Why do patients with ulcerative colitis relapse?

S A Riley, V Mani, M J Goodman, S Lucas

Abstract

To determine the factors responsible for ulcerative colitis relapse a cohort of 92 patients (18 to 78 years, 50 men) with clinically inactive disease have been followed for over 48 weeks. At 12 weekly intervals patients were asked, by means of standardised questionnaires, about infections, compliance with maintenance medication, new drug treatment, dietary changes, episodes of non-bloody diarrhoea, life stresses, and feelings of anxiety and depression. Thirty five patients (38%) relapsed (median interval 17 weeks, range three to 46 weeks). Patients who relapsed had a higher previous relapse rate than non-relapsers ($p<0.001$) and a shorter time from previous relapse to trial entry ($p<0.05$). Other clinical characteristics were equally matched in the two groups. Between and within group comparisons revealed that upper respiratory tract symptoms, antibiotic ingestion, analgesic intake, diarrhoeal episodes and stressful life events were no more common in the four weeks before relapse than before routine attendance. Anxiety and depression ratings were also similar in the two groups. The timing of ulcerative colitis relapse showed a clear seasonal pattern with 26 patients relapsing from August to January and only nine from January to July ($p<0.001$). In addition, a retrospective case note analysis revealed significant seasonality of onset of ulcerative colitis. We conclude that seasonal factors may contribute to both onset and relapse of ulcerative colitis.

Most patients with chronic ulcerative colitis run a relapsing course. The reasons why such relapses occur, however, remain unknown. Emotional stress,^{1,2} upper respiratory tract infection,³ drug ingestion,^{4,5} and diarrhoeal episodes⁶ have all been implicated. It has also been suggested that colitis relapse may follow a seasonal pattern.^{7,8} Unfortunately, much of the data are uncontrolled, retrospective, and conflicting.

We have therefore followed a cohort of patients with quiescent colitis in order to study: (a) the clinical features that may predict relapse; (b) the events preceding relapse; and (c) the timing of ulcerative colitis relapse. We have also undertaken a retrospective case note analysis to assess the timing of onset of first attack of ulcerative colitis.

Methods

PROSPECTIVE COHORT STUDY

The study population comprised adult out-patients with chronic ulcerative colitis diagnosed on the basis of clinical history and previous

sigmoidoscopic and histological findings. All patients were taking maintenance sulphasalazine (2 to 4 g daily) or delayed release mesalazine (800 mg to 1600 mg daily) treatment. No patient had received either oral or rectal steroids within one month of study entry and all were in clinical remission as judged by the absence of blood in the stool and the macroscopic appearance of either normal mucosa or erythema only on sigmoidoscopy.

On entry to the study a clinical history was taken and physical examination and rigid sigmoidoscopy performed. Patients were then asked to complete three standardised questionnaires. The first enquired about events that had occurred in the four weeks before attendance. Specific note was made of the symptoms of upper respiratory tract infection, compliance with maintenance medication, new drug treatment, dietary changes and episodes of non-bloody diarrhoea. Patients were also given the opportunity to cite other events they felt relevant in the four weeks before attendance. A Hospital Anxiety and Depression (HAD) scale was next completed. This patient rated scale comprises 14 questions which grade the symptoms of anxiety and depression (Table I). Responses to each question are graded 0 to 3 and patients scoring more than 8 (maximum 21) on either subscale may be regarded as suffering from anxiety or depression.⁹ Finally, patients completed a modification of the Paykel Life Events scale¹⁰ which lists 56 commonly encountered life stresses (Table II). Patients were asked to indicate and date events that had occurred since their previous outpatient attendance.

During the trial period each patient kept a daily symptom diary. Patients were reassessed at 12, 24, 36, and 48 weeks or at any other time should they wish. The questionnaires were completed at each clinic attendance. Unused tablets were returned to assess drug compliance.

Patients were followed to either relapse or completion at 48 weeks. Throughout the study patients were asked to report promptly with symptomatic deterioration. Sigmoidoscopy was then undertaken and relapse confirmed by

TABLE I The hospital anxiety and depression (HAD) scale

Anxiety subscale	Depression subscale
I feel tense or 'wound up'	I still enjoy the things I used to enjoy
I get a sort of frightened feeling as if something awful is about to happen	I can laugh and see the funny side of things
Worrying thoughts go through my mind	I feel cheerful
I can sit at ease and feel cheerful	I feel as if I am slowed down
I get a sort of frightened feeling like 'butterflies' in the stomach	I have lost interest in my appearance
I feel restless as if I have to be on the move	I look forward with enjoyment to things
I get sudden feelings of panic	I can enjoy a good book or radio or TV programme

Department of Medicine,
Hope Hospital, Salford
S A Riley

Leigh Infirmary
V Mani

Bury General Hospital
M J Goodman

Department of Medical
Computing, University of
Manchester, Manchester
S Lucas

Correspondence to: Dr S A
Riley, Department of
Medicine, Clinical Sciences
Building, Hope Hospital,
Eccles Old Road, Salford
M6 8HD.

