Original Paper

Microscopic Colitis- Its Prevalence and Characteristics in Diarrhoea Predominant Irritable Bowel Syndrome- A Study of 100 Cases

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Abstract

Introduction: Irritable bowel Syndrome (IBS) is a functional disorder of abdominal pain or discomfort associated with altered bowel habit. Microscopic colitis is a chronic inflammatory condition associated with non bloody diarrhoea and characteristic histological finding. The subset of diarrhoea predominant IBS is having similarity in presentation with microscopic colitis.

Objective: To assess the prevalence and characteristics of microscopic colitis in Diarrhoea predominant Irritable Bowel Syndrome (IBS-D).

Materials and Methods: This observational study was conducted at the department of Gastroenterology, Combined Military Hospital, Dhaka during the period of January 2011 to June 2011. Initially 100 cases of diarrhoea predominant IBS who met Rome III criteria were included. Among those 100 cases, 57 were male and 43 were female. Mean age was 46 years ±2.8 SD(range 18-72). Six patients were subsequently excluded because of some macroscopic abnormalities at colonoscopy. Finally 94 patients of clinical IBS-D whose colonoscopy were normal, biopsy specimens were taken from caecum, transverse colon, descending colon, sigmoid and rectum. Microscopic colitis was diagnosed on the basis of evidence of increased intraepithelial lymphocytes of ≥20/100 inter cryptal epithelial cells and infiltration of lamina propria by mixed inflammatory cells. Overlap of other symptoms between Microscopic Colitis (MC) and IBS-D were also evaluated.

Results: Among the 94 patients of clinical IBS-D, 23(24%) patients were histologically proved to have microscopic colitis. Besides Rome III criteria, there was significant overlap of other symptoms. Occasional fever and infrequent arthralgia 7% and 26% vs 4% respectively) but tenesmus, passage of excessive mucus and heart-burn were more prevalent in IBS-D than MC (35% vs 13%, 32% vs 4% and 32 vs 9% respectively). Among the 23 cases of MC, 13(57%) patients were female and 10(43%) patients were male. Mean age of microscopic colitis was 56 years ±2.6 SD (range 25-72). Regarding subtypes of microscopic colitis, 21(91%) patients had lymphocytic colitis (LC) and 2 (9%) patients had collagenous colitis (CC). Of the lymphocytic colitis 11 were female and 10 were male and of the 02 cases of collagenous colitis all were female. MC affected mostly the transverse colonie 11(48%) cases and the next common site was caecum ie 8(35%) cases.

Conclusion: A good percentage of diarrhoea predominant IBS are actually having microscopic colitis. MC is more common in female and elderly persons. In all elderly patients of IBS-D full colonoscopy should be done and biopsy should be taken from multiple sites to exclude microscopic colitis.

Key-words: Irritable bowel Syndrome (IBS), Microscopic Colitis (MC), lymphocytic colitis (LC), collagenous colitis (CC).

Introduction

Microscopic colitis(MC) is a common cause of chronic diarrhea without blood and is often accompanied by abdominal pain[1–5]. It accounts for 2%-16% of patients with chronic diarrhoea[6]. One recent study suggest that microscopic colitis now represent up to 20% of cases of diarrhoea predominant Irritable bowel Syndrome (IBS)[7]. Initially the disease was seemed to be more common in women than men, but recent data have shown no significant difference in prevalence in the sexes[8]. It is now considered to be a new form of idiopathic inflammatory bowel disease[9]. Clinical manifestations are substantially milder than

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other form of idiopathic inflammatory bowel disease. Here blood tests are normal, no signs of malabsorption, normal microbiology and radiology[10]. The mucosa appears grossly normal or nearly normal at colonoscopy. In the presence of appropriate clinical symptoms, the diagnosis of microscopic colitis is made histologically, based on the presence of intraepithelial lymphocytosis and a mixed inflammatory infiltrate in the lamina propria[11]. Microscopic colitis includes two primary subtypes: collagenous and lymphocytic colitis. They are similar clinically and histologically but are distinguished by the presence or absence of a thickened sub-epithelial collagen band[12]. Increased recognition of microscopic colitis in recent years is likely due to increased awareness of its existence, so that gastroenterologist routinely take biopsy with endoscopically normal appearing colon. The presence of histopathological changes diffusely throughout the colon has been described but it may be limited to the transverse colon or right colon. MC typically present in the sixth and seventh decades of life, but it has been reported in all age groups, including children[12]. There are very limited studies on microscopic colitis in this subcontinent to see its prevalence and disease pattern.

