Inflammatory bowel disease (IBD) – current state of affairs; a review based on clinical experience

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Abstract

Objective: To study,

- epidemiology of IBD in an adult Welsh population,
- pattern of clinical presentations,
- the role of laboratory parameters employed to assess the activity of the disease,
- relationship between endoscopic assessment and histology,
- the role of screening for colo-rectal carcinoma,
- profiles of medical and surgical treatment.

Design & Setting: Review of case notes of IBD patients either attending out-patients' gastroenterology clinics or admitted to Withybush Hospital, U.K. from 01/01/93 to 01/01/95.

Main outcome measures: Problems in the management were identified.

Results: ESR and CRP were the commonest laboratory indices used to assess the disease activity. In 5, suspected of having Ulcertive colitis UC on endoscopy, histology showed Crohn's Disease CD. This was not obseved in CD. Five normal looking mucosae showed non-specific colitis on biopsy. There were 11 smokers and 29 non-smokers in UC group. 13 smokers and 6 non-smokers in CD group. Screening for CRC showed dysplasia in 1 out of 9.

Conclusions:

- ESR and CRP did not correlate well with the disease activity. ESR was a more accurate predictor of activity in UC while CRP in CD.
- Endoscopic may be misleading in suspected UC.
- Smokers had less UC and more CD.
- The yield for screening for CRC was low.

Introduction

Inflammatory bowel disease (IBD) is a major concern for the Gastroenterologist in the west. All gastroenterology clinics have a fair number of IBD patients attending them either as direct referrals from the general practitioners or as follow-up patients on discharge from the hospital. Ulcerative colitis (UC) and Crohn's disease (CD) represent two of the major challenges faced by the gastroenterologists today. We are largely unaware of their aetiology, genetics and pathogenesis. From the clinicians' point of view there may be initial diagnostic difficulties, precise differentiation of CD from UC and problems of accurate assessment of the activity of the disease as reflected by this study causing therapeutic and management dilemmas. From the patients point of view, both the disease and the treatment may give rise to considerable morbidity which is often unpleasant resulting in mandatory surgical intervention.

Methodology

A retrospective study was designed to look into various clinical aspects of IBD affecting the adult population in Pembrokeshire-Wales attending the out patients' gastroenterology clinics of Withybush District General Hospital. The case notes of such patients who were attending the said clinics over a period of 2 years, i.e. from 01/01/93 to 01/01/95 were re-examined. The date obtained are as follows:

Results

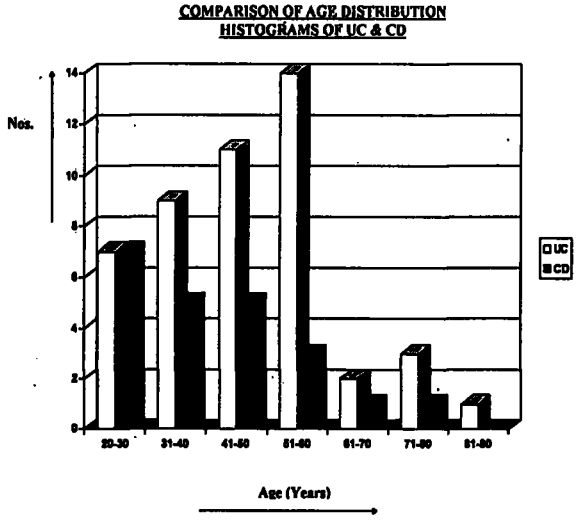
Sex distribution

	Male		Female
UC	21	:	26
CD	12	:	10
Total	33	:	36

Smoking habits

Disease	No. of smokers	No. non-smokers	No. of undocumented
UC	11	29	07
CD	13	06	03

Age distribution (in years)	Disease – Diagnosed on overall clinical features and investigations	
	UC	CD
20-30	7	7
31-40	9	5
41-50	11	5
51-60	14	3
61-70	2	1
71-80	3	1
81-90	1	0
Total	47	22



Major symptoms at presentations

	UC	CD
Uncomplicated diarrhoea	8	10
Blood and/or mucus diarrhoea	24	4
Bleeding per rectum alone	3	1
Abdominal pain alone	1	4
Anemia alone	0	1
Asymptomatic follow-up patients	11	2