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TABLE II The Modified Paykel Life Events Scale

Event	Grade (median and range)	
	Non-relapsers	Relapsers
Bereavement and loss		
Death of child	20 (18–20)	20 (18–20)
Death of spouse	20 (18–20)	20 (17–20)
Death of close family member	19 (12–20)	20 (15–20)
Death of close friend	15 (10–20)	14 (7–20)
Separation from close friend/relative	10 (5–17)	10 (7–15)
Loss of valuable item	10 (5–15)	12 (10–19)
Marital and family difficulties		
Divorce	20 (15–20)	20 (12–20)
Marital separation	19 (15–20)	18 (14–20)
Break engagement	12 (10–20)	16 (12–20)
Finish with steady date	15 (4–20)	10 (2–20)
Marriage	11 (4–24)	9 (0–17)
Engagement	2 (0–16)	3 (0–15)
Marital reunion	10 (2–15)	10 (0–16)
Wife becomes pregnant (for man)	8 (5–15)	9 (2–17)
Wanted pregnancy	4 (0–12)	2 (0–10)
Unwanted pregnancy	12 (6–20)	15 (8–20)
Miscarriage	20 (15–20)	18 (12–20)
Birth of child	10 (4–20)	12 (2–20)
Arguments with spouse	14 (7–20)	10 (5–20)
Arguments with financee/steady date	14 (5–17)	8 (0–14)
Partner unfaithful	20 (15–20)	20 (12–20)
Start extramarital affair	16 (10–20)	15 (5–20)
Child marries with approval	2 (0–10)	5 (0–10)
Child marries against wishes	14 (10–20)	18 (6–20)
Child becomes engaged	2 (0–10)	5 (0–10)
Child leaves home (eg college)	10 (4–15)	10 (6–18)
Arguments with close relatives	12 (4–18)	10 (3–20)
Arguments with in-laws	10 (2–15)	14 (2–17)
New person in house	10 (2–20)	10 (0–20)
Financial problems		
Heavy debt/bankruptcy	20 (15–20)	20 (7–20)
Large loan taken	15 (10–20)	15 (4–20)
Minor difficulties	12 (5–15)	14 (8–17)
Occupational/educational problems		
Fired	20 (15–20)	20 (14–20)
Demoted	16 (12–20)	14 (5–20)
Promoted	5 (2–14)	10 (0–18)
Business failure	12 (7–20)	17 (10–20)
Unemployed/redundancy	16 (10–20)	14 (5–20)
Argument with boss	12 (7–20)	10 (3–20)
Changed job conditions	10 (5–15)	8 (2–19)
Changed work hours	10 (2–15)	7 (0–20)
Changed type of work	10 (2–15)	10 (5–18)
Important exam taken	10 (5–20)	16 (10–20)
Important exam failed	14 (10–20)	15 (10–20)
Start new course	5 (0–10)	7 (0–13)
Stop full-time education	5 (0–10)	8 (0–16)
Retirement	8 (0–20)	10 (0–18)
Legal difficulties		
Jail sentence	20 (17–20)	20 (15–20)
Court appearance	15 (12–20)	20 (14–20)
Minor offence	15 (10–20)	12 (5–20)
Medical problems		
Major illness (hospitalisation)	15 (10–20)	15 (9–20)
Minor illness	5 (0–12)	5 (2–16)
Family member seriously ill	15 (8–20)	18 (13–20)
Situation change		
Move to another country	15 (5–20)	16 (0–20)
Move to another town	10 (2–20)	10 (4–20)
Move within same town	8 (2–15)	10 (2–17)
Change schools	10 (2–15)	10 (2–18)

The 56 life stresses comprising the Modified Paykel Scale. Patients were asked to report these events at 12 weekly intervals throughout the study. In addition, on completion of the study, relapsers and non-relapsers were asked to grade all events (0 to 20). Results (median and range) show that relapsers grade life events no more stressful than non-relapsers.

