Collagenous colitis in Örebro, Sweden, an epidemiological study 1984–1993

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Abstract
The incidence and prevalence of collagenous colitis are unknown. An epidemiological study was undertaken between 1984–93. All patients living in the immediate catchment area of Örebro Medical Center Hospital with the diagnosis collagenous colitis were identified. Biopsy specimens classified as unpecific intestinal fibrosis were re-examined to identify cases not correctly diagnosed at first. Medical records were scrutinised and colorectal biopsy specimens re-evaluated. Thirty patients with collagenous colitis were diagnosed during the study period. The female: male ratio was 9:1. The median age at diagnosis was 64 (28–78) years. The prevalence at 31 December 1993, was 15·7/10^5 inhabitants (95% CI; 9·8 to 21·6/10^5). The mean annual incidence during the period 1984–93 was 1·8/10^5 inhabitants (95% CI; 1·2 to 2·4/10^5). A peak incidence was found in women 70–79 years old. Collagenous colitis occurs mainly in middle aged women, and the frequency is higher than earlier anticipated. The prevalence and incidence is similar to primary biliary cirrhosis. In women 70–79 years of age, the incidence for collagenous colitis approaches the incidence for ulcerative colitis.

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Methods

Catchment area
The area is of a mixed urban rural type, with limited migration. From 1984 to 1993 the population increased 4·6% from 164 063 to 172 006 inhabitants. In this area there is one hospital, 16 primary health clinics, and a few private practitioners. Colonoscopy is performed solely at our hospital, where the only pathology department of this region is situated. All information about the population and the sex and age distribution was obtained from the Swedish Bureau of Statistics.

The study was approved by the ethical committee of Örebro Medical Center Hospital.

Patients
All cases were identified at the medical department, either among ambulatory patients referred by the primary health care, or among patients in hospital. In our department, patients with chronic diarrhoea are referred to a diagnostic colonoscopy instead of a barium enema, and mucosal biopsy specimens are always taken. During the study period patients diagnosed with CC were prospectively registered. The biopsy specimen or surgical material from these patients were re-evaluated. To ensure that all cases with CC were identified, all colorectal biopsy material with the histopathological diagnosis of unpecific intestinal fibrosis were scrutinised. This diagnosis was only computerised from 1986 onwards and thus not available for 1984–85.

Diagnostic criteria
The diagnosis of CC was based on both clinical and histopathological criteria. The clinical criterion was chronic watery diarrhoea, and the histopathological criteria as follows.

(1) A subepithelial collagen layer adjacent to the basal membrane with a thickness of 10 μm or more, measured by an ocular micrometer on a well orientated – that is, a perpendicular section of the mucosa, stained according to van Gieson.

(2) Increased infiltration of the lamina propria with lymphocytes and plasma cells.

(3) Epithelial damage, with either detachment of the surface epithelium, flattening of epithelial cells, or infiltration with lymphocytes, or all three. All colorectal biopsy material was re-evaluated by the same pathologist (SE). The date of diagnosis was defined as the date of the histopathological diagnosis of CC, or in five cases, the date of that colonoscopy during which relevant biopsy
Material was obtained, but the original histological scrutiny overlooked the correct diagnosis. The date of onset of symptoms was defined as that year and month, when the patient first experienced longstanding watery diarrhoea. Duration of symptoms, was the period between the onset of symptoms and the date of diagnosis.

Calculations
Age is reported as median (range). The prevalence was calculated as crude, and age adjusted to the 1988 Swedish population and presented with 95% confidence intervals (95% CI) estimated from the Poisson distribution. As CC runs a relapsing course, it is considered a chronic disease. For that reason patients in clinical or histopathological remission at 31 December 1993, were regarded as prevalent cases.

Results
Patients
Up till 31 December 1993, 40 patients from our immediate catchment area, were suspected of suffering from CC. After re-evaluation by the pathologist, nine of these did not fulfil the diagnostic criteria; in seven cases lymphocytic colitis was diagnosed and in two patients a normal mucosa was seen. One of the patients was diagnosed in 1980 – that is, before the study period – leaving 30 patients in total with CC diagnosed from 1984 to 1993. Three of these 30 patients were identified from the histopathology register and the remaining from the clinical register. Three of them have died of unrelated diseases and one had moved out of the area before 31 December 1993. We are not aware of any patient with CC, having moved into the area (Fig 1).

Histopathological and endoscopic assessment
The median thickness of the collagenous layer was 20 (10–50) μm. All patients had infiltration with inflammatory cells in the lamina propria, epithelial damage or lymphocyte infiltration in the epithelium. In nine of 30 patients endoscopic assessment showed subtle abnormalities such as patchy mild oedema, erythema or minor abnormalities of the mucosal vascular pattern.

Age and sex
The median age at diagnosis was 64 (28–78) years, for women it was 64 years (28–78) years, and for men 69 years (54–77). The median age at onset of symptoms was 57 (20–78) years. Twenty seven of 30 patients were female, which gave a female: male ratio of 9:1.

Prevalence
On 31 December 1993, 27 patients with CC were living within our catchment area. Thus, the prevalence on that date was 157/10⁵ inhabitants (95% CI; 9.8 to 21.6/10⁵). Twenty four of 27 patients were women, yielding a female prevalence of 27.2/10⁵ (95% CI; 16.3 to 38.1/10⁵), and a male prevalence of 3.6/10⁵ inhabitants (95% CI; 0.0 to 7.7/10⁵).

