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CLINICAL REVIEW

THE ARTHRITIS OF COELIAC DISEASE: PREVALENCE AND PATTERN IN 200 ADULT PATIENTS

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SUMMARY

Arthritis has often been alluded to as an extra-intestinal clinical manifestation of coeliac disease, but definitive data regarding its prevalence are still lacking. We therefore evaluated the overall prevalence of articular involvement in 200 consecutive adult coeliac patients attending routine gastroenterology follow-up and in 40 controls, and determined whether the prevalence and pattern of articular involvement varied according to the dietary status. An arthritis was present in 26% of patients and in 7.5% of controls, prevalences ranging from 41% in patients on a regular diet to 21.6% in patients on a gluten-free diet ($P < 0.005$). Arthritis was peripheral in 19 patients, axial in 15 and an overlap of both in 18 subjects. These data suggest that arthritis is much more common than previous reports have indicated, particularly in patients receiving an appropriate dietary regimen, and support the need for combined gastrointestinal and rheumatological follow-up in coeliac patients.

KEY WORDS: Coeliac disease, Arthritis.

COELIAC disease (CD) is a gluten-sensitive enteropathy characterized by a wide spectrum of clinical manifestations, such as diarrhoea, weight loss, anaemia and herpetiform dermatitis [1–3]. Most of these are related to malabsorption which may be limited to one or a few nutrients up to a complete malabsorptive syndrome [4–6]. On the other hand, patients with CD are also characterized by an abnormal intestinal permeability which is also present in their first-degree relatives [7–9]. Recently, several epidemiological studies have reported an increasing prevalence of CD and have shown a shift towards an older age of onset together with a wider spectrum of clinical manifestations [1–3, 10]. In this respect, a number of reports have highlighted an association between arthritis and CD, with a reduced likelihood of arthritis and a remission of articular symptoms when the patient is on a gluten-free diet (GFD) [11–16]. Articular involvement is reported prevalently as an acute and non-erosive arthritis, involving axial or peripheral joints and, in some instances, it may be the heralding sign of an occult CD [14–16]. The absence of coincidental arthropathies of different aetiology and the fact that joint symptoms subside after a GFD suggest a link between CD and arthritis. The aims of the present study were to establish the overall prevalence of articular involvement in a cohort of CD patients, to determine whether prevalences, clinical, radiological and immunological features varied according to the dietary status of the patients, and to investigate whether a relationship existed between articular involvement and the duration of intestinal disease.

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PATIENTS AND METHODS

From April 1993 to April 1995, 200 adult patients with CD (46 male, 154 female, mean age 32.54 ± 15 yr, range 18–65) were consecutively seen by the same rheumatologist and gastroenterologist.

To avoid a selection bias due to possible articular complaints, patients were not told that they would be seen by rheumatologists in the gastroenterology clinic. Most patients were seen on the occasion of their routine annual visit, which is needed to obtain a prescription for gluten-free nutrients, in accordance with the Italian Health Care Regulations. Of the 200 patients, 157 (78.5%) (34 male, 123 female, mean age 32.82 ± 13.7 yr, range 18–65) had been on a GFD for an average of 58 months (range 12–144 months) with complete remission of intestinal symptoms, confirmed by histology. The remaining 43 patients (21.5%) (12 male, 31 female, mean age 32.9 ± 9.9 yr, range 21–64) were seen immediately after the diagnosis of CD, while they were still on a regular diet. In all patients, the diagnosis of CD was based on clinical, endoscopic and histological evaluation. A jejunal biopsy was considered suggestive of CD when it showed total or subtotal atrophy of intestinal villi, crypt hyperplasia and lymphoplasmacellular infiltration. Histology included measurement of villous height and crypt depth [17]. In all patients, diagnosis of CD was confirmed when, after at least 6 months of a GFD, histology showed normal mucosa or reduced inflammatory infiltration with improvement of villous height and crypt depth, compared with baseline findings.

Before the clinical attendance, all patients were administered a questionnaire regarding a possible history of articular involvement and then they underwent an extensive physical examination. All data regarding arthritis in this study were obtained from the clinical observation of present arthritis, regardless of previous history of articular complaints.

