Arthritides associated with Crohn's disease

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ABSTRACT: A controlled prospective study was undertaken to determine the incidence and characteristic features of peripheral arthritis, sacroiliitis, ankylosing spondylitis and hypertrophic osteoarthropathy in a group of patients with Crohn's disease, and to define the relationship of such arthritides with disease site, duration and activity. Peripheral arthritis occurred in 14.5% of the patients; it was not seen in the control group. This arthritis, which tended to be pauci-articular, was more common in females with large bowel disease and post dated the bowel symptoms in all but one patient. There was close correlation with disease activity. Radiographic sacroiliitis occurred in 12.7% of the patients and ankylosing spondylitis in 7.3%; neither of these were seen in the control group. Sacroiliitis was more common in females and showed no correlation with either disease activity or human lymphocyte antigen (HLA) B27. Ankylosing spondylitis was seen equally in males and females and showed close correlation with both disease activity and HLA B27. Hypertrophic osteoarthropathy occurred in 9.1% of patients. It was not seen in the control group. All patients were asymptomatic. It showed no correlation with disease activity, finger clubbing, age of disease onset, or HLA B27. *Can J Gastroenterol* 1990;4(8):497-502

Key Words: Ankylosing spondylitis, Arthritis, Crohn's disease, Hypertrophic osteoarthropathy, Sacroiliitis

Arthrites associées à la maladie de Crohn

RESUME: Une étude contrôlée prospective a été effectuée afin de déterminer l'incidence et les caractéristiques de l'arthrite périphérique, de l'iliite, de la spondylarthrite ankylosante et de l'ostéo-arthropathie hypertrophique dans un groupe de patients atteints de maladie de Crohn, et pour définir le rapport existant entre ces types d'arthrite et le site de la maladie, sa durée et son évolution.

RHEUMATOLOGICAL ASSOCIATIONS of Crohn's disease may be divided into four major categories. First, a form of peripheral arthritis, often termed 'enteropathic' arthritis, is well characterized. Reported incidences vary from 2.2% (1) to 22.2% (2).

Prior to the 1960s the mean incidence was 6.8%. In five subsequent papers and 496 patients studied, the mean incidence was 15.9% (2-6) (Table 1). Peripheral arthritis is non-deforming, seronegative, disease activity-related (5), and human lymphocyte antigen (HLA) B27-unrelated; knees and ankles are characteristically affected (4,7). The onset tends to be abrupt, typically leading to a red hot swollen joint within 24 h (8).

Second, radiographic sacroiliitis, a form of axial arthropathy, is also seen in Crohn's disease (9). The reported incidences vary from 4.1% (5) to 19.8% (4). In an uncontrolled study using technetium pyrophosphate scanning (10), an incidence of 52% was reported, but normal uptake values with this technique are still in dispute. Sacroiliitis alone is asymptomatic, not associated with HLA B27, and may not progress to true spondylitis (11); it may

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L'arthrite périphérique est survenue chez 14,5% des patients et n'était pas présente dans le groupe de contrôle. Cette affection, qui tendait à être de type oligo-arthrite, était plus fréquente chez les femmes dont le gros intestin était atteint; les symptômes se sont manifestés après ceux de l'affection intestinale chez tous les patients sauf un. Il semble exister une corrélation étroite entre ce type d'arthrite et l'évolution de la maladie de Crohn. L'iliite confirmée par radiographie est survenue chez 12,7% des malades et la spondylarthrite ankylosante chez 7,3%; aucune de ces affections n'était présente dans le groupe de contrôle. L'iliite était plus fréquente chez les femmes et ne présentait aucune corrélation avec l'évolution de la maladie de Crohn ou l'antigène tissulaire HLA-B27. La spondylarthrite ankylosante se manifestait également chez les hommes et les femmes et indiquait une corrélation étroite à la fois avec l'activité de la maladie et le HLA-B27. L'ostéo-arthropathie hypertrophique s'est manifestée dans 9,1% des cas. Elle n'était pas présente dans le groupe de contrôle. Tous les patients étaient asymptomatiques. Il n'existait aucune corrélation entre cette affection et l'évolution de la maladie de l'intestin, l'hypocratisme digital, l'âge de la survenue de la maladie de Crohn ou le HLA-B27.

precede the onset of bowel symptoms and does not correlate with Crohn's disease activity (12).

