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Incidence and clinical course of Crohn's disease during the first year — Results from the IBD Cohort of the Uppsala Region (ICURE) of Sweden 2005–2009

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Abstract

Background and Aims: As a part of the Swedish ICURE study where the epidemiological results of ulcerative colitis and microscopic colitis recently have been published, we hereby present the corresponding figures for Crohn's disease.
Methods: All patients diagnosed with Crohn's disease in Uppsala County (305,381 inhabitants) were prospectively registered during 2005–2006 and the same for all new patients with Crohn's disease in Uppsala Region (642,117 inhabitants) during 2007–2009.
Results: 264 patients with Crohn's disease were included. The mean annual incidence was 9.9/100,000/year (95% CI: 7.1–12.6). Incidence among children <17 years was 10.0/100,000/year (95% CI: 3.8–16.3). 51% of the patients had ileal involvement (L1: *n* = 73, 28%. L2: *n* = 129, 49%. L3: *n* = 62, 23%, L4: *n* = 47, 18%) and 23% had a stricturing or penetrating disease (B1: *n* = 204, 77%. B2: *n* = 34, 13%. B3: *n* = 26, 10%. p: *n* = 27, 10%). Intestinal resection rate during the first year was 12.5%. Patients with complicated disease had longer symptom duration before diagnosis compared to patients with non-complicated disease (median months 12.0, IQR: 3.0–24.0 vs 4.0, IQR: 2.0–12.0, $p = 0.0032$). Patients 40 years or older had an increased risk for surgery (HR: 2.03, 95% CI: 1.01–4.08, $p = 0.0457$).

Abbreviations: IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; MC, Microscopic colitis; AZA, Azathioprine; 6-MP, Mercaptopurine; MTX, Methotrexate; TNF, Tumor necrosis factor; CRP, C-reactive protein.

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Conclusions: The incidence of Crohn's disease in a region of Sweden is one of the highest reported in Europe. Long symptom duration precedes stricturing or penetrating behaviour. Old age is an independent risk factor for surgery.

1. Introduction

The geographical and temporal variation in the incidence of inflammatory bowel disease (IBD) has been formulated as the first of "the 10 remaining mysteries of inflammatory bowel disease".[1] The Scandinavian countries have among the highest incidence of IBD in the world and studies describing the long term incidence have previously been published.[2–5] The important Norwegian IBSEN cohort of IBD patients diagnosed in 1990–1993 has reported on the clinical course of Crohn's disease (CD) over ten years.[6]

These early epidemiological studies of CD are often limited to a presentation of location of inflammation, but seldom report on the behaviour of the disease.[7] Furthermore, in the Vienna classification from 1998 each of the four locations of the disease was mutually exclusive.[8] It was therefore difficult to evaluate small or large bowel involvement in patients classified with upper gastrointestinal disease (L4). Since the Montreal classification was presented,[9] prospective population based epidemiological studies regarding the natural history of the disease have been sparse.[10–14]

The changing pattern of the incidence of CD as well as the introduction of new pharmaceutical agents and the increased use of old ones (i.e. antimetabolites) have made it important to establish new IBD cohorts, describing the course of these non-curable diseases in the light of contemporary treatment. It has been stated that "the initiation of new population-based natural history studies in CD to address this issue is urgently needed".[15]

As a part of the ICURE study (The IBD Cohort of Uppsala Region) where the epidemiological results of ulcerative colitis (UC) and microscopic colitis (MC) recently have been published,[16,17] we hereby present the corresponding figures for Crohn's disease.

2. Material and methods

One university hospital, four county hospitals and one county district hospital participated in the present study. In Uppsala County patients were included in the study from the 1st of January 2005 and in the remaining counties from the 1st of January 2007. The study was closed for all centres on the 31st of December 2009. The mean population in the study region was 305,381 in 2005–2006 and 642,117 in 2007–2009. General practitioners in the area refer patients only to these hospitals. The Swedish health care system does not allow patients resident in one county to receive health care in another county, except for emergency care. There are no private gastroenterologists in the region. Detailed demographic data concerning the uptake area are presented elsewhere[16].

