III. Clinical characteristics and results of histocompatibility typing (HLA B27) in 50 patients with both ankylosing spondylitis and inflammatory bowel disease

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SUMMARY A study was made, in co-operation with several gastroenterology and rheumatology centres, of the clinical and genetic characteristics (HLA B27) of 50 patients suffering from both inflammatory bowel disease (38 Crohn's disease (CD), 12 ulcerated colitis (UC)) and ankylosing spondylitis (AS), the latter diagnosis being established according to the New York criteria. 20 CD (52.6%) and 8 UC (66.7%) patients were HLA B27 positive. The presence of HLA B27 was studied in relation to clinical parameters, such as first occurrence of symptoms of AS or inflammatory bowel disease (IBD), a history of peripheral arthritis, iridocyclitis, and a positive history of AS or IBD.

Our patients were found to have heterogeneous clinical features: on one side of the spectrum a group of cases was distinguished with the typical characteristics of idiopathic AS, often being HLA B27 positive. On the other side a smaller group of HLA B27 negative patients was observed, with severe intestinal inflammatory pathology, lacking most of the typical clinical features of idiopathic AS ('secondary' form of AS). Finally, between these two extremes a group of patients was found with less pronounced clinical or genetic characteristics. These different clinical and histocompatibility patterns suggest a mixed aetiopathogenesis of AS in IBD patients. Such a 'syndrome' of AS might harbour both idiopathic AS and forms of AS 'secondary' to the intestinal inflammatory pathology.

It is well known that the incidence of inflammatory bowel disease (IBD) is increased in patients suffering from ankylosing spondylitis (AS) (Romanus, 1953; Steinberg and Story, 1957; Wilkinson and Bywaters, 1958; McBride *et al.*, 1963; Jayson and Bouchier, 1968; Jayson *et al.*, 1970; Meuwissen *et al.*, 1978). On the other hand, there is an increased frequency of AS in IBD (Acheson, 1960; Moll *et al.*, 1974; Dekker-Saeys, 1977). Because of the high frequency of the histocompatibility antigen HLA B27 in AS, this antigen has been studied in diseases associated with AS such as IBD, but the results of the HLA typing are conflicting. The frequency of HLA B27 in patients with both AS and IBD has been reported to be increased, but not to the same extent as in patients with AS alone (Morris *et al.*, 1974; Nagant de Deuxchaisnes *et al.*, 1974; Brewerton and James,

1975). The number of patients in these studies is small, however, and the results show a wide scatter of frequencies (Table 1).

Table 1 Frequency of the histocompatibility antigen HLA B27 in patients with ankylosing spondylitis and inflammatory bowel disease from published reports

Author	Year	No. of patients	B27+ (%)
Morris <i>et al.</i>	1974	8	6 (75)
Nagant de Deuxchaisnes <i>et al.</i>	1974	21 CD	3 (14), sacroiliitis included
Jacoby & Jayson	1974	3 CD	1 (33)
Brewerton & James	1975	23 (18 UC, 5 CD)	13 (72) 4 (80)
Russell <i>et al.</i>	1975	11 CD	10 (91)
Deshayes <i>et al.</i>	1976a, b	6 CD	4 (66)
Hyla <i>et al.</i>	1976	4	3 (75)
Mallas <i>et al.</i>	1976	7 (5 UC, 2 CD)	4 (80) 1 (50)

CD = Crohn's disease; UC = ulcerative colitis

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Because of the inconclusive data, a study in collaboration with gastroenterology and rheumatology centres in The Netherlands and one in Belgium analysed in detail the clinical and genetic characteristics of patients suffering from both IBD (ulcerative colitis (UC) or Crohn's disease (CD)) and established AS, thereby excluding all patients with asymptomatic radiographic sacroiliitis.