Third, spondylitis, clinically and radiologically indistinguishable from idiopathic ankylosing spondylitis, occurs in 2.3% (13) to 11% (14) of patients with Crohn's disease. It was originally thought to predominate in males, but several recent studies have shown a more uniform sex distribution (15-17). Spondylitis follows a chronic progressive course and is unrelated to disease activity (7), but is HLA B27-related (18). Joint symptoms usually occur after the onset of bowel symptoms, but may precede them by several years (7).

The fourth category includes an array of less common rheumatological entities. One of these, hypertrophic osteoarthropathy, was studied by the authors in detail; while this has been previously reported in association with Crohn's disease, the association has been merely in the form of isolated case reports (19-27). Indeed, it was not found in one previous prospective study (9) and was found in only one of 72 patients (1.4%) in another such study (28). Because two of the isolated case reports came from the same unit, and the two prospective studies only investigated symptomatic patients, it was felt that the incidence might have been previously underestimated.

This study is the first prospective controlled study of these four arthritides in patients with Crohn's disease.

PATIENTS AND METHODS

Fifty-five consecutive patients attending the department of medicine and gastroenterology and diagnosed as suffering from Crohn's disease entered the study. Patients were diagnosed as suffering from Crohn's disease if they fulfilled the definite or probable criteria of Garland and his colleagues (29). Fifty-five irritable bowel syndrome patients who were age- (within three years) and sex-matched were studied as controls (30).

All 110 patients were interviewed by one author (JMG). The extent, duration and activity of Crohn's disease were recorded in each case. The macroscopic site was recorded as small bowel, small and large bowel, or large bowel disease alone. The duration was estimated from the time of diagnosis. The disease was deemed to be quiescent if: the patient felt well; there was no increase in bowel habit; weight was stable; there was no evidence of finger clubbing; and five or all of the following investigations were normal: hemoglobin, platelets, erythrocyte sedimentation rate, C-reactive protein, serum albumin and one acid glycoprotein.

Skeletal symptoms (bone and/or joint pain), whether past or present, and signs (finger clubbing, wrist and/or ankle tenderness, joint swelling or decreased range of movement, Schober test and chest expansion) were recorded. Finger clubbing was graded as slight, moderate or severe (31).

TABLE 1
Reported incidence of peripheral arthritis in Crohn's disease

Author (Reference)	Number of patients	% arthritis
Van Patter 1954 (38)	600	4.5
Crohn and Yarnis 1958 (1)	674	2.2
Daffer and Brown 1958 (39)	100	6.0
Cornes and Stecher 1961 (3)	131	10.7
Ansell and Wigley 1964 (4)	91	15.4
Hammer, Ashurst and Naish 1968 (2)	45	22.2
Haslock 1973 (5)	116	20.4
Passo 1986 (6)	58	16.0
Present study 1989	55	14.5

TABLE 2
New York criteria for diagnosis of ankylosing spondylitis

Diagnostic criteria

Limitation of motion of the lumbar spine in all three planes: anterior flexion, lateral flexion, extension
History of pain at the dorsolumbar junction or in the lumbar spine
Chest expansion limited to 2.5 cm or less at the level of the fourth intercostal space

Grading

Definite ankylosing spondylitis
Moderate bilateral sacroiliitis plus one diagnostic criterion
Moderate unilateral or minimal bilateral sacroiliitis plus limitation of movement
Moderate unilateral or minimal bilateral sacroiliitis plus back pain and limited chest expansion

Radiographs on all symptomatic joints and anteroposterior views of sacroiliac joints, wrists, ankles and hands were performed on all patients. All films were reported by another author (FK) without prior knowledge of clinical details. Symptomatic joints were recorded as normal or abnormal. Sacroiliac joint radiology was recorded on a scale of 0 to 4 according to Bennett and Burch (1967) (32): 0 for normal; 1 for a suspicious joint; 2 for an abnormal sacroiliac joint with sclerosis and/or erosions (minimal); 3 for an unequivocally abnormal joint with erosions, sclerosis, widening or narrowing or partial ankylosis (moderate); and 4 for

total ankylosis. The diagnosis of ankylosing spondylitis was made according to the 'New York criteria' (Table 2) (32). Periostitis was graded as minimal, obvious and florid when there was evidence of periosteal calcification (33).

