INFLAMMATORY BOWEL DISEASE

Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Örebro, Sweden, 1993–1998

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Background: Microscopic colitis, including collagenous colitis and lymphocytic colitis, mainly affects middle aged and older subjects, with a female predominance in collagenous colitis. The diseases have previously been regarded as rare. We present an epidemiological study of microscopic colitis in a well defined Swedish population.

Methods: Patients were retrospectively searched for in colonoscopy reports of those who had a colonoscopy in the period 1993–1998 for non-bloody diarrhoea. All colonic mucosal biopsies were reassessed using strict diagnostic criteria.

Results: Biopsies from 1018 patients were reassessed. Fifty one (45 female) collagenous colitis patients and 46 (31 female) lymphocytic colitis patients were diagnosed. Median age at diagnosis was 64 years in collagenous colitis and 59 years in lymphocytic colitis. The mean annual incidence of collagenous colitis was $4.9/10^5$ inhabitants (95% confidence interval (CI) $3.6–6.2/10^5$) and of lymphocytic colitis $4.4/10^5$ inhabitants (95% CI $3.1–5.7/10^5$). The annual incidence of collagenous colitis increased from $3.7/10^5$ in 1993–1995 to $6.1/10^5$ in 1996–1998 (difference $2.4/10^5$ (95% CI $-0.3–5.1/10^5$)) whereas the incidence of lymphocytic colitis increased from $3.1/10^5$ to $5.7/10^5$ (difference $2.6/10^5$ (95% CI $0.1–5.2/10^5$)).

Conclusions: The annual incidences of collagenous colitis and lymphocytic colitis are higher than considered previously and are now equal to the incidence of Crohn's disease in Sweden, and combined rates approach the incidence of ulcerative colitis. Microscopic colitis was diagnosed in 10% of all patients with non-bloody diarrhoea referred for colonoscopy and in almost 20% of those older than 70 years.

Collagenous colitis (CC) and lymphocytic colitis (LC) belong to the group of microscopic colitides (MC). CC was first described by Lindström in 1976[1] and LC by Lazenby *et al* in 1989.[2] Both diseases are characterised by chronic watery diarrhoea and a macroscopically normal or near normal colonic mucosa.[3–6] The diagnosis relies on microscopic assessment of colonic mucosal biopsies where characteristic features are found.[2]

The epidemiology of CC and LC has been poorly studied and only a few population based studies exist.[7–11] It is well known that CC affects mainly 60–70 year old women whereas the female predominance is less pronounced in LC.[10 11] In our previous epidemiological study of CC during 1984–1993, we reported a mean annual incidence of $1.8/10^5$ inhabitants.[7] Recently, higher incidence values have been reported from Iceland where the mean annual incidence of CC was $5.2/10^5$ inhabitants and of LC $4.0/10^5$ inhabitants in the period 1995–1999.[11] Here, we conducted an epidemiological study of MC (1993–1998) which follows our previous study of CC.[7]

METHODS

Catchment area

The area is of a mixed urban rural type, with limited migration. From 1993 to 1998, the population increased by 3.0% from 170 927 to 176 243 inhabitants. In this area there is one hospital, 17 primary health clinics, and a few private general practitioners. Colonoscopy is performed solely at our hospital where the only pathology department of the region is situated. All information on population and sex and age distributions was obtained from the Swedish Bureau of Statistics.

Patients

Patients were retrospectively searched for by scrutiny of all colonoscopy reports of patients living within the catchment area who had a colonoscopy in the period 1993–1998 for non-bloody diarrhoea and where the colonic mucosa was macroscopically normal or near normal. All colonic mucosal biopsy specimens were reassessed histopathologically. The year 1993 was included both in the present and previous study of CC, allowing comparison between the methods of case ascertainment in the two studies.

Diagnostic criteria

The diagnoses of CC and LC were based on both clinical and histopathological criteria. The clinical criterion was non-bloody diarrhoea of at least three weeks' duration. The histopathological criteria are detailed below.

Collagenous colitis

- A diffusely distributed and thickened subepithelial collagen layer ⩾10 μm.
- Epithelial damage such as flattening and detachment.
- Inflammation in the lamina propria with mainly mononuclear cells.
- Increased number of intraepithelial lymphocytes (IEL) may be present.

Abbreviations: CC, collagenous colitis; IEL, intraepithelial lymphocytes; LC, lymphocytic colitis; MC, microscopic colitis

Lymphocytic colitis

- IEL ⩾20 per 100 surface epithelial cells.
- Epithelial damage such as flattening and mucin depletion.
- Inflammation in the lamina propria with mainly mononuclear cells.
- A subepithelial collagen layer <10 μm.