TABLE III The clinical characteristics of relapsers and non-relapsers

	Non-relapsers (n=57)	Relapsers (n=35)
Age (yr, median and range)	44 (22–78)	30 (20–78)
Sex (M:F)	32:25	18:17
Disease duration (yr, median and range)	8 (0.5–4.5)	4 (0.75–25)
Disease extent:		
Proctitis or proctosigmoiditis	32	18
Left sided	11	12
Total	14	5
Maintenance treatment:		
Sulphasalazine	27	17
Oral 5-ASA	30	18
Previous relapse frequency > × 1/year (%)	33 (56%)	p<0.001 34 (97%)
Months from previous relapse to trial entry	12 (2–72)	p<0.01 7 (1–37)

TABLE IV Frequency of events before relapse or routine attendance

	Relapsers (n=35)		
	Non-relapsers (n=57)	Attending in remission	Attending in relapse
Upper respiratory tract symptoms	33%	31%	23%
Stressful events	18%	22%	20%
Analgesic intake	18%	27%	20%
Antibiotic ingestion	8%	6%	3%
Non-bloody diarrhoea	4%	8%	3%

Frequency of events (%) in the four weeks before relapse or prior to routine attendance. Data for relapsers are shown at times of disease relapse and also at times of routine attendance while patients were still in remission.

worsening of the macroscopic appearance of the rectal mucosa. The patients symptom diary was used to corroborate the date of onset of symptoms of relapse. Each patient submitted a stool sample to exclude bacterial or amoebic infection and the three questionnaires were again completed.

In order to assess whether patients who relapsed found life events generally more stressful than those who stayed in remission, all patients were asked to grade (0 to 20) the 56 events that comprise the modified Paykel scale after completion of the study.

CASE NOTE ANALYSIS

The case notes of patients with a diagnostic label of ulcerative colitis attending Leigh Infirmary were analysed. Where the diagnosis could be confirmed the date of onset of symptoms of first attack of ulcerative colitis was noted provided that this could be localised to a specific month of the year. Patients who had not undergone sigmoidoscopic confirmation of colitis during the first attack were excluded from the study.

STATISTICAL ANALYSIS

Results are expressed as median (range) unless otherwise stated. Continuous data were analysed using Wilcoxon's matched pairs test to assess within patient differences and the Mann-Whitney U test to assess between patient differences. Enumeration data were analysed using the χ^2 test, Fisher's exact test or McNemar's test as appropriate. Seasonal data were analysed by Hartley's method of harmonic analysis.¹¹ As patients entered and left the study over a 30 month period the data were standardised before harmonic analysis to compensate for the month to month variation in patients at risk of relapse throughout the study period.

Results

PROSPECTIVE COHORT STUDY

One hundred patients were enrolled into the study, 51 men and 49 women, ages ranged from 20 to 78 years. Eight patients were withdrawn, 35 relapsed (median interval 17 weeks, range three to 46 weeks), and 57 patients remained in remission for the 48 week study period. All 35 patients who relapsed had a negative stool culture.

The group who stayed in remission and those who relapsed were comparable for age, sex, maintenance drug treatment, drug compliance, disease duration, and disease extent. Only two clinical features separated the two groups: previous relapse frequency, which was significantly higher in the group who relapsed ($p<0.001$), and time from previous relapse to trial entry, which was significantly shorter in the group who relapsed ($p<0.01$) (Table III).

All 35 patients who relapsed during the course of the study completed the three questionnaires at the time of relapse. In addition, these patients attended on a further 51 occasions whilst still in remission, before relapse, providing data for within group comparison. The 57 patients who stayed in remission throughout provide data for between group comparison.

Table IV shows the frequency of events reported in the four weeks before routine attendance or before relapse. Relapsers and non-relapsers show no significant differences in the reporting of upper respiratory tract symptoms, analgesic or antibiotic ingestion, stressful life events or non-bloody diarrhoeal episodes. Moreover, the frequency of such events is similar in the patients who relapse both at times of relapse and at times of routine attendance before subsequent relapse.

Compliance with maintenance medication was remarkably good throughout the study with 43% of patients being totally compliant. In none of the other patients did compliance fall below 95% of the prescribed dose. Too few patients took non-steroidal anti-inflammatory drugs or underwent major dietary changes to allow meaningful analysis.

Anxiety and depression ratings throughout the study were similar in relapsers and non-relapsers, as were the number of patients in each group, with scores in excess of 8 points (Table V). The patients themselves were unable to suggest consistent associations with disease relapse but many felt that stress was a major contributor. After completion of the study patients graded the 56 life stresses of the Paykel Life Events form. Although a remarkably wide range of grading was apparent relapsers and non-relapsers did not significantly differ (Table II).

The timing of ulcerative colitis relapse was determined by the date of onset of clinical deterioration. This was corroborated using the patients' symptom diary and in all cases relapse was confirmed by sigmoidoscopy. The timing of

TABLE V Hospital Anxiety and Depression (HAD) scale ratings

	Non-relapsers		Relapsers	
	Entry	Completion	Entry	Relapse
Anxiety				
Total score median (range)	6 (1-17)	7 (0-16)	7 (0-16)	5 (2-18)
Score >8	25%	30%	23%	29%
Depression				
Total score median (range)	2 (0-15)	3 (0-16)	2 (0-10)	3 (0-14)
Score >8	9%	11%	9%	17%

Anxiety and depression subscale ratings in non-relapsers and relapsers throughout the study. Patients scoring more than 8 on either subscale may be regarded as suffering from anxiety or depression.