In addition, all patients had the following investigations performed: uric acid levels, titres of rheumatoid and antinuclear factor and the presence or absence of HLA B27.

The fifty-five patients with irritable bowel syndrome were identically studied and investigated.

RESULTS

There were 21 males and 34 females with Crohn's disease; their ages ranged from 17 to 76 years (mean 36.5). The irritable bowel syndrome patients studied ranged in age from 18 to 73 years (mean 34.8).

Of the patients with Crohn's disease, eight had small bowel disease; 32 had small and large bowel disease; and 15 had large bowel disease alone. Disease duration ranged from 0 to 20 years (mean 4.75), and 13 were deemed to have active disease at the time of assessment. Twenty-four patients, 16 females and eight males, complained of skeletal symptoms, 12 of these patients had abnormal clinical signs and 16 had abnormal radiology.

Five of the 55 patients (four females and one male) with irritable bowel syndrome did complain of low back pain, but none exhibited abnormal physical signs and the relevant radiology was normal.

Peripheral arthritis: Eight patients (14.5%) with Crohn's disease, six females and two males, had a past or present history of acute arthritis. Their ages ranged from 20 to 35 years (mean 24). All eight affected patients had or had had documented signs of swelling, erythema and decreased range of movement. The knee was the affected joint in four, the ankle was in two, the elbow in two and the shoulder in one.

The duration of arthritis ranged from five to 42 days (mean 16). The arthritis preceded the diagnosis of Crohn's in one patient, was concurrent in two and postdated it in five.

Radiographs of all symptomatic joints were normal. Uric acid levels were normal in all patients, and all had negative titres for rheumatoid and antinuclear factors. One patient was HLA B27 positive.

Four patients had large bowel disease; three had both small and large bowel disease; and one had small bowel disease. The disease duration ranged from onset to six years (mean 2.3). Seven patients (87%) were deemed to have active disease at the time of acute arthritis. There was no evidence of peripheral arthritis in the control group.

Sacroiliitis: Seven patients (12.7%), four females and three males, had sacroiliitis. Their ages ranged from 19 to 62 years (mean 37.3). All patients were asymptomatic and had no abnormal physical signs. Radiographs revealed grade 1 sacroiliitis in three cases and grade 2 in four (Figure 1). Uric acid levels were normal, and titres of rheumatoid and antinuclear factors were negative in all seven patients. One patient was HLA B27 positive. Five patients had large bowel disease, and two had both small and large bowel disease. The disease duration ranged from 16 to 72 months (mean 42). One patient had active disease. There was no radiological evidence of sacroiliitis in the control group.

Ankylosing spondylitis: Four patients (7.3%), two females and two males, had evidence of ankylosing spondylitis. Their ages ranged from 32 to 45 years (mean 38.7). All four complained of low back pain and had abnormal Schober tests and diminished chest expansion. Radiographs revealed grade 3 sacroiliitis in three cases and grade 4 in one. Rheumatological investigations were normal, and three of the four patients were HLA B27 positive. One patient had large bowel disease, and three had both small and large bowel disease. The disease duration ranged from two to eight years (mean 5.3). Three of the patients had active disease. There was no evidence of ankylosing spondylitis in the control group.

Hypertrophic osteoarthropathy: Five of the Crohn's disease patients (9.1%), four females and one male, had

evidence of hypertrophic osteoarthropathy. Their ages ranged from 26 to 60 years (mean 41.2). All of the patients were asymptomatic and none had bony tenderness. Two had evidence of moderate finger clubbing. Radiographs showed minimal periostitis in two cases, obvious in three, and there was no evidence of periosteal calcification. The distal fibulae were involved in four cases and the distal radii in one. Uric acid levels were normal and titres of rheumatoid and antinuclear factor negative. No patient was HLA B27 positive. Four had large bowel disease; one had both small and large bowel disease. The disease duration ranged from two to six years (mean 3.6). Two patients had active disease. There was no evidence of hypertrophic osteoarthropathy in the control group.

DISCUSSION

The association between disease of the bowel and arthritis has been well recognized since the early 1900s (34). In 1935, Hench (35) described a peripheral arthritis associated with chronic ulcerative colitis. This was followed in 1959 by Wright and Watkinson (36) and Bywaters and Ansell (37), who described a form of arthritis distinct from rheumatoid arthritis occurring in patients with inflammatory bowel disease (either ulcerative colitis or Crohn's disease).

