clinical features of IBD may develop CD 5 to 9 years later[31]. These findings may be supported by our study, in which onset of AS preceded the start of IBD in most cases.

AS and inflammatory back pain were found frequently in this population based study of patients investigated 6 years after diagnosis of inflammatory bowel disease. In the patients with inflammatory back pain exclusively, typical features of SpA were rare. Additionally, the high prevalence of fibromyalgia in these cases indicates that IBP is not a precursor or manifestation of AS or other forms of SpA in patients with IBD.

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