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder encountered both by primary care and gastroenterological practice. IBS is defined as a functional bowel disorder presented with abdominal pain or discomfort and associated with altered bowel [13]. IBS affects approximately 20% of the adults and adolescent, account for about 12% of general practioners visits and about 40% of referrals to gastroenterology consultation. It is 1.5 times more common in women. There is no biologic, anatomic or physiologic marker for IBS, and, if performed colonoscopy and biopsy, these remains unremarkable[13]. The diagnosis is therefore symptom-based and experts have developed criteria for the diagnosis of IBS. The Manning, Rome I, II and III criteria are widely used to identify IBS patients in research studies[14]. However, the usefulness of these symptom-based criteria in the clinical setting is uncertain. There is increasing evidence that at least a subset of IBS patients have some sort of organic gastrointestinal basis and regarding treatment only symptom base therapy is not the solution rather some disease modifying therapy is required. The prevalence of IBS in North America is approximately 10%–15% or 100 times more common than microscopic colitis[15].

Microscopic colitis and IBS have similar symptoms and endoscopic appearance, and both have a substantial negative impact on quality of life. The quality of life of patients with microscopic colitis correlates directly with the degree of diarrhea and incontinence[16.] IBS is associated with significant emotional distress, impaired health-related quality of life, and high health care costs. The number of studies regarding diagnosis of microscopic colitis who present like IBS are not very large in the world. Many cases of microscopic colitis are being missed in the coverage of irritable bowel syndrome. So it requires to investigate properly to rule out microscopic colitis especially in diarrhoea predominant irritable bowel syndrome because of potentially different treatments for each disorder.

Materials and Methods

This observational study was conducted at the department of Gastroenterology, Combined Military Hospital, Dhaka Cantonment, Dhaka during the period from January 2011 to June 2011. Patients presented with chronic non bloody diarrhoea, abdominal pain, or discomfort who met Rome-III criteria for IBS, were initially selected for the study. One hundred patients were selected for the study.

Inclusion criteria:

a. Age 18 years and above

b. Patient fulfilling Rome III criteria for diagnosis of IBS with diarrhoea predominant

c. Willing to undergo colonoscopy and biopsy

Exclusion criteria:

a. Alarm features like weight loss, dysphagia, blood in stool, recurrent vomiting, haematemesis, significant anaemia, abdominal mass

b. Systemic illness like Diabetes mellitus, Hyperthyroidism

c. Lactose intolerance

d. Prior abdominal surgery

e. Patients taking drugs like NSAIDs, cholinergic drugs

f. Elevated ESR and/or CRP

Patients who met Rome III criteria a full evaluation like detailed history, physical examination and routine investigations with full blood count, thyroid function test (eg thyroid stimulating hormone), plasma glucose, stool routine and microscopic examination, faecal fat estimation(qualitative) and X-ray chest PA view were done. All the patients were evaluated for the safety and

possible complication of colonoscopy. After getting informed written consent patients were prepared for full colonoscopy with Mannitol-20% 350 ml taken orally. One hundred patients of IBS-D underwent colonoscopy and biopsy. Six patients had macroscopic abnormalities at colonoscopy. In 94 patients, colonoscopy were macroscopically normal and two biopsy specimen were taken from each of caecum, transverse colon, descending colon, sigmoid colon and rectum. Biopsy specimen were fixed in 10% formalin in separate container and sent for histopathology. Tissue section were stained with hematoxylin and eosin and Massion'strichrome stain. Measurements of the subepithelial collagen layer and count of intraepithelial lymphocytes (IEL) were performed on well oriented biopsies (section perpendicular to the mucosal surface). The number of surface IEL was estimated by counting in every patient (lymphocytes per 100 intraepithelial cells). At least five non-contageous intercryptal spaces including, excluding areas over lymphoid follicles were examined and the mean number of IEL was expressed per 100 epithelial nuclei. The thickness of the subepithelial collagen band was measured with an optical micrometer. MC was considered those who were found to have histologic evidence of increased intraepithelial lymphocytes of >20 cell /100 epithelial cells and mixed lamina propria inflammatory infiltrate. lymphocytic colitis and collagenous colitis distinguished from each other by the presence or absence of subepithelial collagen band of >10μm. Histopathological examination of the biopsy specimen were undertaken by an expert Histopathologist who was blinded to the patients' underlying symptoms and whether or not they met criteria for diagnosis of IBS.