Materials and methods

A rheumatologist and a gastroenterologist interviewed all patients entered into the study regarding their musculoskeletal and gastrointestinal history. Each patient underwent a detailed rheumatological and gastrointestinal examination. Usually at the same time an anteroposterior radiograph of the sacroiliac joints was made, using a standard technique and, when not already available, x-ray films of the lumbar spine were taken. The films were examined by 2 independent experienced radiologists, without prior knowledge of the clinical findings (Dekker-Saeyns *et al.*, 1978). SI joint pathology was graded on a scale of 0-4 (Bennett and Burch, 1967). For inclusion in this study a diagnosis of definite AS was required, according to the New York criteria (Bennett and Burch, 1967). In addition, recent x-rays of the small intestine and colon were studied, and when not available the intestinal tract was re-examined radiologically using a duodenal intubation method (Sellink, 1974) and/or barium enema. Diagnosis of UC and CD was made according to accepted clinical, endoscopic, radiological, and histological criteria, or was confirmed at surgery, in agreement with criteria of Schachter and Kirsner (1975).

A modified NIH microlymphocytotoxicity technique was used for histocompatibility testing (Engelfriet *et al.*, 1972), to study the HLA B27 antigen. 58 patients were to be included in this study, but the sacroiliac abnormalities of 4 were of insufficient degree, and the diagnosis of IBD was questionable in 4. Therefore, 50 of the 58 cases were selected for final analysis. None of the patients was related to each other.

The approximate time of onset of AS symptoms was based on the first occurrence of recurrent symptoms, such as low back pain, early morning stiffness, peripheral arthritis, iritis, or 'sciatica'. The approximate onset of symptoms in UC was based on the first occurrence of bloody mucoid diarrhoea, with or without fever and abdominal pain. In CD the onset of symptoms was usually associated with progressive anorexia, weight loss, abdominal pain, and/or diarrhoea. IBD and AS symptoms were considered to have occurred simultaneously when

the time difference between the onset of IBD and AS was less than 2 years. For statistical analysis, χ^2 values were calculated from 2×2 tables.

Results

Fifty patients (mean age 43.5 years, range 20-70 years) were studied, 37 males and 13 females (mean ages 45.8 and 36.8 years respectively). 38 patients suffered from CD (mean age 43.7 years): 19 with localised disease of the terminal ileum, 12 with ileocolitis, and 7 with disease of the colon. 21 patients (55.2%) had been operated upon. Internal fistulae were found in 7, and external fistulae in 6. 12 patients suffered from UC (mean age 42.8 years). 1 had undergone a proctocolectomy. The mean age of onset of AS symptoms in the CD group was 27 years and in the UC group 29.7 years, while IBD symptoms started in the CD group at a mean age of 30.6 years and in the UC group at a mean age of 27.8 years. In 17 patients (34%) AS symptoms preceded IBD symptoms (3-32 years earlier), in 20 (40%) AS and IBD symptoms occurred simultaneously, and 13 (26%) IBD symptoms occurred earlier (from 3 to 47 years).

52.6% of the CD-AS patients were HLA B27 positive, which differed significantly from the frequency of HLA B27 in a group of CD patients without AS (3.9%) studied separately (van den Berg-Loonen *et al.*, 1977) ($P < 0.001$). The frequency of HLA B27 in UC-AS patients was 66.7%. In comparison, UC patients without AS had a frequency of 19% (van den Berg-Loonen *et al.*, 1977), but this was not significant. The frequency of HLA B27 in CD-AS and UC-AS patients differed significantly from the frequency of HLA B27 in a nonselected group of patients with idiopathic AS with no evidence of IBD (81.7%) (van den Berg-Loonen *et al.*, 1977) ($P < 0.01$ and $P < 0.01$ respectively).

The most relevant clinical and HLA data in CD-AS and UC-AS patients are given in Tables 2 and 3. A striking male preponderance was observed in the CD-AS group, while the sex ratio was equal in the UC-AS group. There was no obvious difference in frequency of HLA B27 between males and females, either in the CD-AS or in the UC-AS patients. The number of CD-AS patients in whom AS symptoms occurred first was higher than in the UC-AS group. In contrast to CD-AS patients with AS symptoms occurring first or simultaneous occurrence of symptoms, all CD-AS cases, starting with abdominal symptoms, were found to be HLA B27 negative. This pattern was not detected in the UC-AS group. Patients with a positive family history of AS or a history of iridocyclitis (occurring in CD only) were frequently HLA B27 positive. 19