A total colonoscopy with multiple mucosal biopsies from different parts of the colon was required for inclusion. Patients with stool examinations positive for ova, parasites, *Clostridium difficile* toxin, *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia* were excluded, as well as those with other obvious causes of diarrhoea, except for coeliac disease. The Marsh classification was used for histopathological assessment of coeliac disease.[12] Patients positive for human immunodeficiency virus were excluded.

Histopathology

The original colonic mucosal biopsy specimens, stained with haematoxylin-eosin, were used at reassessment. If the quality was insufficient for reassessment, new sections were made from the original paraffin wax embedded biopsy blocks. The thickness of the examined sections was 4 μm.

At the histopathological reassessment, cases with entirely normal biopsies were first identified and not subject to further analysis. In the remaining cases, the thickness of the subepithelial collagen layer and the number of IEL were quantified. Cases with CC were identified by measurement of the subepithelial collagen layer after van Gieson stain by an ocular micrometer in a representative and well orientated section of the mucosa where three adjacent crypts were cut in a vertical manner and extending all the way down to the muscularis mucosa. Cases with LC were identified by counting of IEL. The number of IEL per 100 epithelial cells was calculated by counting the number per 300 epithelial cells divided by three. Only the surface epithelium was examined, and areas overlying lymph follicles in the lamina propria were avoided. Counting was performed on at least two biopsies from different parts of the colon, one of which was from the proximal colon, and the mean number for each patient was recorded. Counting of IEL was performed in sections stained with haematoxylin-eosin. For lymphocyte confirmation, immunohistochemical examination with a polyclonal antibody against T lymphocytes (Dako rabbit anti-human T cell, CD3; Glostrup, Denmark) was performed.[13 14] The severity of epithelial cell damage and lamina propria inflammation were estimated. Occasional crypt abscesses, cryptitis, crypt distortions, or neutrophil leucocytes in the lamina propria were allowed.[2 14]

Clinical data

The medical notes of each patient were scrutinised for clinical data. The date of diagnosis was defined as the date of colonoscopy when biopsies led to a diagnosis of CC or LC. The date of onset of symptoms was defined as the year and month when the patient first experienced long lasting non-bloody diarrhoea. Duration of symptoms was the period between onset of symptoms and date of diagnosis.

Statistics

Data on thickness of the collagen layer, number of IEL, age, duration of symptoms, and number of bowel movements are presented as median (25–75 percentiles) and the Mann-Whitney U test was used to detect differences. Fisher's exact test was used to assess differences in the frequency of coeliac disease. Incidence calculations were based on the date of diagnosis. Incidence was calculated as crude and age adjusted to the 1995 Swedish population. The 95% confidence interval (CI) was calculated assuming that the observed cases of CC and LC followed a Poisson distribution.

Table 1 Patients excluded from the study (n = 921)

- Histopathological normal colonic mucosa (n = 846)
- Histopathological features of ulcerative colitis or Crohn's disease (n = 30)
- Lymphocytic colitis-like but IEL <20 per 100 surface epithelial cells (n = 34)
- Miscellaneous conditions (infectious colitis, carcinoid syndrome, ischaemic colitis) (n = 7)
- Diarrhoea of less than three weeks' duration (n = 4)

IEL, intraepithelial lymphocytes.

Ethics

The study was approved by the ethics committee of Örebro University Hospital.

RESULTS

Patients

During the study period, 1018 patients underwent colonoscopy and microscopic evaluation of colonic mucosal biopsies for non-bloody diarrhoea. We found 51 patients fulfilling the criteria of CC and 46 patients fulfilling the criteria of LC. Subjects excluded from the study are shown in table 1.

In 44 of 51 CC patients (86%) and in 25 of 46 LC patients (54%) the original histopathological diagnosis was correct. In six CC and 18 LC cases the colonic mucosa was considered abnormal at the original histopathological examination but the definite diagnosis was made first after reassessment of biopsies. In only four cases had the biopsies been considered entirely normal before re-evaluation (table 2). Eight other patients diagnosed primarily as LC did not fulfil the histopathological criteria for LC at reassessment.

Collagenous colitis

Between 1 January 1993 and 31 December 1998, CC was diagnosed in 51 patients. The number of CC cases in 1993 was the same as in our previous epidemiological study. Median thickness of the collagen layer was 20 (14–24) μm. Forty five of 51 patients were women, giving a female:male ratio of 7.5:1.