Profile of clinical complications

Feature	Disease	No.
Intestinal		
RIF Mass a female patient presented to the gynecology unit as a pelvic lump	CD	01
Appendicitis Two male patients presented to the surgeons	CD	02
Anal Problems		
• Perianal abscess	CD	01
• Fissure-in-ano	CD	01
• Fistula-in-ano	CD	02
• Anal stricture	CD	02
• Skin tags	CD	01
Intestinal Obstruction	CD	02
Intestinal Perforation	CD	01
Toxic Megacolon	UC	02
Extra Intestinal		
Septicemia	UC	01
Arthropathy		
• Peripheral	UC	03
• Isolated sacroilitis	UC	01
• Ankylosing spondylitis	CD	01
Sclerosing cholangitis	UC	01
Pyoderma gangrenosum	UC	01
Erythema nodosum	CD	02
Nutritional deficiencies		
• Iron deficiency type	03 CD 09 UC	12
• Foliate deficiency	CD	02
• Vitamin B_{12} deficiency	CD	01
Acute painful 'red eye'	*UC*	*03*

Colonospic findings

Macroscopic appearance

- Suggestive of UC — 43
  4-proved to have CD on histology.
  1-had indeterminate colitis on histology gaving features of both CD & UC: later proved to be having CD.
- Suggestive of CD — 11
  Histology correlated well with endoscopic appearances in all.
- Normal — 07
  5-biopsy showed evidence of non specific colitis
  1-small bowel enema showed evidence of CD
  1-an exploratory laporotomy showed evidence of CD
- Not done — 08
- Additional features

Pseudopolyposis	05
Cobblestone appearance	02
Backwash ileitis	01
Malignancy in patients who were screened for colorectal cancer	00

- Extent of involvement

Recto-Sigmoid region - 4 proved to have CD on histology	23
Total colitis - all had UC	07
Variable extent - all had UC	31
Total	61

Histology

Suggestive of UC	25
Suggestive of CD	15
Suggestive of Non specific colitis	14
Indeterminate (had features of both CD & UC)	01
Normal -	06
Not done	08
Total	69

Endoscopic surveillance to detect colo-rectal cancer

Total number of patients under surveillance 09

	Disease duration (years)	No.
UC	10	02
	11-20	04
	31-30	01
	Comment: No evidence of malignancy detected.	
CD	10	01
	11-20	01
	Comment: Dysplasia was found in one biopsy in the patient having the disease for 10 years.	

Laboratory parameters used to monitor activity

Investigation (Ix)	Number of patients who had the Ix done at least over 5 times	Correlation between the Ix & symptoms	
		Correlated	*Un-correlated*
ESR	64	UC33, CD5	UC16, CD10
CRP	60	UC5, CD17	UC35, CD3
Plasma Viscosity	30	UC8, CD4	UC10, CD8
Platelet Count	35	UC10, CD5	UC14, CD6

Treatment profile

Medical	Nos.	
5-ASA Derivatives		
• Sulphasalazine	07	
• Mesalazine	46	
• Olsalazine	03	
Total	56	
Steroids alone	00	
Steroids +5-ASA Derivatives	30	
Azothiaprine	09	
Questran (in a CD patient having terminal ileal disease)	01	
None	10	
Elemental diet	02	*(both had CD which included a pregnant patient)*

Note:

Complications of medical treatment resulting in discontinuation of therapy with

1. *Sulphasalazine*
   - Neutropenia in one patient, needing Granulocyte Colony Stimulating Factor (GCS-F) for treatment.
   - Oligospermia in one patient who complained of subfertility.
2. *Mesalazine*
   - Nausea, vomiting and worsening of diarrhoea in 2 patients.
3. *Azothiaprine*
   - Acute pancreatitis in one patient.
   - Bone marrow depression in one patient.
4. *Steroids*
   - Osteopenia and vertebral collapse with paraplegia in one patient.
     (diabetes mellitus was found in 9 steroid recipients causing management difficulties)

Surgery

Nature of surgery	No.	Disease
Limited Ileal resection	04	CD
Total Colectomy	04	UC-one had toxic dilatation of colon.
Left Hemicolectomy	06	UC
Ileo-Anal Pouch construction	03	UC-one had 'pouchitis'.