All patients with probable IBD recruited to the study were evaluated by at least two participating gastroenterologists at different hospitals. In applicable cases microscopic samples were reviewed together with experienced pathologists whereas all radiological images were displayed together with radiologists. Presence of diarrhoea, blood in stools and abdominal pain were recorded at the first visit before diagnosis was established. CRP levels at diagnosis and before treatment were measured.

The patients were classified as CD, UC, IBD unclassified (IBDU), observational cases or were excluded. The diagnosis of CD was based on endoscopic findings, physical examination, microscopic features and radiological images in accordance with the criteria of Lennard-Jones.[18] Patients with aphthous lesions only in the small bowel and concomitant NSAID intake were not included, nor patients with self-limiting disease together with findings in faecal cultures.

Location and behaviour according to the Montreal classification were assessed at the time of diagnosis, including the first twelve months of disease after diagnosis, allowing for planned investigations to provide additional information. Pure ileal CD (L1) included patients with inflammation of the ileum including the cecal pole, but excluding inflammation distal to the ileocecal valves. Stricturing CD (B2) required radiological findings consistent with bowel dilatation proximal to the affected segment or obstructive symptoms. Penetrating CD (B3) required intra-abdominal fistula, intra-abdominal abscesses and/or inflammatory masses palpated or found with radiology.[8,9]

2.1. Statistics

All data analysis were performed using the software STATISTICA, version 10 (2011), StatSoft Inc. Oklahoma, USA (http://www.statsoft.com). Population data were obtained from the governmental Swedish agency Statistics Sweden (http://www.scb.se). Depending on the characteristics of the data, continuous variables are presented as means and standard deviations (SD) or medians and inter-quartile range (IQR). Group differences were evaluated using Student's *t*-test and Mann–Whitney U-test, respectively. Data from contingency tables were analysed using χ2-test or Fisher exact *P*-test. *P*-values <0.05 were considered statistically significant. The 95% confidence intervals (CI) of incidence were calculated assuming a Poisson distribution and age adjusted for the Swedish population for each corresponding year. Survival analyses were performed using Kaplan–Meier product limit methods and log-rank tests. Age, location, behaviour, perianal disease, upper GI disease, gender and heredity were tested with chi-square, Mann–Whitney or log-rank test for correlation to risk for surgery during the first twelve months. Age, behaviour and location significantly correlated and were included in a Cox regression analysis.

2.2. Ethical considerations

The study was approved by the local Ethics Committee at Uppsala University.

3. Results

A total of 293 potential CD patients were identified during the inclusion period. Four patients did not reside in the study area and were excluded from the study. Thirty-four patients with segmental colitis or terminal ileitis did not fulfil the criteria for CD and were excluded. For a majority of these patients no clear alternative diagnosis was found. Nine patients initially diagnosed as CD were later reclassified as UC and excluded. Seven patients with an initial IBDU diagnosis were diagnosed with CD during follow up and were included. Eleven patients originally considered as UC patients changed diagnosis to CD and were also included. In total 264 patients with CD were included in this study.

261 (99%) of the patients had complete follow up during the first twelve months. Three patients moved outside the region and were lost to follow up. All patients lost to follow up had their initial investigations completed, the CD diagnosis was established and they were included in the analyses. Seven patients died during the first year.

3.1. Diagnostic procedures

All diagnostic procedures are presented in Table 1. Colonoscopy was performed for all patients except two; for one patient diagnosis was established solely from ileal stenosis on small bowel contrast radiology together with typical longstanding symptoms. A second patient was diagnosed during surgery with no endoscopic follow-up.

MRI enterography was considered the most accurate radiology method providing information of the highest quality, followed by CT enterography and plain enteroclysis. Many patients underwent several radiological procedures, but only the most accurate method for each patient is presented in Table 1. Ileal investigation of any modality (ileocolonoscopy, capsule endoscopy, radiology or during surgery) was performed in 249 (94%) of the patients.

Table 1 Procedures, location and behaviour.

