A family study of ulcerative colitis

With particular reference to ankylosing spondylitis and sacroiliitis

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Numerous studies have demonstrated that there is an association between ankylosing spondylitis and ulcerative colitis (Steinberg and Storey, 1957; Wilkinson and Bywaters, 1958; Fernandez-Herlihy, 1959; Zvaifler and Martel, 1960; Acheson, 1960; McBride, King, Baikie, Crean, and Sircus, 1963; Wright and Watkinson, 1965; Jayson, Salmon, and Harrison, 1970). The prevalence of these diseases in combination appears to be at least ten and perhaps fifty times greater than would be expected if the association was by chance, on the basis of estimates of prevalence in normal populations (Kellgren, 1964; Evans and Acheson, 1965; Ansell and Lawrence, 1966).

Familial aggregation in ankylosing spondylitis has been conclusively demonstrated (Kellgren, 1964; Emery and Lawrence, 1967) and it is believed that this has a genetic basis. The data with respect to ulcerative colitis are rather less satisfactory, but several studies have demonstrated familial aggregation which may be at least partially due to genetic factors (Kirsner and Spenser, 1963; Morris, 1965; McConnell, 1966).

In view of the evidence for a genetic basis in the aetiology of both ankylosing spondylitis and ulcerative colitis, it seemed possible that the association between these two diseases could itself be due to genetic factors. If this were so one would expect to find an unduly high prevalence of one of these diseases in the families of patients with the other disease. We have explored this possibility by conducting a survey to determine the prevalence of ankylosing spondylitis and sacroiliitis in the families of probands with ulcerative colitis.

Material and methods

The probands were drawn from patients attending the Colitis Clinic at Leeds. All the patients fulfilled our

diagnostic criteria for ulcerative colitis, which were essentially clinical, comprising a compatible history with unequivocally positive findings on sigmoidoscopy and/or barium enema. In those cases which had been treated surgically, histological confirmation was obtained. The probands were categorized according to the type and extent of disease in a similar fashion to that by Bockus and co-workers (Bockus, Roth, Buchman, Kalser, Staub, Finkelstein, and Valdes-Dapena, 1956).

The probands were selected on the basis of residence within 20 miles of Leeds and a willingness to cooperate in the survey. No account was taken of severity of the disease apart from the exclusion of cases of mild proctitis. The population surveyed comprised the probands, their spouses, all first-degree relatives, and certain second-degree relatives, namely parents' siblings. Those under 18 years of age were excluded.

All those who resided within 20 miles of Leeds were examined clinically. They answered a questionnaire, underwent a clinical examination which included an assessment of motion of the lumbar spine (Macrae and Wright, 1969), measurement of chest expansion, and examination of any joints currently or previously symptomatic, and had radiographs of the pelvis (anteroposterior), lateral lumbar spine, hands, and feet. Relatives residing in the British Isles outside this area were requested to attend their local hospital for x ray and were not seen personally.

91 probands, 236 blood relatives, and 56 spouses were surveyed. This represented a completion rate of 66 per cent. for the blood relations including the geographically distant relatives, 73 per cent. for all the relatives and probands, and 75 per cent. for the survey population as a whole including the spouses. The criteria for the diagnosis of ankylosing spondylitis proposed at the New York Conference in 1966 (Bennett and Burch, 1967) were applied to the survey population. The first criterion, a history of the presence of pain in the dorso-lumbar spinal back, was assessed by the response to a detailed questionnaire in which an effort was made to exclude trivial back symptoms.

The second criterion, limitation of motion of the lumbar spine in three planes, was assessed by measurement of forward flexion of the lumbar spine by an objective method (Macrae and Wright, 1969). Those subjects whose range of motion after correction for age and sex fell less

than 2 S.D. below the mean were deemed to have fulfilled this criterion. Chest expansion was measured conventionally.

Considerable care was taken in the grading of films for sacroiliitis (Macrae, Haslock and Wright, 1971). In brief, the films were read independently by two observers, each jointly being graded for erosion, sclerosis, ankylosis, and joint width. Joint width in our experience proved to be an unsatisfactory criterion of abnormality and was not taken into account. Partial ankylosis was considered significant only in the presence of other unequivocal evidence of sacroiliitis. As controls, intravenous pyelography films matched for age and sex were used. The films were selected only on the basis of an absence of gross renal disease. The data were transferred to IBM 80 hole punch cards for analysis.

Results

Ankylosing spondylitis was present in 20 per cent. of male probands and 7.7 per cent. of female probands, 5.1 per cent. of male relatives, and 2.6 per cent. of female relatives. There was no case of ankylosing spondylitis among the spouses of either sex (Table I).