The main rheumatological conditions which are associations or complications of inflammatory bowel disease include peripheral arthritis, sacroiliitis and ankylosing spondylitis; less common arthritides include periostitis, amyloid arthritis, intra-abdominal abscess or generalized septicemia leading to septic arthritis, osteoporosis and/or osteomalacia secondary to malabsorption, and arthritis associated with granulomatous vasculitis or as a complication of long term corticosteroid therapy. Many previous studies have reported on the arthritides in inflammatory bowel disease; however, most have been solely retrospective, and none have included a control group.

The characteristic features of peripheral arthritis in Crohn's disease was

first reported by Van Patter and colleagues in 1954 (38); they showed an incidence of 4.5% and noted that the severity of arthritis reflected the activity of intestinal disease. Control of the intestinal disease resulted in remission of the arthritis, and exacerbation of the joint symptoms almost invariably heralded the onset of intestinal symptoms. Crohn and Yarnis in 1958 (1) reported an incidence of 2.2% predominantly affecting the large joints. A higher incidence of 6% was reported by Daffer and Brown in 1958 (39); this was followed by Cornes and Stecher in 1961 (3) who reported an incidence of 10.7%. Ansell and Wigley in 1964 (4) reported that 14 of 92 patients (15.4%) with Crohn's disease had either past or present histories of polyarthritis. The knee was the most common joint involved. Arthritic symptoms had antedated intestinal symptoms on only one occasion, and all radiographs of involved joints were normal. Hammer, Ashurst and Naish in 1968 (2) reported an incidence of polyarthritis in Crohn's disease of 2.2%. A similar incidence was reported by Haslock *et al* in 1973 (5). Greenstein *et al* in 1977 (40) reported an overall incidence of 23% in 700 patients with ulcerative colitis and Crohn's disease. In children with Crohn's, Passo *et al* in 1986 (6) documented an incidence of 16%.

The incidence of 14.5% reported in this study is compatible with previous reports. The features of peripheral arthritis in this series are typical in that joint involvement tended to be pauciarthritic, not truly symmetrical, and tended to affect the lower extremity joints (7,8). Attacks of arthritis were short in duration (all less than six weeks) and resolved spontaneously or with treatment of the underlying bowel lesion.

It has been suggested previously that arthritis is more common in patients with colonic involvement than in those with small bowel involvement (41); this trend also appertains in this present series – seven of the eight patients had colonic involvement. The present patients are also typical in that the majority had involvement of the

large joints of the lower limb, and all radiographs of the affected joints were normal. This joint disease differs from rheumatoid arthritis in that it is asymmetrical, seronegative, and radiographically normal, with attacks of short duration, and rarely follows a chronic progressive course.

This study is the third of its kind to examine sacroiliac joints in asymptomatic patients, and is the first to include a control group. Asymptomatic sacroiliitis is seen more commonly than ankylosing spondylitis in association with inflammatory bowel disease, and occurs in 4.1 to 19.8% of such patients (4,5). The incidence of 12.7% in this series is comparable. This study supports the view that sacroiliitis does not appear to correlate with the activity of bowel disease in that only one of the seven patients with sacroiliitis had active disease.

Previous studies have shown that sacroiliitis is not associated with HLA B27; the authors again support this view, as only one of seven patients was HLA B27 positive. This is not higher than the incidence of 6 to 14% of HLA B27 positivity in the general population (15,16).

The first statistical support for a significant association between Crohn's disease and ankylosing spondylitis was provided by Acheson in 1960 (13), who reviewed the records of 2320 male patients discharged from Veteran's Administration Hospitals and found that of 742 patients diagnosed as having regional enteritis, 17 (2.3%) had also been diagnosed as having ankylosing spondylitis. Several studies have since reported incidences of 2.3 to 11% (13,14). In two previous prospective studies, incidences of 0.4 and 3.7% were found (9,28). The incidence of 7.1% quoted in this paper, though comparable, is one of the highest recorded.