	All (n = 264)		A1 <17 year (n = 50)		A2-A3 ≥17 year (n = 214)		P value [a]
	n	(%)	n	(%)	N	(%)	
Endoscopy							
Colonoscopy	262	(99.2)	50	(100.0)	212	(99.1)	1.0000
Gastroscopy	135	(51.1)	49	(98.0)	86	(40.2)	<0.0001
Capsule endoscopy	55	(20.8)	3	(6.0)	52	(24.3)	0.0041
Radiology							
Radiology total	178	(67.4)	29	(58.0)	149	(69.6)	0.1143
MRI enterography	55	(20.8)	18	(36.0)	37	(17.3)	0.0034
CT enterography	7	(2.7)	1	(2.0)	6	(2.8)	0.7501
Enteroclysis	52	(19.7)	7	(14.0)	45	(21.0)	0.2606
CT abdomen	64	(24.2)	3	(6.0)	61	(28.5)	0.0008
Location							
L1: Ileal	73	(27.7)	3	(6.0)	70	(32.7)	0.0001
L2: Colonic	129	(48.9)	28	(56.0)	101	(47.2)	0.2622
L3: Ileocolonic	62	(23.5)	19	(38.0)	43	(20.1)	0.0072
L4: Upper GI	47	(17.8)	24	(48.0)	23	(10.7)	<0.0001
Behaviour							
B1: Inflammatory	204	(77.3)	41	(82.0)	163	(76.2)	0.3757
B2: Stricturing	34	(12.9)	5	(10.0)	29	(13.6)	0.4997
B3: Penetrating	26	(9.8)	4	(8.0)	22	(10.3)	0.6261
p: Perianal	27	(10.2)	8	(16.0)	19	(8.9)	0.1346
Symptoms							
Diarrhoea	194	(73.5)	34	(68.0)	160	(74.8)	0.4060
Abdominal pain	169	(64.0)	35	(70.0)	134	(62.6)	0.2465
Blood in stools	99	(37.5)	26	(52.0)	73	(34.1)	0.0135
Additional traits							
Intra-abdominal fistulas	15	(5.7)	2	(4.0)	13	(6.1)	0.5683
Abscesses	9	(3.4)	0	(0.0)	9	(4.2)	0.1401
Palpable mass	17	(6.4)	4	(8.0)	13	(6.1)	0.6175
Inflammatory mass on x-ray	20	(7.6)	2	(4.0)	18	(8.4)	0.2886

[a] A1 vs. A2-A3, $\chi 2$-test or Fisher exact P-test.

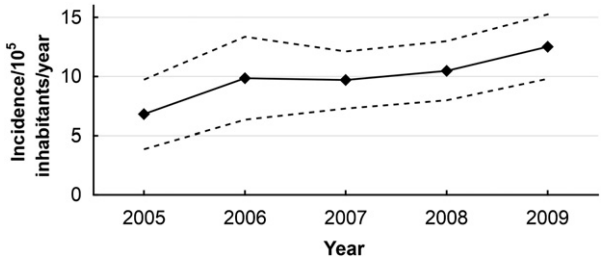

Figure 1 Age adjusted incidence. Dotted lines: upper and lower limits of 95% confidence interval assuming a Poisson distribution.

3.2. Descriptive epidemiology

The mean annual incidence of CD in our study group was 9.9/100,000/year (95% CI: 7.1–12.6), age adjusted for the Swedish population for each corresponding year (Fig. 1). The incidence is separately presented for men and women in Fig. 2. The age adjusted incidence among children under the age of 10 was 3.8/100,000/year (95% CI: 0.0–9.1) and under the age of 17 it was 10.0/100,000/year (95% CI: 3.8–16.3). Thirty-seven patients (14%) had a relative with IBD. The age at diagnosis ranged from four to 84 years and there was a primary peak in the age interval from 10 to 30 years and a secondary peak in the age interval from 70 to 80 years (Fig. 2). There was no gender difference regarding age, symptom duration or heredity.