Comment: All 4 patients who had undergone total colectomy were not offered the treatment options either with Azathioprine or intravenous Cyclosporine A.

Discussion

Although the aetiology of IBD still remains largely unknown, an immunological insult to the gastrointestinal mucosa is favoured[1,2,3]. The impact of smoking seems to be different in the two situations. The smoking seems to be protective against UC[4] whereas the relapse rate is increased in smokers having CD[5]. In the series the rations of smokers: non-smokers were 11:29 and 13:06 for UC & CD respectively. Smoking habits were undocumented in 10 instances. For UC the incidence in the USA and Europe is between 5 & 8 new cases 100,000 population per year. The figure will vary depending on whether the patients with proctitis are included or not. The prevalence of the disease is about 80-90 cases per 100,000 population. CD is a less common than UC. In Northern Europe the incidence is about 2.0 - 4.5 per year with a prevalence rate of 35-45 per 100,000 population respectively. CD seems to be rare in the Indian subcontinent although those who are migrating to Europe or the USA appear susceptible to the disease. In North American blacks the incidence of IBD is probably about 20-30% less than that of the white population. In the series analysed, all patients were exclusively of British origin. The peak age of onset for both diseases is about 20-40 years. In our patients it was difficult to evaluate the exact age of onset of a disease from the case notes but 33 patients were within 41-60 year age group: i.e. - 48%. Only 28 patients were in the age group 20-40 years. i.e. - 41%. As children were not included in the series and owing to the difficulty of finding the age of onset from the case notes, on firm conclusions could be drawn from the study. It is also speculated that there is a secondary peak of onset in the elderly.

Familial clustering of IBD is well documented. If both parents are having such a condition, the children are at a very high risk of developing the disease. 12 out of 33 children born to 19 couples[6]. In one series concerned, 8 out of 47 patients having UC and 5 out of 22 patients having CD gave a positive family history of some sort of 'bowel disease', but specification was poor. The evaluation of case notes revealed that no attempts were made to categorize the nature of the family history of 'bowel disease' any further either in the wards or the clinics. This is most probably attributable to the busy working background found in a District General Hospital in the UK. The pedigree analysis in UC had revealed the presence of a rare single gene with incomplete penetrance of about 20% which may cause the disease[7] and yet to be identified. The proposed genetically altered intestinal permeability predisposing to CD which was shown with one marker (PEG 400) was not demonstrable with other permeability markers[8].

As IBD encompass a spectrum of clinical features the initial presentation may be to the physician. In our series one patient having a right iliac fossa (RIF) mass had presented to the gynecologist as a pelvic lump where an exploratory laporotomy was needed for the precise diagnosis. 2 patients having CD had presented to the surgeons simulating acute appendicitis, once again only surgery revealing the true nature of the pathology. They may also present to the rheumatologists with an arthropathy (n=5 in the series), to the dermatologists (n=1 in the series) or to the ophthalmologists with a painful 'red eye' (n=3 in the series). Abdominal pain is yet another symptom where they will be referred to the surgeons first by the general practitioners. In our series 5 patients had presented with the said symptom alone (UC-1, CD-4) where they had been screened by the surgeons initially, subsequently referring to the

physicians. The peri-anal complications had compelled 7 patients to see the surgeons initially, all of them having CD. In addition there were 2 intestinal obstructions, one intestinal perforation complicating CD and 2 toxic megacolons complicating UC, in the series. Unless special attention is paid to the possibility of IBD the aetiology in such cases could be easily missed thus resulting in many diagnostic and therapeutic problems, when they could rarely be the presenting features. Acute dilatation is said to occur in about 10% of severe attacks. This was only about 3% in our series, i.e. 2 out of 69. Even with a severely inflamed colon, perforation is said to be uncommon and is often associated with acute dilatation but can occur in isolation. The two patients who had intestinal obstruction were having CD and the classical signs of perforation and peritonitis may be absent or even delay, especially if the patient had been on steroids. The absence of free air in the peritoneal cavity does not exclude the possibility of perforation.