Median age at diagnosis was 64 (53–74) years; in women 64 (51–73) years and in men 71 (60–75) years. One patient could not recall the date of onset of symptoms. Median age at onset of symptoms in the other 50 patients was 60 (46–72) years. Mean annual incidence for the period 1993–1998 was $4.9/10^5$ inhabitants (95% CI 3.6–$6.2/10^5$); in women $8.4/10^5$ inhabitants (95% CI 5.9–$10.9/10^5$) and in men $1.2/10^5$ inhabitants (95% CI 0.2–$2.2/10^5$). During the study period, the annual incidence increased from $3.7/10^5$ inhabitants (95% CI 2.0–$5.4/10^5$) in the first three year period to $6.1/10^5$

Table 2 Original histopathological diagnosis in patients finally diagnosed with microscopic colitis

Histopathological diagnosis before reassessment	Histopathological diagnosis after reassessment	
	CC	LC
Normal mucosa (n = 4)	1	3
Non-specific colitis (n = 14)	2	12
Signs of LC but not diagnostic (n = 5)		5
Signs of CC but not diagnostic (n = 2)	2	
LC (n = 27)	2	25
CC (n = 45)	44	1
Total (n = 97)	51	46

CC, collagenous colitis; LC, lymphocytic colitis.

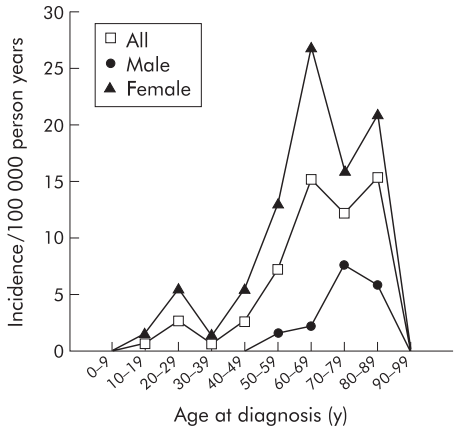

Figure 1 Age and sex specific annual incidences of collagenous colitis for the period 1993–1998.

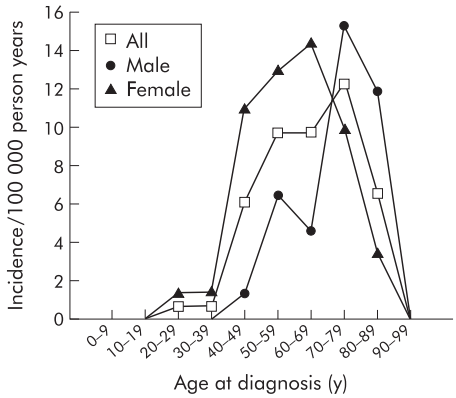

Figure 2 Age and sex specific annual incidences of lymphocytic colitis for the period 1993–1998.

inhabitants (95% CI 4.0–8.2/10^5) in the second period but the difference did not reach statistical significance (2.4/10^5 (95% CI −0.3–5.1/10^5)). All crude incidence rates were equal to age adjusted rates. Figure 1 shows analysis of the age and sex specific incidences. An incidence peak of 26.9/10^5 inhabitants (95% CI 12.3–41.5/10^5) in women aged 60–69 years was seen.

Median duration of symptoms was 13 (8–67) months. In the first 25 patients diagnosed during the study period, median duration of symptoms was 11 (6–68) months, and in the last 25 patients diagnosed during this period it was 20 (10–52) months ($p = 0.26$). The number of daily bowel movements at diagnosis was 7 (5–10) ($n = 47$).

Lymphocytic colitis

Between 1 January 1993 and 31 December 1998, LC was diagnosed in 46 patients. In sections stained with haematoxylin-eosin, the median number of IEL was 39 (34–48) per 100 surface epithelial cells. Immunohistochemical examination confirmed the presence of increased numbers of IEL in all patients. Thirty one of 46 patients were female, giving a female:male ratio of 2.1:1. Median age at diagnosis was 59 (50–72) years; in women 57 (48–67) years and in men 72 (52–78) years. Median age at onset of symptoms was 58 (48–72) years.

The mean annual incidence for the period 1993–1998 was 4.4/10^5 inhabitants (95% CI 3.1–5.7/10^5); in women 5.8/10^5 inhabitants (95% CI 3.8–7.8/10^5) and in men 3.0/10^5 inhabitants (95% CI 1.5–4.5/10^5). During the study period, the annual incidence increased from 3.1/10^5 inhabitants (95% CI 1.6–4.6/10^5) during the first three year period to 5.7/10^5 inhabitants (95% CI 3.7–7.7/10^5) during the second period. This difference was statistically significant (2.6/10^5 (95% CI 0.1–5.2/10^5)). All crude incidence rates were equal to age adjusted rates. Figure 2 shows analysis of the age and sex specific incidences.