Table 2 Relationship between first symptoms, clinical features, and HLA B27 in 38 patients suffering from CD and AS

	No. of patients	AS symptoms first (n = 15)		Simultaneous occurrence of AS and IBD (n = 14)		IBD symptoms first (n = 9)	
		HLA B27+	B27—	HLA B27+	B27—	HLA B27+	B27—
Total number	38	10	5	10	4	—	9
Males	31	7	5	8	4	—	7
Females	7	3	—	2	—	—	2
Family history							
AS	4	2	1	1	—	—	—
IBD	2	—	—	—	1	—	1
Iridocyclitis	11	4	—	5	1	—	1
Erythema nodosum	2	1	—	1	—	—	—
Peripheral arthritis	17	3	2	7	2	—	3
Sacroiliitis							
Grade 2	2	1	—	1	—	—	—
3	18	3	1	5	4	—	5
4	18	6	4	4	—	—	4
No spinal involvement	18	4	1	6	3	—	4
Spinal involvement	18	6	4	4	1	—	3
						(2 patients no spinal x-rays available)	
Severe IBD symptoms	16	3	—	5	1	—	7

Table 3 Relationship between first symptoms, clinical features, and HLA B27 in 12 patients suffering from UC and AS

	No. of patients	AS symptoms first (n = 2)		Simultaneous occurrence of AS and IBD (n = 6)		IBD symptoms first (n = 4)	
		HLA B27+	B27—	HLA B27+	B27—	HLA B27+	B27—
Total number	12	2	—	3	3	3	1
Males	6	1	—	1	—	3	1
Females	6	1	—	2	3	—	—
Family history							
AS	5	1	—	2	—	2	—
IBD	—	—	—	—	—	—	—
Iridocyclitis	—	—	—	—	—	—	—
Erythema nodosum	—	—	—	—	—	—	—
Peripheral arthritis	3	—	—	1	1	1	—
Sacroiliitis							
Grade 2	0	—	—	—	—	—	—
3	7	—	—	1	3	2	1
4	5	2	—	2	—	1	—
No spinal involvement	8	1	—	1	3	2	1
Spinal involvement	4	1	—	2	—	1	—
Severe IBD symptoms	5	—	—	2	1	2	—

CD-AS and 3 UC-AS patients had at some time in their illness a peripheral arthritis, and in 9 and 2, respectively, joint inflammation ran in parallel with inflammatory bowel activity.

The large majority of both CD-AS and UC-AS patients showed a severe form of radiographic sacroiliitis (grade 3 or 4). Although both in UC-AS and CD-AS a long mean duration of AS symptoms existed before the study (average >10 years), only 18 of 28 CD-AS and 4 of 12 UC-AS patients had evidence of spinal involvement. Of the 18 CD-AS cases, 10 were HLA B27 positive, and all 4 UC-AS patients with spinal involvement were B27 positive. In 6 of the 50 patients (2 UC, 4 CD) a 'bamboo-spine' with widespread changes was diagnosed

(12%). CD-AS patients showed no correlation between grading of radiographic sacroiliitis and localisation of overtly affected bowel, presence of external and internal fistulae, or number of surgical interventions. 5 of the 12 UC-AS patients had severe colitis, as judged by the extent of diseased colon and complicated clinical course; 4 were HLA B27 positive. But only 8 of 16 CD patients with extensive involvement of small bowel and/or colon, frequently complicated by internal or external fistulae, and numerous surgical interventions, were HLA B27 positive.

Four patients, correctly diagnosed as suffering from AS (2 CD, 2 UC), 3 of whom were HLA B27 positive, showed during follow-up some regression

of the radiological abnormalities of the SI joints together with a remission of their inflammatory bowel activity after appropriate medical or surgical treatment.

Discussion

Several findings in our analysis of a large series of patients suffering from both AS and IBD deserve emphasis. The large majority of the patients suffered from CD (76%) and not UC. This is in contrast with results from previously published data (Jayson and Bouchier, 1968; Jayson *et al.*, 1970; Brewerton *et al.*, 1973), and also from our own data (Dekker-Saeys *et al.*, 1978) and the recent observation by Woodrow that UC patients possess HLA B27 more frequently than patients suffering from CD (J. C. Woodrow *et al.*, unpublished). However, we have no reason to believe that the CD preponderance has occurred by a selection bias, because patients were gathered at random from various gastroenterology as well as rheumatology centres.