If present, arthritis activity was defined according to the number of affected joints, pain severity (using a visual analogue scale: 0 = no pain; 10 = very severe pain) and duration of early morning stiffness (minutes). Ritchie articular index was calculated according to the presence of tenderness, soft-tissue swelling, pain on motion of affected joints. We also calculated the Health Assessment Questionnaire (HAQ) functional index according to Fries *et al.* [18].

We did not consider arthralgia due to extra-articular origin and no examination of the synovial fluid was performed.

The presence of sacroiliac and/or axial involvement was determined clinically by: (1) direct pressure over the sacroiliac joints; (2) compression of the iliac bones towards each other; (3) hyperextension of one hip, maintaining the contralateral in full flexion; (4) measuring the limitation of lumbar spine motion in anterior and lateral flexion; (5) chest expansion measured at the fourth intercostal space. Patients in whom clinical examination revealed an inflammatory arthritis underwent joint X-ray or scintiscanning. Anteroposterior and oblique views of the pelvis were used for the assessment of sacroiliac joints, the involvement of which was graded according to the New York criteria [19]. Radiographs were read independently and blindly by two experts. Joint scintiscanning was performed using ^{99m}Tc and sacroiliac involvement was defined on the basis of the sacroiliac/sacrum uptake ratio [20]. Laboratory evaluations included CRP, ESR, Latex test, Waaler–Rose, antigliadin (AGA) (IgG and IgA class) and antiendomysium (EMA) antibodies (IgA class) (Eurospital).

The statistical package SPSS for Windows version 6.0 was used for data analysis. These were expressed as mean ± S.D. and analysed by χ^2 test and Student's *t*-test as appropriate.

Controls

Forty age- and sex-matched patients with irritable bowel syndrome (12 male, 28 female, mean age 30.6 ± 13 yr, range 19–59), consecutively seen in the gastroenterology clinic, underwent the same clinical evaluation and were used as controls.

RESULTS

Age, sex and anthropometry of CD patients and controls are shown in Table IA and B. The reported mean duration of disease starting from appearance of symptoms related to CD was 91 ± 95.2 months. Clinical and laboratory findings of CD patients and controls are summarized in Tables II and III. Arthritis was present in 52 patients (26%) (nine male, 43 female, mean age 31.5 ± 10.9 yr, range 22–55) and in three controls (7.5%) (three female, mean age 32.5 ± 10.8 yr). The prevalence of articular involvement was higher in the group of patients who were on a regular diet (41.8%, 18/43) compared to those who were on a GFD (21.6%, 34/157) ($\chi^2 = 7.16$; $P < 0.005$). The arthritis was independent of the duration of the intestinal disease and that found in patients who were on a regular diet was clinically more severe (pain score = 6.3 *vs* 4.6 in those on a GFD, $P < 0.05$).

The Ritchie index showed a mean value of 3.34 in all CD patients with arthritis. This value is in agreement with a painful arthritis. When the Ritchie score was evaluated on the basis of the dietary status, we found a difference between the two groups. In fact, mean

TABLE I

(A) Age and anthropometric data of adult coeliac patients

	Men (n = 46)	Women (n = 154)
Age (yr)	32.54 ± 16.9	35.5 ± 11.6
Weight (kg)	58.4 ± 10.8	49.0 ± 9.7
Height (m)	1.70 ± 0.10	1.60 ± 0.09
Body mass index (kg/m²)	20.4 ± 2.7	19.2 ± 3.3
Patients on a GFD	34	123
Patients on free diet	12	31

(B) Age and anthropometric data of controls (irritable bowel disease patients)

	Men (n = 12)	Women (n = 28)
Age (yr)	32.2 ± 13.0	29.5 ± 15.6
Weight (kg)	61.4 ± 10.8	47.0 ± 9.7
Height (m)	1.72 ± 0.10	1.63 ± 0.09
Body mass index (kg/m²)	22.4 ± 2.7	20.2 ± 1.3

TABLE II

Characteristics observed in adult coeliac patients with or without arthritis

	CD patients with arthritis (n = 52)	CD patients without arthritis (n = 148)	P
Gender (male/female)	9/43	37/111	NS
Age (yr)	31.5 ± 10.9	33.0 ± 15.0	NS
Duration of CD (months)	91.6 ± 97.8	95.1 ± 93.5	NS
Patients on a GFD	34/52	123/148	$P < 0.005$
Patients not on a GFD	18/52	25/148	$P < 0.005$
Number of affected joints	5.72 ± 2.5	0.33 ± 0.33	$P < 0.00001$
ESR	16.77 ± 5.71	8.43 ± 5.95	$P < 0.02$
CRP	1.65 ± 0.51	1.04 ± 0.23	$P < 0.00001$
Dermatitis	0/52	3/148	NS
Conjunctivitis	2/52	6/148	NS
Aphthous	3/52	7/148	NS
EMA	18/52	25/148	NS