Median duration of symptoms was 4 (2–7) months, which was significantly shorter than in CC ($p<0.01$). In the first 23 patients diagnosed during the study period, median duration of symptoms was 4 (2–8) months, and remained unchanged (4 (2–7) months) in the last 23 patients diagnosed during this period. The number of daily bowel movements at diagnosis was 8 (5–10) ($n = 41$), which was similar to CC patients ($p = 0.9$).

Annual colonoscopy rate

Table 3 shows the annual number of colonoscopies in total, the number of colonoscopies performed for non-bloody diarrhoea and the number of CC and LC cases diagnosed during the study period. The annual number of colonoscopies in patients with non-bloody diarrhoea in relation to the total number of colonoscopies was stable (14–18%). The proportion of MC patients in relation to the number of patients with non-bloody diarrhoea was 4% in 1993, 7% in 1994, and thereafter stable (10–12%). MC was diagnosed in 10% of all 1018 patients with non-bloody diarrhoea referred for colonoscopy. The diagnostic yield was higher in older patients, and MC was diagnosed in almost 20% of those older than 70 years (table 4).

Coeliac disease and MC

Forty two of 51 CC patients were investigated for coeliac disease, 38 by microscopic examination of duodenal mucosal biopsies and four by serological analysis of antiendomysial antibodies. Forty of 46 LC patients were investigated for coeliac disease, 34 by microscopic examination of duodenal mucosal biopsies and six by serological analysis of anti-

Table 3 Annual number of all colonoscopies, colonoscopies in diarrhoea patients, and number of diagnosed cases with collagenous colitis and lymphocytic colitis

Year	Total colonoscopies	Colonoscopies in diarrhoea patients*	CC cases diagnosed†	LC cases diagnosed†
1993	896	137 (15%)	4 (3%)	2 (1%)
1994	936	165 (18%)	4 (2%)	7 (4%)
1995	1294	175 (14%)	11 (6%)	7 (4%)
1996	1160	173 (15%)	10 (6%)	9 (5%)
1997	1168	170 (15%)	8 (5%)	11 (6%)
1998	1247	198 (16%)	13 (7%)	10 (5%)
Total	6701	1018 (15%)	51 (5%)	46 (5%)

CC, collagenous colitis; LC, lymphocytic colitis.
*Percentage of all colonoscopies.
†Percentage of patients with non-bloody diarrhoea.

Table 4 Number of patients with a diagnosis of microscopic colitis in relation to sex and age in 1018 patients with non-bloody diarrhoea who had a macroscopically normal or near normal colonoscopy

	Age at colonoscopy			
Sex	<50 y	50–69 y	⩾70 y	All ages
Female	19/327 (6%)	37/225 (17%)	19/114 (17%)	75/666 (11%)
Male	1/180 (0,6%)	8/115 (7%)	13/57 (23%)	22/352 (6%)
All	20/507 (4%)	45/340 (13%)	32/171 (19%)	97/1018 (10%)

endomysial antibodies. Seven of the investigated CC patients (17%) and three of the investigated LC patients (7.5%) had coeliac disease, all with different stages of villous atrophy—that is, Marsh type III. There was no significant difference in the frequency of coeliac disease between CC and LC ($p = 0.31$).

DISCUSSION

Only a few population based epidemiological studies have been performed in MC (table 5).[7–11] Our two studies represent the longest observation period reported to date in CC. The present data on sex and age at diagnosis are consistent with previous studies, in particular with regard to CC. A female:male ratio of 7.5:1 was found in CC which is within earlier reported ratios of 4:1–9:1.[7 9–11] In LC, the female:male ratio was 2.1:1 which is close to the reported ratio of 2.7:1 from Spain[10] but lower than the Icelandic ratio of 5.0:1.[11] Median age at diagnosis of 64 years in CC is consistent with earlier reported median ages of 64–68 years.[7 11] In LC, a median age at diagnosis of 59 years was lower than an earlier reported median age of 70 years.[11] Similar to previous studies, the duration of symptoms before diagnosis was shorter for LC patients compared with CC patients.[5 10] To assess if this was due to more severe disease in patients with LC, we compared the number of daily bowel movements at diagnosis but found no difference between LC and CC patients.