The symptoms of CD are highly variable depending on the side involved. Diarrhoea occurs in 70-90% of the patients but rectal bleeding occurs only in about one third. In the series about 64% of patients having CD had presented with diarrhoeas but only one patient has had rectal bleeding per se. About 10% of the patients with CD have been said to present as acute appendicitis where the real pathology would be an acute ileitis. However long term follow-up studies have shown that the majority of such patients do not relapse and therefore either yerseniosis or a viral aetiology had been responsible for the acute event. Never the less a handful of such patients will reveal a history of intermittent symptoms in the period preceding the acute attack. The variability in bowel habits may be attributed to irritable bowel syndrome (IBS), if bleeding and the constitutional symptoms are absent with normal laboratory parameters of activity, a state of affairs which is not rare to occur.

Roughly one third of all patients with IBD will suffer from at least one of the wide spectrum of extra-intestinal manifestations. Rarely they may precede the development of the gastro intestinal symptoms and in a minority may be the presenting feature. These may be (a) related to the activity of the disease, (b) unassociated with the activity or (c) may arise as a complication of small intestinal involvement and/or resection. Pyoderma gangrenosum (n=1 in the series) and erythema nodosum (n=2 in the series), are the most important skin manifestations reported to be experienced by 2-10% of the patients. Pyoderma is usually more resistant to medical therapy than erythema nodosum and a colectomy may be essential to control the skin lesion. With regard to arthropathy only one patient having CD had ankylosing spondylitis. In contrast to its sporadic type, the incidence of HLA-B27 positivity in such cases is about 75%. The clinical course of spondylitis is completely independent of the severity, extent or the duration of the IBD. Sacroilitis (n=1 in the series) may be asymptomatic and neither will progress to ankylosing spondylitis nor associated with HLA-B27. 3 patients having UC had a peripheral arthropathy which is associated with active disease. Non-steroidal anti-inflammatory drugs should be used cautiously and are best avoided if possible as they may aggravate the colitis. Sclerosing cholangitis was a complication seen in one patient having UC. This association has described in editorials[9] as well, in addition to the observations made. Furthermore, a strong HLA (Human Leucocyte Antigen) association had been described with sclerosing cholangitis[10]. Strong associations with ANCA (Anti Neutrophil Cytoplasmic Antibodies) and sclerosing cholangitis with and without IBD and ulceration per se had also been described[11]. It is now recognised that the disorders of pericholangitis, chronic active hepatitis, primary sclerosing cholangitis and cholangiocarcinoma all represent parts of a spectrum of one single hepato-biliary disorder which is primary sclerosing cholangitis. There is an 10 to 20 fold increase in developing a cholangiocarcinoma in patients with UC. The incidence of bile duct carcinoma too is increased. The iron deficiency was the commonest nutritional deficiency found affecting 9 and 3 patients having UC and CD respectively; i.e.=17%. In one patient having CD it was the major presenting feature. The ESR (Erthrocyte Sedimentation Rate) and the CRP (C-Reactive Protein) were the commonest laboratory indices used to assess the activity of the disease, 64 and 60 respectively, in the series. There was no consistent relationship observed between them. The ESR was done on 64 patients and only 38 showed a consistent relationship to the symptoms which included 33 & 5 UC and CD patients respectively.

The CRP was done in 60 patients were there were 22 patients showing a consistent relationship with the symptoms encompassing 17 & 5 CD and UC patients respectively. As observed in other studies the CRP gave a better index of activity than the ESR in patients having CD and vise versa. Both the plasma viscosity and the platelet count showed inconsistent relationship with the symptoms. It is now been more generally accepted that those indices reflect the severity of the symptoms rather than necessarily the activity[12].