Colonoscopic findings of clinical IBS-D (n=100)

	Number
dings	94
r	01
yp	01
lyp	01
er	01
moiditis	02

Table-I shows out of 100 patients of clinically diagnosed as IBS-D, 06 cases were found to have some macroscopic abnormalities at colonoscopy and finally 94 patients had normal colonoscopic finding at least macroscopically.

Table-II: Histologic findings of clinically diagnosed IBS-D (n=94)

Histological Findings	Frequency	Percentage
Normal histology	65	69.14
Microscopic colitis	23	24.46
Nonspecific colitis	06	6.38
Total	94	100

Table-II shows that, out of 94 patients of diagnosed IBS-D, 23 patients met the histologic criteria for Microscopic colitis. Among the remaining IBS-D patients were 71 cases where normal histology were found in 65(69.14%) patients and 06 patients had non-specific colitis.

Table-III: Rome III criteria overlaping MC and IBS-D

Symptoms	MC(n=23) Number(%)	IBS-D(n=71) Number(%)	p Value
Pain or discomfort	23(100)	71(100)	<0.001
Relieve with defecation	13(56.52)	68(95.77)	<0.001
Change in stool frequency	23(100)	71(100)	<0.001
Change in form of stool	18(78.26)	47(66.19)	<0.050

Table-III shows that the among the component of Rome III criteria, abdominal pain or discomfort were associated with increased stool frequency in 100% cases of IBS and MC. Abdominal pain was associated with change in form of stool was in 78% cases in MC but 66% cases in IBS-D and pain relieved with defecation in 56% cases in MC and 96% cases of IBS-D.

Table-IV: Symptoms other than Rome criteria overlap MC and IBS-D

Symptoms	MC (n=23) number(%)	IBS-D (n=71) number(%)	p value
Occasional fever	11(47.82)	05(7.04)	<0.001
Infrequent arthralgia	06(26.08)	03(4.22)	<0.001
Abdominal bloating	14(60.86)	21(29.57)	0.02
Abdominal distension	12(52.17)	22(30.98)	0.10
Passage of excessive mucus	01(4.34)	23(32.39)	0.01
Incomplete evacuation	03(13.04)	25(35.21)	0.001
Heartburn	02(8.69)	23(32.39)	0.01
Headache	01(4.34)	25(35.21)	0.01

Table-IV shows that all above symptoms except headache and infrequent arthralgiawere present in significant numbers in both IBS-D and MC. Infrequent arthralgia was present in 26 % cases of MC and 4% cases of IBS-D. Headache was more prevalent in IBS-D ie in 35% cases. Abdominal bloating and distension were present in both the condition with insignificant difference in p value. Occasional fever and infrequent arthralgia were more prevalent in MC and incomplete evacuation was more prevalent in IBS-D.

Table-V: Subtypes of Microscopic colitis (n=23)

Disease	Frequency	Percentage
ymphocytic colitis	21	91.30
ollagenous collitis	02	8.69

Table-V shows the subtypes of microscopic colitis. Lymhocytic colitis were much more (ie 91.3%) than collagenous colitis (ie 8.69%) with a ratio LC:MC= 11:1.

Table-VI: Age and Gender distribution of Microscopic colitis(n=23)

	Age Group Distribution			Gender Distribution	
ars	18-30	31-50	51-72	Male	Female
ber	01	07	15	10	13
entage	4.34	30.43	65.20	43.47	56.52

In table-VI we find microscopic colitis mostly affected the age group of 51-72 years(65.20%) and next involved age group is 31-50 years (30.43%). The mean age of microscopic colitis we found 56 years ± 2.6 SD (range 25-72). Among the gender distribution female were affected little more than male by mircocopic colitis ie(56.52% vs 43.47%).