Our previously reported incidence of CC in 1984–1988 was $0.8/10^5$ inhabitants and $2.7/10^5$ inhabitants in 1989–1993. The present data for the period 1993–1995 showed an incidence of $3.7/10^5$ inhabitants, which increased non-significantly to $6.1/10^5$ inhabitants in 1996–1998. The long observation period rules out the fact that the high incidence is caused by a ''sweep of the area''. When this occurs, prevalent but undiagnosed patients become incident cases, which can result in a falsely high incidence. In such cases the incidence declines in the following years. This was not seen in our study.

The apparent rise in incidence is most likely an artefact secondary to increased awareness and better diagnosis, and cases of CC may previously have been unrecognised or erroneously diagnosed with irritable bowel syndrome. The increasing number of annual colonoscopies from 415 in 1984[7] to 1247 in 1998 favours such an interpretation. Furthermore, the proportion of CC cases diagnosed in patients with chronic diarrhoea was fairly stable, except for the first two years (table 3), and argues to some extent against a true rise in incidence. Unfortunately, we have no long term data on LC and cannot comment on a change in incidence. Our major message however is not whether or not the rise in incidence represents a true rise but rather that the diseases are more common than previously considered.

Table 5 Reported annual incidence of collagenous colitis (CC) and lymphocytic colitis (LC) per 10^5 inhabitants in population based epidemiological studies

Region and years	CC	LC
Örebro, Sweden, 1984–88[7]	0.8	
Örebro, Sweden, 1989–93[7]	2.7	
Örebro, Sweden, 1993–95 (present study)	3.7	3.1
Örebro, Sweden, 1996–98 (present study)	6.1	5.7
Franche-Comté, France, 1987–92[8]	0.6	
Uppsala, Sweden, 1992–94[9]	1.9	
Terrassa, Spain, 1993–97[10]	2.3	3.7
Iceland 1995–99[11]	5.2	4.0

Our results for both CC and LC are almost identical to data from Iceland and show that the incidence of each disease is close to values generally reported in Sweden for Crohn's disease.[15–17] Also, the combined rates of CC and LC are approaching the incidence of ulcerative colitis.[16 18] The clinical relevance of MC is significant and the diseases should be considered in patients presenting with chronic non-bloody diarrhoea. We found an incidence peak for CC of $26.9/10^5$ inhabitants in women 60–69 years old. This is as high as the age and sex specific peak incidence of ulcerative colitis in our catchment area.[18]

Ideally, incidence values should be based on data for onset of symptoms. However, in a retrospective study, recall bias and uncertainty with respect to whether early symptoms in fact represented MC make such values uncertain. Therefore, we presented incidence values based on the date of diagnosis.

Case definitions will affect incidence values, and different clinical and histopathological criteria cause difficulties in comparing epidemiological studies. In the Icelandic study,[11] only histopathological criteria were used and a subepithelial collagen layer of 15 μm or more in CC was required compared with 10 μm in our earlier and our present study. This may affect both the incidence of each disease and the sex distribution. In the Spanish study, case definitions were similar to ours, except for disease duration of at least four weeks.

Several other circumstances affect the incidence values for MC. Firstly, awareness of the condition among general practitioners is essential so that a patient with chronic diarrhoea will be referred for colonoscopy. Secondly, the colonoscopist must take mucosal biopsies although the mucosa is macroscopically normal. Finally, the pathologist must consider MC in cases with a typical clinical history. Our general impression is that patients with chronic diarrhoea within our region are referred for colonoscopy instead of a barium enema. This is supported by a comparison with a study from a neighbouring region during the period 1991–1995 which showed that diarrhoea was the indication for colonoscopy in 4% in comparison with 15% in our study.[19] In our endoscopy unit, colonic mucosal biopsies are always obtained when cases of chronic diarrhoea are investigated. The important diagnostic role of the pathologist is clearly illustrated by the present data, showing the difficulty in diagnosing MC, and especially LC, histopathologically. ''Non-specific colitis'' or ''signs of lymphocytic colitis but not diagnostic'' were the two most common incorrect original

diagnoses. The original report describing LC was published only four years prior to our study period whereas the concept of CC was more established at that time. This, together with the fact that the histopathological alterations in CC are more apparent than in LC, may explain why cases with LC were more often overlooked at the first histopathological assessment. Without reassessment of the biopsy material, our incidence value for LC would have been lower.

In summary, we found that the annual incidences of CC and LC were higher than considered previously and were approximately $6/10^5$ inhabitants at the end of our study period. In Sweden, each disease is as common as Crohn's disease and combined incidence values approach those for ulcerative colitis. MC was diagnosed in 10% of all patients with non-bloody diarrhoea referred for colonoscopy but the diagnostic yield was higher in older patients, and 20% of those older than 70 years had MC.

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