Table I *Prevalence of definite ankylosing spondylitis in the survey population (excluding subjects with non-readable films)*

Series	Sex	Number of cases	Definite ankylosing spondylitis	
			No.	Per cent.
Probands	Male	35	7	20
	Female	52	4	7.7
	Total	87	11	12.6
Relatives	Male	78	4	5.1
	Female	115	3	2.6
	Total	193	7	3.6
Spouses	Total	54	0	0

Table II *Percentage distribution of x-ray grading for sacroiliitis*

X-ray grade for sacroiliitis	Probands		First-degree relatives		Second-degree relatives		Spouses		Controls	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0, 1, and 2 unilateral	71.4	86.3	90.5	93.1	90.9	97.1	96.4	92.3	93.9	95.4
2 Bilateral	2.9	5.9	1.4	3.9	4.6	0.0	3.6	7.7	4.3	3.9
3 Unilateral	2.9	0.0	1.4	1.0	0.0	0.0	0.0	0.0	1.7	0.0
3 Bilateral	17.1	5.9	4.1	2.0	4.6	2.9	0.0	0.0	0.0	0.7
4 Bilateral	5.7	2.0	2.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of x rays	35	51	74	102	22	34	28	26	115	153

The prevalence of sacroiliitis in the probands and relatives was likewise far in excess of the prevalence in spouses and in the control group (Table II).

Male predominance was found in respect of both ankylosing spondylitis and sacroiliitis.

The prevalence of ankylosing spondylitis in the relatives of probands who themselves had ankylosing spondylitis was compared with the prevalence of ankylosing spondylitis in the relatives of probands who did not have ankylosing spondylitis. An increased prevalence in the relatives of probands with ankylosing spondylitis was found to be 2.8 per cent. (Table III).

Table III *Prevalence of ankylosing spondylitis in relatives of probands with and without ankylosing spondylitis*

No. of probands	No. of relatives	Relatives with AS	
		No.	Per cent.
With AS	11	2	10.5
Without AS	78	5	2.8

The prevalence of sacroiliitis (Grade 2 bilateral, Grade 3, and Grade 4) in relatives of probands with and without sacroiliitis was similarly compared and found to be approximately the same (Table IV).

Table IV *Prevalence of sacroiliitis (Grade 2 bilateral, Grade 3, and Grade 4) in relatives of probands with and without sacroiliitis*

No. of probands	No. of relatives	Relatives with SI	
		No.	Per cent.
With SI	17	3	8.3
Without SI	74	14	8.7

An analysis was carried out to determine whether the clinical course or the extent of disease with respect to ulcerative colitis in the probands affected the prevalence of sacroiliitis in their relatives.

Table V shows an increased prevalence of sacroiliitis in the relatives of probands with more severe ulcerative colitis which pursued an acute or chronic course compared with the relatives of probands who were classified as having proctocolitis. There was likewise an increased prevalence of sacroiliitis in the relatives of probands who had ulcerative colitis involving the entire colon compared with relatives of probands with distal involvement only (Table VI).

Table V *Prevalence of sacroiliitis (Grade 2 bilateral, Grade 3, and Grade 4) in relatives of probands with differing clinical course of ulcerative colitis*

<i>No. of probands</i>	<i>No. of relatives</i>	<i>Relatives with SI</i>	
		<i>No.</i>	<i>Per cent.</i>
With acute or chronic ulcerative colitis	59 152	10	1
With proctocolitis	32 84	10.5	1.2

Table VI *Prevalence of sacroiliitis (Grade 2 bilateral, Grade 3, and Grade 4) in relatives of probands with differing extent of involvement of colon with ulcerative colitis*

<i>No. of probands</i>	<i>No. of relatives</i>	<i>Relatives with SI</i>	
		<i>No.</i>	<i>Per cent.</i>
With entire involvement of colon	27 65	8	8
With distal or rectal involvement only	62 169	12.3	4.7

Ulcerative colitis was found in two of 197 relatives and these had a prevalence of 1 per cent.

Discussion

The aetiology of ulcerative colitis is in dispute and a number of hypotheses have been proposed. These include infection, auto-immunity, psychological factors, and heredity. Infection, although a feature of established disease, has not been shown to have an aetiological role (Bacon, 1959). Abnormal immunological reactions have been amply demonstrated (Harrison, 1967), but it is not known whether they are related to the cause of the disease or are merely secondary phenomena. The evidence for preceding emotional disturbance is wholly unconvincing (Feldman, Cantor, Soll, and Bachrach, 1967). There are many technical difficulties associated with the

epidemiological investigation of ulcerative colitis, and although familial aggregation has been suggested by reports of multiple cases in families and attempts at systematic family studies, the quality of the data is suspect and no estimate of the contributions of heredity and environment can be made (Kirsner and Spenser, 1963; Almy and Sherlock, 1966).