In most series, spondylitis is seen more commonly in males (36); the present study has shown an equal sex distribution. However, as 34 of the 55 patients were female it occurred relatively more frequently in females. While the majority viewpoint holds that sacroiliitis is unrelated to bowel disease activity (12), such activity was

found in three of the four patients. This may be explained, however, as these patients were assessed at the time when they happened to have active disease.

Radiographically, the spondylitis associated with inflammatory bowel disease is indistinguishable from idiopathic ankylosing spondylitis, and the joints are involved symmetrically. There is a clear association between ankylosing spondylitis in patients with inflammatory bowel disease and HLA B27; previously reported incidences vary from 53% (18) to 75% (42), the latter being identical to the incidence found in the present study. This is lower than the 90% or greater correlation between HLA B27 and idiopathic ankylosing spondylitis (43). The explanation for this lower expression of HLA B27 in the ankylosing spondylitis associated with inflammatory bowel disease remains to be elucidated.

Hypertrophic osteoarthropathy was first described by Bamberger in 1889 (44). Soon afterward it became apparent that it was also associated with nonpulmonary disease (45). There are now numerous known associations (46-57). The etiology is unknown. As hypertrophic osteoarthropathy has been previously described in association with neoplastic or inflammatory conditions, the possibility of it being immune complex deposition-associated arises. However, as hypertrophic osteoarthropathy associated with active disease was not found, the authors believe this an unlikely explanation, although immune complex or complement levels were not measured.

The present study into periostitis was prompted by two observations: periostitis occurred in the absence of symptoms (19,22), and previous prospective studies in cyanotic congenital heart disease (58) and cirrhosis (33), in which multiple asymptomatic areas were radiographed, revealed much higher incidences than previously reported. It was found that periostitis occurred in 9.1% of patients with Crohn's disease, and all of these were asymptomatic. This probably explains why in a large prospective study of 116 patients with Crohn's disease in whom

hands (excluding wrists), pelvis and only symptomatic joints were radiographed, no case of hypertrophic osteoarthropathy was found (27).

In another study (28) in which radiographs of only symptomatic patients were obtained, only one of 72 patients (1.4%) had evidence of periostitis. Though asymptomatic joints were radiographed, such radiology was not as widespread as in a previous prospective study looking at the incidence of hypertrophic osteoarthropathy in primary biliary cirrhosis and other forms of chronic liver disease (33); it is possible that had a similar skeletal survey been undertaken, an incidence approaching the 40% found in that series may have resulted. The present findings show that symptomatic periostitis is rare and highlights the need for a detailed investigation in asymptomatic patients to establish its true incidence.

The overall incidence of clubbing was 45%. This is comparable to previous reports which show incidences of

58% (31), 38% (59), and 32% (60). Clubbing has been shown to reflect disease activity (31,59). Two of the present patients with periostitis had finger clubbing; these patients had active Crohn's disease at the time of examination, whereas the other three had inactive disease. Originally, Alexander (61) stated that hypertrophic osteoarthropathy did not occur without clubbing, while Thompson (46) felt that both were nearly always present in association. Despite numerous theories, the pathogenesis of hypertrophic osteoarthropathy is uncertain (62). Locke and Mendlowitz (63,64) considered it to be a proximal extension of the clubbing process. However, a prospective study of cirrhotic patients by Epstein et al (33) found clubbing and periostitis to be strongly associated in 74 patients with primary biliary cirrhosis but not with cirrhosis of other causes. Clubbing and hypertrophic osteoarthropathy may occur in similar disease processes but not necessarily together. As the authors have shown, the presence of

clubbing is not a prerequisite for diagnosis of hypertrophic osteoarthropathy. A further observation was the lack of association with HLA B27; all patients with periostitis were HLA B27 negative, and none had evidence of sacroiliitis or ankylosing spondylitis, suggesting no association between hypertrophic osteoarthropathy and sacroiliac disease in patients with Crohn's disease.

While hypertrophic osteoarthropathy occurs in at least one in 10 patients with Crohn's disease, whether it occurs as a complication or as an association remains to be determined. Its presence does not relate to disease activity or duration, finger clubbing, or HLA B27, and is of itself likely to be asymptomatic. The incidence and characteristic features of peripheral arthritis, sacroiliitis and ankylosing spondylitis in this study are comparable with previous reports. However, the incidence of hypertrophic osteoarthropathy is much higher than previously recorded.

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