Many characteristics of the CD-AS and UC-AS syndrome were similar, such as mean age of patients, mean age of onset of AS or IBD symptoms, the severity of radiographic sacroiliitis, and the remarkably low incidence of spinal involvement. Differences were the absence of a male preponderance in UC-AS patients, a more frequent positive family history of AS in UC-AS patients, and a more frequent history of iridocyclitis in CD-AS patients.

Particularly notable were the different patterns in the CD-AS and UC-AS patients when analysing data of prevalence of AS or IBD symptoms. Classical features of idiopathic AS, such as early occurrence of rheumatological symptoms, peripheral arthritis, and a family history of AS, occurred in about one-third of the 50 cases. Their rheumatological disease often started many years before IBD symptoms developed. Alternatively, a smaller group of patients—about one-quarter—had predominantly IBD symptoms, with intestinal fistulae, recurrent disease attacks, and multiple operations. In these patients, classical AS features were less impressive. Finally, we found a large group of AS-IBD patients with simultaneous occurrence of rheumatological or intestinal symptoms, often with characteristics less pronounced than in either of the 2 groups.

Even after applying rigid criteria for the diagnosis of AS and IBD it appears that our patient material was heterogeneous. We seriously wonder whether we should continue to consider AS in patients with IBD as identical with idiopathic AS. Perhaps the clinical diagnosis of AS in IBD patients should be called a 'syndrome of AS', consisting of patients with classical idiopathic AS, as well as patients with

'secondary AS'. The inflammatory intestinal process of the latter group could be responsible for the changes in metabolism and structure of the SI joints, either by immunological factors (immune complexes?) or by antigenic substances transported by the lymphatics. Severe intestinal pathology was indeed present in the 9 CD patients with early occurrence of their IBD symptoms. Their sacroiliitis could be considered 'secondary AS'.

Morris *et al.* (1974), Nagant de Deuxchaisnes *et al.* (1974), and Brewerton and James (1975) have shown that the frequency of the antigen HLA B27 in AS-IBD patients is markedly lower than in patients with idiopathic AS. Our results confirm this, again suggesting that the close association between idiopathic AS and HLA B27 does not hold true for 'the syndrome of AS' in AS-IBD patients. Moreover, all 9 CD-AS patients in our study, considered to have a 'secondary AS' due to severe and protracted intestinal inflammation, were HLA B27 negative. The absence of HLA B27 not only in IBD patients with AS but also in patients with an asymptomatic sacroiliitis has been reported by Hyla *et al.* (1976) and by us (Dekker-Saeys *et al.*, 1978). Finally, the detection of a partial remission of sacroiliitis abnormalities in 4 patients seems to be in contrast with the well-known stationary or progressive nature of sacroiliac and spinal features in idiopathic AS.

Although we feel that the 'syndrome of AS' in IBD patients could indeed harbour both classical idiopathic AS and 'secondary' forms, it remains a hypothesis only, needing further elucidation. We could not classify the large number of patients in this study in either of these 2 groups. In addition, the presence of the antigen HLA B27 is not an absolute prerequisite for the development of AS: it may be that some of our HLA B27 negative CD cases had an HLA B27 independent AS predisposing gene (AS 2 gene), as suggested by van der Linden *et al.* (1975) and De Bruyère and Nagant de Deuxchaisnes (1976). It is therefore evident that additional genetic data should be sought in order to differentiate the groups. Moreover, careful longitudinal clinical and radiological follow-up studies, correlating symptoms of AS with periods of activity and quiescence of the IBD, need to be done. Detailed studies of the early histological and immunological abnormalities of the SI joints will ultimately be necessary to unravel the basic abnormalities in IBD-AS patients. Finally, clinical examination should concentrate on detecting IBD in AS patients and vice versa. Early recognition of AS and IBD might improve the prognosis and final outcome through a more timely and appropriate physiotherapeutic, anti-inflammatory, or even immunosuppressive therapy.

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