3.3. Disease phenotype

There were no statistical differences between men and women regarding location and behaviour (Table 1). Patients with ileocolonic disease were significantly younger (26.0 ± 14.8 years) than patients with isolated ileal or colonic disease (40.6 ± 17.9 and 35.8 ± 20.8 years), $P < .001$. Patients with a stricturing disease were significantly older (45.1 ± 23.6 years) than patients with inflammatory or penetrating disease (33.2 ± 18.4 and 34.3 ± 17.4 years), $P = .0100$.

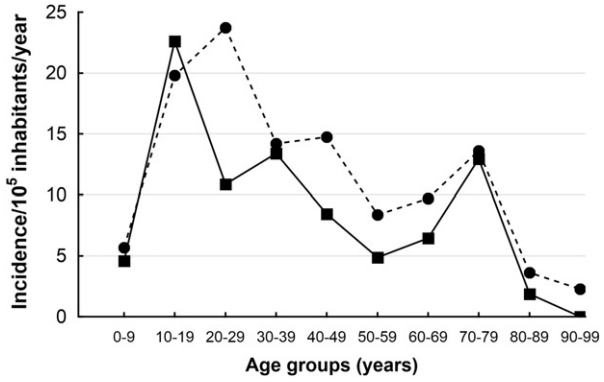

Figure 2 Crude incidence in different age groups. Men (–■–); women (––●–).

Symptoms before diagnosis are presented in Table 1. Patients with B1 had significantly higher prevalence of diarrhoea and blood in stools compared to patients with B2 or B3 (diarrhoea: 79% vs. 55%, $p = 0.0002$, blood in stools: 44% vs. 17%, $p = 0.0001$), whereas pain was a more prominent symptom among B2 and B3 compared to B1 (77% vs. 60%, $p = 0.0202$). Blood in stools was more common among children than adults (Table 1).

Median CRP levels were progressively higher with increasing behaviour level (B1: 15.0, IQR: 5.0–58.0, B2: 33.0, IQR: 6.0–54.0, B3: 59.0, IQR: 13.0–170.0, $p = 0.0476$). CRP levels for children and adults are presented in Table 2.

One patient who developed CD in 2009 was previously diagnosed with collagenous colitis in 2002. No case of transition was observed between MC and CD inside the ICURE-cohort.

3.4. Symptom duration

The patients with a more complicated disease (B2 or B3) had significantly longer symptom duration before diagnosis (median months 12.0, IQR 3.0–24.0) compared to patients with pure inflammatory behaviour (median months 4.0, IQR 2.0–12.0) as shown in Fig. 3 ($P = .0032$). Older (A3) patients tended to have longer symptom duration compared to younger (A1–A2) patients (median months 6.5, IQR 1.5–19.0 vs. 5.0, IQR: 2.0–12.0), but this difference was not statistical significant. There were no statistical differences in symptom duration regarding gender, heredity or perianal disease.

3.5. Medication and intestinal resection

Only one patient in the cohort did not receive any medical or surgical treatment during follow up (Table 2, Fig. 4). Twelve (4.5%) patients were diagnosed at the time of surgery (Fig. 3). The indication for surgery was stenosis of the small bowel in four of these patients, suspected appendicitis in three patients and perforation in four patients. One patient had an adenocarcinoma of the ileum as well as terminal ileitis diagnosed with capsule endoscopy. Additional two patients were appendectomized but no small or large bowel was resected and they are not included in the surgery group.

A further 21 patients required surgery during the first year after diagnosis (Fig. 3). Five of these patients had a severe colitis not responding to medical treatment. Thirteen patients had a stenosis of the ileum. Three patients had a perforating disease with intra-abdominal abscess or fistula.

3.6. Intestinal damage

In 27/33 (82%) of patients subject to surgery, small bowel was resected (with or without simultaneous large bowel resection) with a median length of 15.0 cm (IQR 10.0–39.0). Four patients were colectomized. A single partial large bowel resection was performed in two patients.

In 28/231 (12%) of the patients not requiring surgery during the first year there was radiological evidence of small bowel strictures with a median length of 15.0 cm (IQR 8.5–35.0). Among the patients with stricturing disease no

Table 2 Demography and medication.