As far as ankylosing spondylitis is concerned, the main aetiological suggestions have been pelvic infection and heredity. There is evidence for an association between non-specific genitourinary infection and ankylosing spondylitis (Romanus, 1953; Mason, Murray, Oates, and Young, 1958; Oates, 1959). It has not been proved however that the association is aetiological. The evidence of a temporal relationship is crucial but unconvincing; it has not been shown that infection is a necessary antecedent to the development of ankylosing spondylitis, nor is pelvic infection frequently followed by the disease (Wright, Catterall, and Cook, 1965; Julkunen, Pietila, and Elo, 1966). Moreover the peripheral manifestations are not readily explained by this theory.

Evidence from inspection of family pedigrees, concordance in monozygotic twins, and surveys of families of probands with ankylosing spondylitis strongly suggests that ankylosing spondylitis is hereditary (Kellgren, 1964; Emery and Lawrence, 1967). Emery and Lawrence (1967) found familial aggregation of sacroiliitis as well as ankylosing spondylitis, and in the more extensive data on sacroiliitis they suggested a multifactorial pattern of inheritance and offered a more satisfactory explanation of their findings than the previously held theory of an autosomal dominant mode of inheritance.

In this survey it has been found that both clinical ankylosing spondylitis and radiographic sacroiliitis are more prevalent in the relatives of probands with ulcerative colitis than would be expected in a normal population. Population surveys of ankylosing spondylitis have yielded prevalences of between 0.1 and 0.2 per cent. (Kellgren, 1964), and this is to be compared with the prevalence of 3.6 per cent. found in the relatives. The methodology of this survey differs from that used in previous surveys and may have yielded a higher prevalence than would have been found had the same methods as used in previous surveys been employed. This is suggested by the fact that the prevalence of ankylosing spondylitis in the probands in this survey was 12.6 per cent. compared with prevalences of between 2.0 and 6.4 per cent. reported in other series of patients with ulcerative colitis. Despite this, and in view of the zero prevalence in the spouses together with the 20-fold increases compared with prevalences reported in normal populations, it seems unlikely that dissimilar epidemiological technique and diagnostic criteria could account for the observed occurrence of ankylosing spondylitis in these relatives.

With regard to sacroiliitis, there was a significantly increased prevalence among the relatives compared with a matched control series. The prevalence in the spouses did not differ significantly from that in the controls.

Although numbers were small it was of interest to find that the relatives of probands with ankylosing spondylitis were themselves more likely to have ankylosing spondylitis than relatives whose probands did not have ankylosing spondylitis. With sacroiliitis no such association was found. There was, however, a positive association between more severe ulcerative colitis (in terms of both clinical course and extent of disease) in the probands and sacroiliitis in their relatives. It may be noted that there is also a positive association between more severe ulcerative colitis and the prevalence of sacroiliitis in patients with ulcerative colitis (Wright and Watkinson, 1965). It is tempting to speculate that these findings may be accounted for by a greater concentration of genetic material predisposing to both colitis and ankylosing spondylitis/sacroiliitis in some families compared with others, though the data do not allow for environmental factors to be considered.

The occurrence of two cases of ulcerative colitis among the relatives, giving a prevalence of 1 per cent., is greater than the estimates of prevalence in normal populations (Evans and Acheson, 1965).

In seeking an explanation of an association between ankylosing spondylitis and ulcerative colitis, it is possible that one disease causes the other. Despite difficulties in dating the onset of either disease, this seems unlikely since either disease may antedate the other by many years (Wright and Watkinson, 1965). Certainly the findings in this survey would be difficult to explain on this basis. An alternative explanation is that there is a common aetiology. Pelvic infection and heredity are not mutually exclusive suggestions, but the evidence for hereditary factors is more compelling. Results of this survey

would be in keeping with the hypothesis that the association between ulcerative colitis and ankylosing spondylitis has a genetic basis.

Summary

A series of 91 probands aged 18 years or more with ulcerative colitis, who lived within a 20-mile radius of Leeds was studied, and 236 blood relatives and 56 spouses of this colitic group were also studied by clinical examination, and antero-posterior radiographs of the pelvis, lateral lumbar spine, hands, and feet. Control pelvic films were taken from intravenous pyelograms.

Among the probands, ankylosing spondylitis was found in 20 per cent. of the men and 7.7 per cent. of the women. Among the relatives 5.1 per cent. of the men and 2.6 per cent. of the women had spondylitis, but no cases were found in the spouses. Similarly, sacroiliitis was found more commonly among probands and relatives than in the control films, the male predominance being maintained. Sacroiliitis occurred more frequently among probands with severe colitis than in probands with proctocolitis.

More ankylosing spondylitis (10.5 per cent.) was found in relatives of probands with spondylitis, but the incidence (2.8 per cent.) in the relatives of those without spondylitis was still higher than that in the general population. The incidence of sacroiliitis did not show a similar differentiation, although it did occur more frequently (12.5 per cent.) in the relatives of probands with colitis involving the whole colon than of those with only the distal part affected (4.7 per cent.). Ulcerative colitis was found in 1 per cent. of relatives.

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