Table-VII: Gender distribution in the subgroup of Microscopic colitis(n=23)

	Lymphocyticcolitis (n=21)		Collagenouscolitis (n=2)	
	Male	Female	Male	Female
uency	10	11	00	02
entage	47.61	52.38	00	100

The Table-VII shows that the gender distribution in case of lymphocytic colitis were almost nearer ie a bit more common in female than male (52% vs 48%). But in case of the collagenous colitis, all were female (ie 100%).

Table-VIII: Segmental distribution of Microscopic Colitis (n=23)

ment of the colon involved	Frequency	Percentage
um/ascending colon	08	34.78
nsverse colon	09	39.13
ending colon	04	17.39
moid colon	02	8.69
um	00	00

The above table-VIII shows that, microscopic colitis most commonly affected the transverse colon (47.82%), second common site of involvement was caecum/ascending colon (34.78%) third and fourth common site were descending colon and sigmoid colon respectively. Rectum was not involved in any cases. So it had a relative order of involvement from proximal to distal colon.

Discussion

Irritable bowel syndrome is one of the most common causes of chronic non bloody diarrhoea. Microscopic colitis is now also considered as one of the important cause of chronic non bloody diarrhoea. Pathophysiology of both the diseases are not yet completely understood. As having similarities in presentation, only biopsy from colon can exclude the microscopic colitis.

In this study patients with chronic watery diarrhoea who met the Rome III criteria for diagnosis of irritable bowel syndrome demonstrated a good percentage that is 24% of these were actually microscopic colitis. So this significant amount of microscopic colitis patients had symptomatic overlap with irritable bowel syndrome. Besides Rome criteria other symptoms like bloating, abdominal distension, heartburn and fever were present in both the condition. In another study of 132 patients who had undergone colonoscopy for chronic diarrhoea and abdominal pain lymphocytic and collagenous colitis were found in 21(16%) and 7(5%) of patients respectively[17]. Tuncer C et al conducted one study of 30 patients with IBS found 23.3% with lymphocytic colitis and none had collagenus colitis. So far one study conducted in our country comprising 60 patients of IBS-D found 36% were proved histologically to be microscopic colitis and none was collagenous colitis[18]. Most of the world studies shows among Rome criteria based IBS 10-25% cases are supposed to be microscopic colitis.

Regarding subtypes of MC, present study revealed out 23 cases 21 were lymphocytic colitis and only 2 were collagenous colitis (LC:CC=10.5:1). So lymphocytic colitis are much commoner than collagenous colitis. Fernandez-Banares et al in a study showed that the incidence of lymphocytic colitis is three times higher than that of collagenous colitis[4]. In a Turkish study comprising 129 patients with chronic non-bloody diarrhoea revealed Lymphocytic colitis in 12(9%) patients (female 7 and male 5), mean age was 45 years (range 27-63) and collagenous colitis were in only 3(2.5%) patients all were female with mean age 60 years (range 54-65). In that study lymphocytic colitis were 4 times more common than collagenous colitis[19]. Studies from Iceland showed sex ratio of microscopic colitis as female:male=5:1 and it is 2:1 from Iceland study[20]. Marshall et al encountered 13 lymphocytic colitis and 1 collagenous colitis in their 111 patients of chronic diarrhoea with unexplained etiology[21].

In another study of 132 consecutive patients who had undergone colonoscopy for chronic diarrhoea and abdominal pain, lymphocytic colitis and collagenous colitis found in 21(16%) and 7(5%) of patients respectively[17].

In this study, the mean age of patients of microscopic colitis was 56 years±2.6 SD (range 25-72), with about 57% female and about 43% male. So it revealed that, MC predominantly affect after the age of 50 years. In western countries microscopic colitis develop more in six decade and older. In this study older age population were less in number, as median age was 48 years (range 18 to 72) because of relatively less life expectancy in our countries than those of western countries and female patients were found to have less interest in colonoscopy One Turkish study conducted with 138 patients of diarrhoea predominant IBS with mean age 34.7 years (female 55% and male 45%), identified 13(9.4%) patients with microscopic colitis[19].