Incidence
Thirty patients residing within our catchment area were diagnosed as having CC between 1 January 1984 and 31 December 1993, yielding a mean annual incidence of 1.8/10⁵ inhabitants (95% CI; 1.2 to 2.4/10⁵). Twenty seven of 30 patients were women, giving a mean annual female incidence of 3.1/10⁵ (95% CI; 1.9 to 4.3/10⁵), and a male incidence of 0.4/10⁵ (95% CI; 0.0 to 0.8/10⁵) inhabitants. The annual incidence increased during the 10 year period, it was 0.8/10⁵ inhabitants (95% CI; 0.2 to 1.4/10⁵) in the first five year period, and 2.7/10⁵ (95% CI; 1.6 to 3.8/10⁵) in the second five year period. All crude incidence rates were equal to the age adjusted rate. Figure 2 shows an analysis of age and sex specific incidence. An incidence peak of 14.6/10⁵ (95% CI; 6.3 to 22.9/10⁵) inhabitants for women 70–79 years old is seen.
Duration of symptoms
The median duration of symptoms, decreased from 24 months (4–300) for the first 15 patients diagnosed in the study period, to six months (2–216) for the last 15 patients diagnosed in this period. Figure 3 shows the relation between onset of symptoms and diagnosis.

Incidence based on the date of onset of symptoms
For 21 of 30 patients the date of onset of symptoms was within the study period 1984–93. Based on this date a mean annual incidence of 1.3/10^5 (95% CI: 0.6 to 1.9/10^5) inhabitants was found.

Annual colonoscopy rate
From 1984 to 1993 there was a gradual increase in the annual colonoscopy rate from 415 in 1984 to 896 in 1993. From 1 January 1989 to 31 December 1993, 4247 colonoscopies (irrespective of indication) were performed. Twenty-five patients with CC were found, including two patients not living in the catchment area, corresponding to a frequency of 5.9 cases per 1000 colonoscopies.

Discussion
This is the first population based epidemiological study reporting the incidence and prevalence of CC. Others have tried to estimate the comparative frequency of CC. Based on patients in a gastroenterological community practice within a well defined catchment area, three cases of CC per 1000 patients with chronic diarrhoea was found. The diagnosis was based on rectal biopsy specimens only, however, which may have underestimated the true frequency, as the mucosal changes usually are more prominent in the proximal colon.

Another report found six cases of CC out of 1469 patients with diarrhoea on the basis of colorectal biopsy specimens. In that study, however, the catchment area was not clearly defined. A German group reviewed all colonic biopsy specimens collected in a defined catchment area with 660 000 inhabitants during 28 months. A total of 980 specimens were included, and two cases of CC were found. On the basis of this finding, they estimated a frequency of 1 case per 330 000 inhabitants. The study period, however, seems too short for any reliable epidemiological conclusion.

A French group diagnosed 40 patients with CC during 6254 colonoscopies, which corresponded to a frequency of 6.4 per 1000 colonoscopies. In that study the indications for colonoscopy were not only diarrhoea, but various gastrointestinal symptoms. During 1989 to 1993 we performed 4247 colonoscopies, also on various gastroenterological indications, and diagnosed 25 cases of CC. Our frequency of 5.9 per 1000 colonoscopies, is in accordance with the French figures. Another French group reported 22 patients with CC diagnosed during five years, and calculated an annual incidence of 0.6/10^5 inhabitants. This is also close to our findings.

The age and sex distribution in our study is similar to previous findings. The incidence reached a maximum for women in the age group 70–79 years. Obviously, in this age group, the female incidence may be similar for CC and ulcerative colitis.

In our department, patients with chronic diarrhoea are referred to a diagnostic colonoscopy instead of a barium enema, and mucosal biopsy specimens are always taken. This may contribute to the apparently high frequency of CC presented here.

The annual incidence increased during 1984–93 and reached a maximum in 1990 (Fig 1). This is certainly explained by an increasing interest and clinical awareness of the disease, an assumption supported by the fact that the median duration of symptoms before diagnosis decreased from 24 to six months. In addition the colonoscopy rate increased during the study period and has contributed to the apparent rise in incidence. In Fig 3, the year of onset and the year of diagnosis are seen and shows that the onset of the disease in many cases lies years ahead of the histologically verified diagnosis.

We therefore compared the incidence based on the two different figures; year of onset of symptoms and year of the histological diagnosis. These two estimates are close to each other, being 1.3/10^5 and 1.8/10^5 inhabitants respectively. The first rate based on the year of onset of symptoms is independent of the time interval between onset of symptoms and diagnosis, but recall bias and uncertainty whether early symptoms in fact represents CC cause disadvantages with this estimate. The second estimate based upon the year of diagnosis may cause, on the other hand, an artefactual peak of incidence if the time interval between onset of symptoms and diagnosis diminishes during the study period.

We have earlier reported other epidemiological results from our catchment area. The prevalence for ulcerative colitis was 234/10^5 and for Crohn’s disease 146/10^5 and for adult coeliac disease 95-5/10^5 inhabitants aged 15 years or more. For primary biliary cirrhosis, the prevalence was 12/8/10^5 and the annual incidence 1.4/10^5. The prevalence and annual incidence for CC, 15-7/10^5 and 1.8/10^5 respectively, are similar to those for primary biliary cirrhosis,
and shows that CC is not as rare as has been considered earlier. Furthermore the age and sex distribution of CC is similar to that of primary biliary cirrhosis and other autoimmune diseases. This could support a hypothesis of CC having an autoimmune aetiology, though all criteria for autoimmunity are not proved; responsiveness to corticosteroid treatment has only been tried prospectively in a small trial, and the findings of a disease specific antibody, or a specific HLA antigen are still awaited.

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