	All patients (n = 264)		A1 <17 year (n = 50)		A2-A3 ≥17 year (n = 214)		P value [a]
Median age, years (IQR)	31.0 (18.0–47.0)		14.0 (12.0–15.0)		36.0 (25.0–54.0)		n.a.
Mean age, years (SD)	34.8 (19.4)		13.2 (3.1)		39.9 (18.1)		n.a.
Men: women	131:133		29:21		102:112		0.1881
Symptom duration before diagnosis, median months (IQR)	6.0 (2.0–12.0)		4.7 (2.0–10.0)		6.0 (2.0–15.0)		0.4431
CRP, median mg/L (IQR)	18.0 (5.0–60.0)		12.0 (4.8–55.5)		21.0 (5.0–61.0)		0.2363
	n	(%)	n	(%)	n	(%)	
Smoking							
Yes	52	(19.7)	3	(6.0)	49	(22.9)	0.0068
Former smoker	29	(11.0)	0	(0.0)	29	(13.6)	0.0058
No	113	(42.8)	26	(52.0)	87	(40.6)	0.1443
Missing data	70	(26.5)	21	(42.0)	49	(22.9)	0.0059
Medication during first 12 months							
5-ASA	173	(65.5)	44	(88.0)	129	(60.3)	0.0002
Systemic steroids	208	(78.8)	37	(74.0)	171	(79.9)	0.3577
AZA/6-MP/MTX	112	(42.4)	30	(60.0)	82	(38.3)	0.0052
Anti-TNF-alpha antibodies	29	(11.0)	9	(18.0)	20	(9.3)	0.0781
Exclusive enteral nutrition	16	(6.1)	12	(24.0)	4	(1.9)	0.0149

[a] A1 vs. A2-A3, Mann–Whitney U-test or χ2-test.

differences were found in medication between the surgery and non-surgery group.

3.7. Risk for surgery

We performed a Cox regression analysis for age, behaviour and location as factors affecting surgery rate. Patients 40 years or older at diagnosis (A3) had an increased risk for surgery (HR: 2.03, 95% CI: 1.01–4.08, P = .0457). Both stricturing (HR: 10.59, 95% CI: 3.84–29.23, $P < .0001$) and penetrating (HR: 36.55, 95% CI: 12.82–104.16, $P < .0001$) disease were strongly associated with an increased risk for surgery. Ileal disease (L1 and L3) was associated with higher surgery rates compared to pure colonic disease (L2), log-rank test $P < .0001$. However, presence of ileal disease did not result in an increased hazard ratio in the regression model.

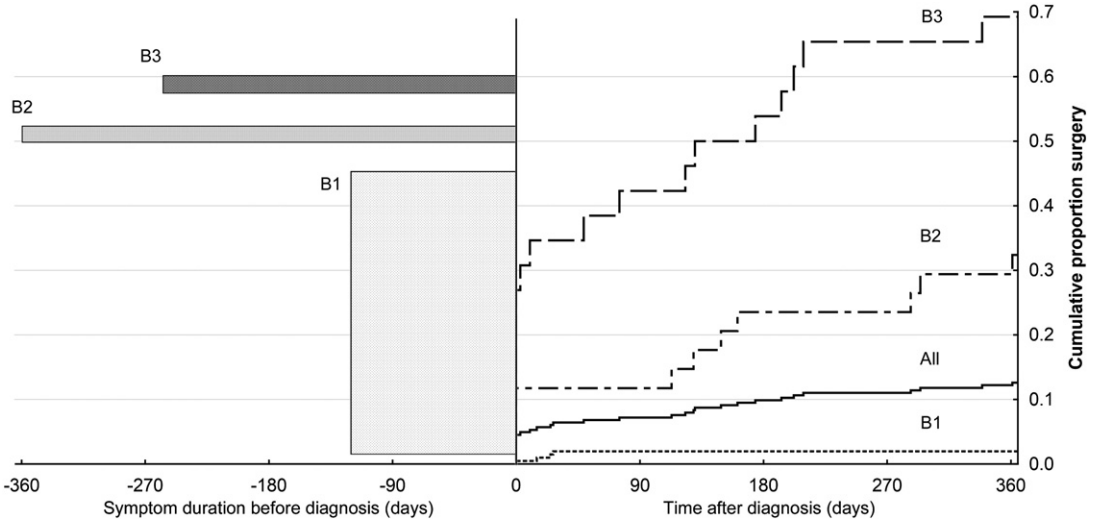

Figure 3 Symptom duration and cumulative proportion of patients subject to surgery, stratified for behaviour at diagnosis. Symptom duration bars as median days before diagnosis (IQR: B1 2.0–12.0, B2 6.0–24.0, B3 0.75–24.0). Area of bars corresponds to percentage of patients in total cohort. All patients (–), B1 (…), B2 (–.-) and B3 (––-).