Endoscopic assessment was done in 61 patients, in 8 the diagnosis was known at the time of presentation. It was evident that the macroscopic appearances of the mucosa at endoscopy could be quite misleading at times. 5 patients who enabled as having UC at endoscopy were in fact found to have CD on histology, subsequently. There was a remarkable accuracy of correlation between the endoscopic appearance and histology with regard to CD. All 11 patients who endoscopically appeared as having CD were subsequently confirmed by histology. 5 patients out of 7 whose mucosa appeared normal on endoscopy, in fact had evidence of non-specific colitis. The recto-sigmoid region was affected in 23 total colon in 7 and to a variable extent in 31 respectively, who were endoscopically thought to have UC. 4 patients who had recto-sigmoid involvement were proved to have CD on histology. These findings reflect that the initial impression at endoscopy could be quite misleading and therefore biopsies should be taken for histology always to avoid pitfalls in the diagnosis and management. It was also clear that the endoscopic appearances always do not correlate with the mucosal activity as 7 normal looking mucosae had evidence of non-specific colitis in 5 and normal histology reports in 6 who were thought to have IBD. The reasons for the latter observation could be (a) inadequate exploration (b) inadequate biopsy samples (c) patients in remission & (d) use of topical steroids by the general practitioners prior to hospital consultation thus altering the mucosal activity. The criteria used in the GETAID French multi-centre assessment to quantify the endoscopic appearances may be helpful in defining the endoscopic end points in clinical trials, although there was in fact, surprisingly little change between, before and after a clinically effective course of corticosteroids[13].

Screening for colo-rectal cancer in patients having extensive or total colitis for a long period plays an important role in the management of IBD. The risk of developing severe dysplasia or colorectal cancer in such patients having the disease more than 10 years duration is about 0.5% per year. As such one leading article described screening for colorectal cancer in UC is of dubious benefit at a high cost[14]. In the series concerned there were altogether 9 patients who were screened annually for colo-rectal cancer, having the disease for more than 10 years duration (UC:CD = 7:2). Only one biopsy had shown evidence of dysplasia in a patient having CD for 10 years, resulting in surgery. In a Scandinavian study it was shown that the cumulative risk of developing, at least a low grade dysplasia was estimated at 14% after 25 years from the onset of the disease[15]. This was reconfirmed by a US study[16]. In there series, Nugent et al.[17] concluded that the returns beyond the initial screening are small. Patients in whom CD developed before the age of 30 years had a much higher relative risk (20.9), than those diagnosed at an older age (2.2)[18] of developing a colo-rectal cancer.

With respect to drug therapy the vast majority was on 5-aminosalycilate (5-ASA) compounds; i.e = 81% (sulphasalazine : mesalazine : olsalazine = 7 : 46 : 3). Sulphasalazine is an established proven cost effective treatment for mild to moderate exacerbation of UC & CD and for the maintenance of remission in UC. The carrier component – sulphapyridine is responsible many of the side effects of sulphasalazine including headache, nausea, vomiting, skin rashes and subfertility in men[19]. In the series it has caused serious neutropenia in one patient and oligo-spermia in yet another patient, both receiving treatment for UC. Mesalazine was the most fashionable 5-ASA drug used (n=46). The role of 5-ASA in the maintenance therapy in CD is not yet clearly established. Nevertheless 15 CD patients were on continuous therapy even though they were in remission. Perhaps it may benefit a sub group of patients. In this regard, a study where a group of CD patients in remission who were given 5-ASA 0.5 g tds, compared to a placebo over 12 months showed no major differences except for a reduction in relapse rates, particularly in those with ileal disease[20]. Similar results were obtained in a series of 161 patients with inactive CD taking 5-ASA (Pentasa) 2 g daily, over 2 years compared with a

placebo[21]. In contrast no patient in the series having CD had been prescribed Pentasa – a slow release 5-ASA compound. Serious nephrotoxicity following ingestion of 5-ASA compounds has been reported in 9 patients in the UK[22], the mechanism of which remains unknown at present. The vast majority of patients in the series had tolerated the 5-ASA compounds very well without much side effects. On present evidence the newer 5-ASA compounds should minimize the nephrotoxic risk and have become the trend of practice as evident from the data. There have been several excellent summaries of published clinical trials of the new 5-ASA therapy, recently[23,24].

Elemental diet had been used in the management of CD during acute exacerbations. In the series 2 patients; one 28 year old female with a 22 weeks old pregnancy and a 30 year old male, who were having gastrointestinal intolerance to other drugs were treated successfully with elemental diets to induce remissions. Elemental diets have been proved to be as effective as prednisolone[25] when given over a few weeks to the patients with active CD. The problems associated with this approach are the poor compliance, relapse on stopping the diet and the high cost. Unfortunately there are no published controlled clinical trials with combination therapy of steroids and elemental diets. A critical review of the dietary and nutritional management of CD has been published recently[26].