TABLE III

Characteristics observed in controls compared to adult coeliac patients regardless of arthritis

	Controls (n = 40)	CD patients (n = 200)	P
Gender (male/female)	12/28	46/154	NS
Age (yr)	30.6 ± 13	32.54 ± 15.0	NS
Duration of CD (months)	60.2 ± 45.8	91 ± 95.2	NS
Patients with arthritis	3/40	52/200	$P < 0.001$
Number of affected joints	0.25 ± 0.9	0.98 ± 2.09	$P < 0.001$
ESR	4.2 ± 1.6	9.21 ± 5.97	$P < 0.01$
CRP	0.5 ± 0.09	1.14 ± 0.38	$P < 0.001$
Dermatitis	0/40	3/200	NS
Conjunctivitis	2/40	8/200	NS
EMA	0/52	43/200	

Ritchie index was 3.94 in patients on a regular diet, whereas it was 3.02 in those on a GFD ($P < 0.05$). The mean HAQ value in all CD patients with arthritis was 2.03, implying a moderate impairment of mobility. When the HAQ mean value was calculated on the basis of the dietary status, it was 2.4 in patients on a regular diet and 1.82 in those on a GFD ($P < 0.05$).

According to clinical and radiological findings, patients with arthritis were classified into three subgroups.

Subgroup 1

Patients with recurrent asymmetrical oligopoly-arthritis (19/52, 36.5%) (three male, 16 female, mean age 29.1 ± 9.63 yr) localized in the upper and lower limbs (often self-limiting, of a few weeks duration) with negligible morning stiffness. Large joints were often involved (shoulder, elbow, wrist, knee) with tenderness on motion, and minimal synovial effusion. Patients usually self-administered NSAIDs or analgesic to control pain. The mean duration of symptoms which were later related to CD was 108 ± 12 months. Of these patients, 35.2% (12/34) were on a GFD, whereas 38.8% (7/18) of cases belonged to the group on a regular diet. Compared to patients without arthritis, CRP and ESR of arthritic patients were significantly increased (ESR mean value = 16.3 ± 6.07 mm/1st h; $P < 0.02$; CRP mean value = 1.62 ± 0.6 mg/dl; $P < 0.00001$), while rheumatoid factor was negative in all CD patients. Radiological examinations revealed soft-tissue swelling and joint space narrowing without sclerosis of subchondral bone. These findings are in agreement with early phases of arthritis. Nevertheless, erosion of the left sternoclavicular joint was noted in one case (a patient on a GFD).

Subgroup 2

Patients with axial and/or sacroiliac involvement (15/52, 28.8%) (five male, 10 female, mean age 32.86 ± 13.7 yr). The mean duration of the intestinal disease which was later related to CD was 115 ± 13 months. Of these patients, 26.4% (9/34) were on a GFD and 33% (6/18) belonged to the group on a regular diet ($P = 0.4$). All patients reported a history of pain at the thoracolumbar junction, but none of them showed a significant limitation of motion of the lumbar spine in the three planes (anterior, lateral flexion and extension). Chest expansion, measured at the fourth intercostal space, was normal in all cases. Low back pain was present in six cases (40%), of which 5/34 (14.7%) were on a GFD and 1/18 (5.55%) were on a regular diet ($P = 0.1$). In all 15 patients, sacroiliac involvement was clinically detected by direct pressure over the joints and confirmed radiographically. Grade 2 unilateral sacroiliitis was present in 80% (12/15) of cases, grade 2 bilateral sacroiliitis in 13% (2/15) of cases and a grade 3 unilateral sacroiliitis in the remaining patient. Of note, the latter was present in a patient on a regular diet. X-rays showed narrowing of articular spaces and enthesopathic changes (whiskering of iliac crest and ischial tuberosities) in six cases (40%), but no erosions or syndesmophytes were seen. Scintiscanning revealed an abnormal uptake of ^{99}Tc on sacroiliac joints and on the entheses (iliac crest and ischial tuberosities) in 10 cases (66%).