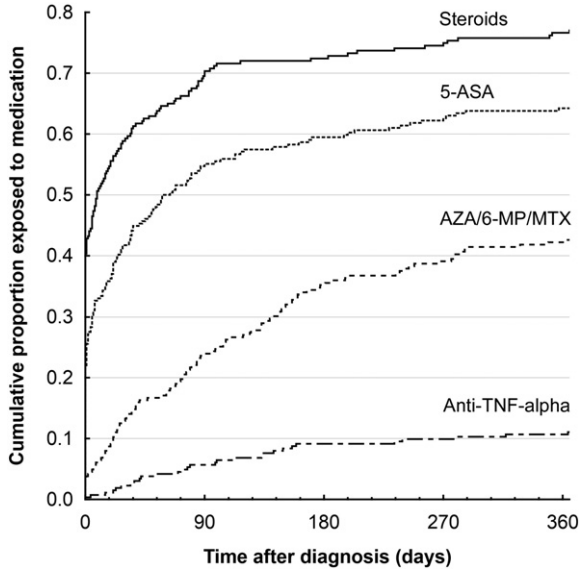

Figure 4 Exposure to medication after diagnosis.

4. Discussion

The incidence of CD in our region is one of the highest reported in Europe. This together with our previous report regarding a UC incidence of 20.0 and an MC incidence of 11.8/100,000 inhabitants/year in the same study area underlines the fact that the Swedish population is highly susceptible to IBD with a total incidence of 41.7/100,000 inhabitants/year.[16,17]

In contrast to the previously presented UC cohort, where a patient with lymphocytic colitis after six month developed UC, no similar transition could be observed among the patients with CD. However, one patient with collagenous colitis since 2002 developed Crohn's disease in 2009.

Since there has been a doubled incidence of CD in our region of Sweden over the last 40 years,[2,19] environmental factors are suspected to be responsible. This increase in incidence affects not only adults, but also the paediatric patient group, with rates even slightly higher than in the neighbouring district of Stockholm.[20] As previously reported, the incidence of UC in the age group <17 years was 8.9/100,000 inhabitants/year.[16] The total incidence of IBD in the paediatric part of the cohort was thus 18.9/100,000 inhabitants/year (95% CI: 10.2–27.4). The secondary incidence peak in the elderly population was also registered among UC male patients, but not among the women.[16]

Despite last decade's intensive research regarding the pathogenesis of CD, no definitive single etiological factor has been identified explaining the global increase in incidence.[21] Several hypotheses have been proposed over the years but remain to be proven.[22–25] Smoking has been identified as an important risk factor for CD, but since the percentage of smokers among Swedish citizens have decreased markedly,[26] this cannot contribute to the increased incidence in our region. The Swedish diet is characterized by high intake of milk, vitamin D and short fatty acid, and low intake of dietary fibre compared to other European countries,[27,28] but a causal relationship has been difficult to establish.