In the present study regarding gender difference, in case of 21 lymphocytic colitis 11 were female and 10 were male (56.52% vs 43.48%) and in cases of 2 collagenous colitis all were female. So lymphocytic colitis affected female a little more but collagenous colitis had female preponderance. World literatures shows, microscopic colitis are having a female predominance, and it has been described particularly for collagenous colitis, with female to male ratio to be as high as 20:1. The gender difference for lymphocytic colitis is less striking than for collagenous colitis in some studies. In this study female included less in number than male, if more female would be included the ratio might be more different. And if the study can be increased with large number of patients the chance of male patients of collagenous colitis will increase.

Regarding distribution of microscopic colitis in the colon, out of 23 cases, it was found to be 9(39.13%) cases in the transverse colon, 8(34%) cases in the caecum/ascendingcolon and 4(17.39%) cases in descending colon and 2(8.69%) cases in sigmoid colon. As per area is concern MC affected right side (caecum to splenic flexure) in 19(82.60%) cases, and only right side in 16(69.56%) cases and isolated left colon involvement (splenic flexure to rectum) were only in 4(17.39%) cases and 13% had diffuse involvement and rectum was not involved in any case. It can be said from this study that patchy involvement is much more than diffuse involvement and right side of the colon is mostly affected. So for diagnosis of microscopic colitis, biopsies are required from multiple sites of the colon that is definitely from caecum and transverse colon and also from left colon. Here if only sigmoidoscopy would done, it would miss the 16 cases out of 23 cases of microscopic colitis. So it is the colonoscopy, not sigmoidoscopy should be done to exclude MC. In comparison to other studies, the presence of histological changes diffusely throughout the colon has been described in different studies, but may be limited disease as well. Some reports have suggested that in microscopic colitis the histological abnormalities are not distributed evenly throughout the colon, but may be located mainly in the right and transverse colon. Another study reports that in 40% of patients, the diagnosis of microscopic colitis would be missed if sigmoidoscopy would have been performed instead of colonoscopy, implying that sigmoidoscopy is insufficient for diagnosis of this disease. Thijs WJ et al found 13 cases of microscopic colitis out of 103 patients, the distribution were diffuse through the colon in 10(77%) and restricted to the right colon in 3(23%) patients[22]. In that 3 patients of right colon MC, diagnosis would have been missed if only sigmoidoscopy had been performed[22.] Macintosh et al obtained rectal biopsy in 89 patients with IBS and found no significant pathologic findings. They concluded that patients with normal colonoscopy and diagnosis of IBS, were unlikely to have histologic abnormalities in the rectum and rectal biopsies are unnecessary in the investigation of IBS[23]. In this study, MC was also more common in the right side of the colon which is almost equivalent to World literature.

A subgroup of IBS patients develop symptoms after an episode of enteric infection[24]. Post infectious irritable bowel syndrome (PI-IBS) patients have been found to have increased enterochromaffin cells and lamina propria T-lymphocytes on rectal biopsy[25]. One study shown that PI-IBS patients did not have an increase in IEL,8.2 IEL/100 epithelial cell, with control 8.6 IEL/100 epithelial cells) and no patients met histologic criteria for MC. Another study noted a minor increase of IEL in patients with PI-IBS following Camphylobacter enteritis (2.5/100 epithelial cell) but this increase declined over 12 weeks period to 0.9/100 enterocytes. Another study found, no significant increase in IEL in PI-IBS (9.6/100 epithelial cells versus 6.7/100 epithelial cells in controls)[25].

Conclusion

IBS is a relatively common disease and diagnosed mainly by symptom based criteria with exclusion of organic causes. In the process of exclusion, colonscopy should be included. This study demonstrates that 24% of patients of diarrhoea predominant irritable bowel syndrome were diagnosed to have microscopic colitis, though they were having normal colonoscopic appearance. Proximal colon ie caecum to splenic flexure are affected mostly by microscopic colitis. Therefore it is clear that symptom based criteria are not sufficient enough for the diagnosis of irritable bowel syndrome. In all diarrhoea predominant IBS patients full colonoscopy, not the sigmoidoscopy and biopsy especially from caecum and transverse colon are required to exclude the presence of microscopic colitis at least if the disease is not controlled by symptomatic therapy.