Corticosteroids therapy had caused serious problems in one patient resulting in severe osteopenia, vertebral collapse and spastic para paresis. 9 patients receiving steroids were also found to have diabetes later adding problems to the management. Steroids were withdrawn in the former case. Azathioprine was the sole immunosuppressive agent other than steroids which was used to treat the patients in the series. 9 patients were on azothiaprine therapy and was withdrawn in due to side effects leaving 5 & 2 CD and UC patients respectively on the drug. The role of immunosuppressive agents in IBD has been reviewed[27]. The results of the full survey of the New York experience of the toxicity of 6 mercaptopurine, the active metabolite of azothiaprine has been published[28]. The most common side effects were pancreatitis (3.3%), bone marrow suppression (2.2%), allergy (2.0%) and infections (7.4%) of which a quarter were severe. The two patients in the series aforementioned developed acute pancreatitis and bone marrow suppression respectively, resulting in withdrawal of the therapy. The use of azathioprine seems to be safe during pregnancy with delivery of normal children[29]. In our series there were 3 CD patients on azothiaprine therapy who were in the child bearing age. The long term use of azathioprine in IBD has not been associated with increased incidence of malignancies when compared its use in other conditions according to paper published by St. Marks hospital in London, recently[30], which encourages its use in IBD. Cyclosporine A had also been found useful in steroid resistant or dependent CD patients[31], improvement occurring within 2 weeks of treatment. The use of intravenous Cyclosporine A has been recommended in the management of severe UC, resistant to high dose steroids, where it was thought to induce a remission in about a week[32]. In addition Cyclosporine A enemas have been shown to be beneficial in the treatment of resistant severe distal UC as well[33,34]. There were 4 cases of refractory UC including a case of toxic megacolon, in the series ending up with total colectomies who were not offered the option of treatment with either azothiaprine or cyclosporine A at any point of their illness which may have had helped to salvage their colons. The same observations were applicable to the three patients who had ended up with ileo-anal pouch construction.

Limited ileal resection had been offered to 4 patients having CD. The present situation with regard to surgery in CD has been well summarized by Alexnder-Williams[35]. A European muliti-centre study comparing radical and conservative resections for CD has shown that conservative resections are associated with a lower recurrence rate. The recurrence rate was even lower after treatment with sulphasalazine 3 g daily for 2 years. This was the first study to suggest that 5-ASAs may have some effect in reducing the recurrent disease following resection for CD, contrary to the earlier belief[36]. Although no children were included in the study it has been shown that the outcome of surgery for CD in childhood with respect to symptom relief and growth, had been good for those who had undergone ileo-caecal resection that those who had a subtotal colectomy with ileostomy[37]. The surgical alternatives for surgical treatment of UC have been reviewed recently[38]. 13 patients in the current series having

UC were offered surgical treatment. Total colectomy in 4 patients, 3 ending up with ileo-anal pouches with ileo-rectal anastomoses and left sided hemicolectomy in 6 patients. The outcome for UC treated by ileal pouch- anal anastomosis seemed to be encouraging in a study comparing 758 colitics and 94 having familial adenomatous polyposis, undergoing the same operation. Patients undergoing surgery for UC had rather more day time stools (mean 5.8 daily) more nocturnal faecal spotting (40%) and more instances of pouchitis[39]. The pouchitis usually responds well to treatment with metranidazole or co-amoxiclave the only patient in the series having pouchitis was satisfactorily treated with the former drug. A few patients may require topical steroids or 5-ASA compounds for its treatment. Although the age is not an absolute bar, patients under 60 years have the best functional results. The 3 patients mentioned in the series were all between 40-60 years of age and had no major problems pertaining to the function of the pouches. There had been several instances where the pouches were constructed, initially misdiagnosing the patients as having UC, later turning out to be having CD, but continuing having an intact pouch with good results[40]. It has been also found that in patients with UC treated by ileo-anal J pouch, body fat, total body protein and total body water had returned to pre-operative levels within 3 months of surgery[41].

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