Rheumatoid factor was negative in all patients, but ESR and CRP were significantly higher in arthritic patients than in those without articular involvement (ESR mean value = 15.6 ± 5 mm/1st h; $P < 0.02$; CRP mean value = 1.466 ± 0.4 mg/dl; $P < 0.00001$).

Subgroup 3

Patients with an overlap of the clinical manifestations of subgroup 1 and 2 (18/52, 34%) (one male, 17 female, mean age 32.94 ± 9.9 yr). The mean duration of symptoms which were later related to the intestinal disease was 112.8 ± 13 months. Of these, 38.2% (13/34) were on a GFD, whereas 27.7% (5/18) of patients belonged the group on a regular diet ($P = 0.1$). They had tender peripheral joints [hand (MCP, PIP), wrist, shoulder, ankle] associated with tenderness on motion of the cervical and lumbar spine. Their morning stiffness was negligible and improved with exercise. Scintiscanning revealed an abnormal uptake of ^{99}Tc on sacroiliac joints and on most of the entheses (iliac crest, ischial tuberosities, Achilles tendon and calcaneal spurs) in four cases (22.2%). Radiological findings did not differ from those observed in subgroup 1, although one grade 2 unilateral sacroiliitis was found. ESR and CRP were significantly higher than in patients without arthritis (ESR = 15.77 ± 5.71 mm/1st h; $P < 0.02$; CRP mean value = 1.55 ± 0.5 mg/dl; $P < 0.00001$), while rheumatoid factor was negative in all patients. The prevalence of arthritis in the three subgroups is given in Fig. 1.

Extra-articular manifestations

All extra-articular manifestations occurred in 15 patients (15/200, 7.5%), 11 of whom were on a regular diet (11/43, 25%).

In particular, dermatitis herpetiformis was present in 3/43 (7%) of patients on a regular diet, but in none of the patients on a GFD (0/157). Conjunctivitis was present in 8/200 (4%) of the patients, showing no preferential association between patients with (2/52, 3.8%) or without (6/148, 4.0%) arthritis. Similarly, aphthous ulcerations were found in 10/200 (5%) of the patients, with no clustering between patients with (3/52, 5.76%) and without (7/148, 4.72%) arthritis. Coeliac disease was associated with a scleroderma-like lesion of the skin on the right leg in one patient and with primary biliary cirrhosis in another. Both patients were on a GFD.

Serum antibodies

Increased levels of AGA (IgG and IgA) and EMA (IgA) antibodies were found in all CD patients who were on a regular diet ($n = 43$). Of these patients, 18 (18/43, 41.8%) had arthritis, while the remaining 25 (25/43, 58.1%) did not suffer from any articular complaints (P = NS).