Figure 1: The monthly variation of ulcerative colitis relapse (35 relapses in 92 patients). The solid line depicts the predicted model, from the data, of harmonic variation at a fundamental frequency of one year.

relapse (Fig 1) shows a clear seasonal pattern with 26 relapses occurring from August to January and only nine relapses from February to July ($p<0.001$). The peak incidence of relapse occurred in September and October.

Upper respiratory tract symptoms also showed a seasonal distribution (Fig 2). Eighty of the 117 episodes being reported from September to February and only 37 from March to August ($p<0.05$). The peak incidence of symptoms, however, occurred in January, some three months after the peak of colitis relapse.

CASE NOTE ANALYSIS

One hundred and fifty nine case notes were

Figure 2: The monthly variation of upper respiratory tract symptoms (117 episodes reported by 92 patients). The solid line depicts the predicted model of harmonic variation at a fundamental frequency of one year.

Figure 3: The monthly frequency of onset of ulcerative colitis. Data from 92 case notes in which the month of onset of symptoms of first attack of colitis could be precisely determined. The solid line depicts the predicted model of harmonic variation at a fundamental frequency of one year.

retrieved for analysis. On review, eight patients had probable Crohn's disease and seven had had only one attack of disease. In 92 it was possible to date the onset of symptoms of first attack of colitis to a specific month. Harmonic analysis again revealed a significant seasonal variation at the fundamental frequency of one year ($p < 0.05$) (Fig 3).

Discussion

Study of the factors that may induce ulcerative colitis relapse are surprisingly few. Early workers suggested that colitis was a psychosomatic disease^{12,13} and many have noted the high prevalence of psychopathology.^{14,15} Several groups have shown, however, that psychiatric diagnoses are no more common in ulcerative colitis than in control populations.¹⁶⁻¹⁸ Despite anecdotal reports of stress induced relapse longitudinal studies of life stresses and ulcerative colitis activity had not been studied previously.

Upper respiratory tract infections have also been implicated in disease relapse. In one of the few quantitative studies undertaken, Mee and Jewell³ found that a history of upper respiratory tract infection was twice as common in the four weeks before relapse than before routine attendance. In a similar study, however, Rampton *et al*⁴ were unable to confirm this association, finding instead a history of increased analgesic intake before relapse. Several well documented cases of relapse associated with non-steroidal anti-inflammatory drug ingestion have also been reported.^{5,19}

Antibiotics may also lead to recrudescence of colitis activity. This may be related to the development of antibiotic diarrhoea,⁶ to clostridium difficile infection,²⁰ or perhaps to alterations in sulphasalazine bacterial metabolism.²² Finally, a number of bacterial enteric infections have been implicated in disease exacerbation.²²⁻²⁴

In order to study events that may precipitate ulcerative colitis relapse we have followed a

cohort of patients in established remission. This has clear advantages over previous studies as it allows both within and between group comparisons. All studies that rely on the patients' history, however, will be biased towards finding a positive association between colitis relapse and external events as rumination, by both patient and doctor, is common and likely to be more marked at times of relapse. Despite this bias we could find no evidence that upper respiratory tract infection, drug ingestion, dietary changes or diarrhoeal episodes predispose to colitis relapse. The frequency and severity of life stresses were also equally matched before relapse and in remission. Furthermore, there was no evidence that the patients who relapsed found life events more stressful than those who stayed in remission. Anxiety and depression ratings were also similar in the two groups and did not correlate with disease activity.

Of the clinical features of disease studied, previous relapse frequency showed the closest correlation with risk of relapse. Allied to this, active disease in the recent past increased the likelihood of relapse within the study period.

Seasonality of ulcerative colitis relapse was first suggested by Myszor and Calam⁷ who in a small retrospective postal survey found relapse more common from September to February. Don and Goldacre,²⁵ however, were unable to confirm this finding when assessing hospital admissions data but more recently Sellu⁸ has reported a similar pattern. In the present study seasonality was apparent with respect to both ulcerative colitis relapse and to symptomatic onset of disease. Although we could find no evidence of bacterial pathogens in the stools of patients at relapse it is possible that relapse may be related to an enteric pathogen, as yet unidentified. It is interesting to note that salmonella and campylobacter infection (both excluded by stool culture in the present study) and enterovirus infection show seasonal patterns of occurrence that peak in the late summer and autumn (N D Noah, PHLS, personal communication).

For most patients with ulcerative colitis there is no obvious trigger to disease relapse. The seasonal patterns described here suggest that longterm follow up with detailed microbiological surveillance would be worthwhile.

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