Surgery has been a cornerstone treatment for CD in the past, but is an irrevocable intervention with permanent loss of intestine. Abysmal surgery rates of 95% bowel resection after ten years in the 1960s have been presented in our own region.[29] Even in reasonable modern studies of patients diagnosed in the 1990s, the ten year surgery rate was 29–38%.[6,30]

In this study we have demonstrated that 4.5% of the patients were subject to surgery before diagnosis was established. A further 8.0% had a surgical intervention short after diagnosis, reflecting the time to collect information regarding the established structural damage to the intestine. This corresponds well to other studies presenting 9.8–13.6% surgery rate year one.[6,10,30,31] Despite current study's high use of medical treatment, e.g. 42% use of antimetabolites vs. 6% in the IBSEN study, surgery rate was similar (12.5% vs. 13.6% within one year).[6] In three of the patients thought to have appendicitis, but instead diagnosed with CD, one could question whether the ileocecal resection was truly necessary. Without these misdiagnosed patients the surgery rate is down to 11.4%. Thus, our figures are similar to those presented in a recent paper discussing hospitalization and surgery in CD.[32]

One important finding in this study was that patients presenting with advanced disease have longer symptom duration. A possible explanation for this could be that these patients less often suffered from blood in faeces and thus the disease process could continue for a longer time. Patients with B1 at diagnosis more often presented with blood and diarrhoea, thus possibly making them more prone to seek early medical advice.

When discussing disease burden and the concept of intestinal damage one must remember the pre-diagnostic phase of the disease that relates to patient's and/or doctor's delay. In this phase, it is not possible for the health care system to prevent intestinal damage. Thus, in order to change the course of disease, it seems necessary to minimize the time period between onset of symptoms and the diagnostic moment with ensuing treatment, especially if one considers the current models of disease progression from inflammatory to more severe forms of CD.[33,34] This assumption gets support from the fact that there were no differences in the use of antimetabolites or anti-TNF treatment between patients with B2 that were treated with bowel resection and patients with B2 that did not need surgery during the first year. Furthermore, an incentive to treat CD early is the very low surgery rate for pure inflammatory disease compared to complicated disease (2% vs 48%).

Young age has been highlighted as an important risk factor for advanced disease both in UC[35] and CD.[6,36] We have recently reported that among our UC patients there were no difference regarding severity or need for surgery for patients <17 years old compared to patients 17 years or older[16] and likewise in the present report patients in the A1 category did not suffer a worse outcome. However, since our primary outcome was surgery and the younger patients had less often pure ileal involvement, this could possibly contribute to less need for surgery.

On the contrary, in our cohort, older patients (A3) suffered higher risk for complicated disease as well as surgery during the first year after diagnosis. This could possibly be related to an increased proportion of stricturing behaviour in this age group. Albeit not statistically

significant, this age group also demonstrated a longer pre-diagnostic symptom phase compared to A1 and A2. The spectra of alternate diagnoses, including malignancy, are widened with higher age when a patient presents with an intra-abdominal mass or bowel obstruction, thus lowering the bar for surgery.

The weakness of the present study is the inherent shortcomings of an observation study, where a strict uniform treatment regimen has not been used. Thus, any conclusions regarding outcome of different treatment must be interpreted with caution. The strength of the study is the prospective population based design, with all patients and all age groups diagnosed within a certain time frame and in a defined geographic area included. We believe that very few patients with CD resident in Uppsala region were unidentified due to diagnosis outside the region. However, it is possible that patients may have been diagnosed in an emergency setting elsewhere and never completed a follow up visit at their home hospital.

Furthermore, antimetabolites were used in a reasonably high proportion and, to a lesser degree, anti-TNF agents. This study of CD was performed parallel with our study of UC and MC in the same population and transitions between CD/UC and MC seems to be rare.

In conclusion, the burden of CD in our region of Sweden is high. Medical treatment with intestinal resection as outcome must always be valued after taking into account the damage already present at diagnosis. Despite the use of modern treatments, we have not been able to reduce the need for surgery during the first year after diagnosis. Thus, an earlier diagnosis of CD is probably required in order to change the natural course of the disease. The observation that patients with structural bowel damage less often have alarm symptoms such as blood in the faeces makes this a demanding challenge for the gastroenterologist. Future analyses of this cohort will hopefully answer the question if the ensuing course of the disease can be changed.

Conflict of interest

None.

Acknowledgments

DS and AR carried out the studies and data analyses and drafted the manuscript. AE, LH, AN, ML and TH conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Dr Steven Lucas and Dr Lars Åkerberg have contributed in finding patients for the study. Dr Maria Hårdstedt and Dr Erika Björs contributed with valuable comments regarding the manuscript.

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