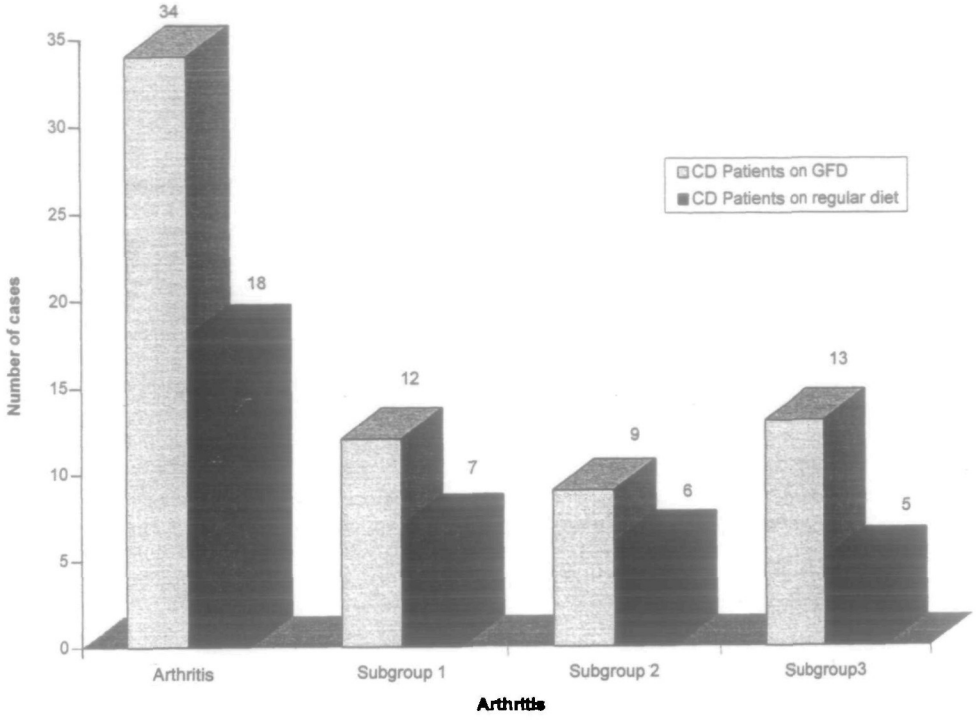

FIG. 1.—Distribution of arthritis in three subgroups related to GFD.

DISCUSSION

The pathogenetic link between articular involvement and gastrointestinal diseases is as yet unclear [21]. An arthritis complicating inflammatory bowel diseases was first described in 1930 [22]. In 1964, the American Rheumatism Association distinguished these conditions, on the grounds of clinical, radiological and serological features, from rheumatoid arthritis [23]. In 1976, Wright and Moll [24] introduced the concept of 'enteroarthritis' and included this group of disorders into the family of seronegative spondyloarthropathies. The actual definition of enteroarthritis applies to ulcerative colitis, Crohn's and Whipple disease [25]. CD is a disease characterized by an abnormal intestinal permeability induced by gluten. It is unknown which antigens, if any, are implicated in the development of extra-intestinal symptoms. Malabsorption in CD may be either generalized or limited to a few nutrients [4–6], allowing for the variability of the clinical spectrum of the disease in adult patients. Among the extra-intestinal manifestations of CD, arthritis is thought to be rare, although in adult patients it may occasionally represent the heralding sign of a gluten enteropathy [11–16]. The occurrence of well-defined immune-mediated complications and of arthritis has been often related to gluten intake, and complete remissions were described after the introduction of a GFD [11–16]. However, some autoimmune disorders may complicate the course of CD despite a GFD, suggesting that remission of intestinal lesions and prevention or remission of extra-intestinal manifestations do not always run in parallel [26, 27]. Changing trends in prevalences and clinical presentations are modifying the conventional concepts of the malabsorption syndromes. In fact, recent reports have described clinical presentations which misled and delayed the recognition of a malabsorptive disorder [3, 28]. The high prevalence of articular manifestations found in the present study (26%, regardless of a GFD) confirms our preliminary report [29] and the study of Maki *et al.* [15], and challenges the previous notion that arthritis represents a rare complication of CD (11). The articular involvement found in our patients was most frequently a non-erosive, non-deforming oligopoly-arthritis associated with axial and/or sacroiliac joint involvement, in the absence of the classic rheumatoid factor, a picture closely similar to that of other enteropathic arthritides. Arthritis was more frequently noted in patients who had not yet started a GFD than in those who were already on a GFD (46% *vs* 21.6%, $P < 0.005$), although no difference was seen when data were analysed according to the different pattern of articular involvement. Probably, an appropriate dietary regimen may partially protect from the development of joint disease, in line with previous studies on food intolerance in rheumatic diseases [30, 31]. The arthritis present in patients who were seen before the introduction of a GFD was independent of the duration of their intestinal disease, but was clinically more severe (number of affected joints and pain score) than that of patients on a GFD, although there were no radiological or serological differences between them. In adult patients, it is presumably difficult to obtain an optimal compliance to a GFD even in the absence of rising levels of AGA and EMA, and persistent subclinical mucosal damage is difficult to rule out. The

latter would favour an activation of the immune system with possible connective tissue involvement [27–32]. Since data regarding a possible role of other antigens, alimentary or bacterial, in the pathogenesis of arthritis in CD are lacking, the improvement of joint disease after a GFD at least suggests a link with gluten. The arthritis of patients with CD is very similar to that of the other enteroarthritides, which in turn belong to the larger family of the seronegative spondyloarthropathies. Further cooperative studies (gastroenterologists and rheumatologists) assessing the prevalence and the pathogenesis of articular involvement in CD will help elucidate whether the arthritis of CD should be included among the seronegative spondylarthropathies.

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