References

1. Pardi DS, Ramnath VR, Loftus EV Jr et al. Lymphocytic colitis: Clinical features, treatment and outcomes. Am J Gastroenterol 2010; 97:2829–33.

2. Bohr J, Tysk C, Eriksson S et al. Collagenous colitis: A retrospective study of clinical presentation and treatment in 163 patients. Gut 2006; 39:846–51.

3. Baert F, Wouters K, D'Haens G et al. Lymphocytic colitis: A distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis. Gut 2009; 45:375–81.

4. Fernandez-Banares F, Salas A, Esteve M et al. Collagenous and lymphocytic colitis: Evaluation of clinical and histological features, response to treatment, and long-term follow-up. Am J Gastroenterol 2003; 98:340–7.

5. Olesen M, Eriksson S, Bohr J et al. Lymphocytic colitis: A retrospective clinical study of 199 Swedish patients. Gut 2004; 53:536–41.

6. Fernandez-Banares F, Salas A, Forne M et al. Incidence of collagenous and lymphocytic colitis: A 5-year population-based study. Am J Gastroenterol 1999; 94:418–23.

7. Cross A, Treanor D, Keegan D et al. 'Microscopic colitis: Increased incidence or increased recognition?', Gastroenterology 2002; 122(4A):602-3.

8. Bohr, Tysk C, Eriksson S et al. 'Collagenous colitis: A retrospective study of clinical presentation and treatment in 163 patients,' Gut 1996; 39(96):846-51.

9. Marijana P, Njejica J, Daniela B et al. 'Mechanism of diarrhea in microscopic colitis', World J Gastroenterol 2005; 11(35):5535-9.

10. Chris JJ, Mulder, Ivar M et al. 'Microscopic colitis'. Folia Gastroenterol Hepatol 2004; 2(2):81-6.

11. Pardi DS. 'Microscopic colitis: An update', Inflamm Bowel Diseases 2004; 10:860-70.

12. Gremse DA, Boudreaux CW, Manci EA. 'Collagenous colitis in children', Gastroenterology 1993; 104(3):906-9.

13. Drossman DA, Camilleri M, Mayer EA et al. AGA technical review on irritable bowel syndrome. Gastroenterology 2002; 123:2108–31.

14. Manning AP, Thompson WG, Heaton KW et al. Towards positive diagnosis of the irritable bowel. BMJ 1978; 2:653–4.

15. Brandt LJ, Bjorkman D, Fennerty MB et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 2002; 97:S7–S26.

16. Mullhaupt B, Guller U, Anabitarte M et al. Lymphocytic colitis: clinical presentation and long term course. Gut 1998; 43:629–33.

17. Gineston JL, Sevestre H, Descombes P et al. Biopsies of the endoscopically normal rectum and colon: A necessity. Incidence of collagenous colitis and microscopic colitis. Gastroenterol Clin Biol 1989; 13:360-3.

18. Rahman A. Symptomatic overlap in patients with diarrhea predominant irritable bowel syndrome and microscopic colitis in a subgroup of Bangladeshi population (Thesis). Dhaka: BSMMU 2009:48-58.

19. Erdem L, Yildrrim S, Akbayir N et al. Prevalence of microscopic colitis in patients with diarrhea of unknown etiology in Turkey. World J Gastroenterology 2008 July 21; 14(27):431-2.

20. Agnarsdottir M, Gunnlaugsson O, Orvar KB et al. Collagenous and lymphocytic colitis in Iceland. Dig Dis Sci 2002; 47: 1122-8.

21. Marshall JB, Singh R, Diaz-Arias AA. Chronic unexplained diarrhea: Are biopsies necessary if colonoscopy is normal? Am J Gastroenterology 1995; 90:372-6.

22. Thijs WJ, Van Barlin J, Kleibeuker JH et al. Microscopic colitis: Prevalence distribution throughout the colon in the patients with chronic diarrhea. Netharlands Journal of Medicine 2005; 63(4):137-40.

23. Macintosh DG, Thomson WG, Patel DG et al. Is rectal biopsy necessary in irritable bowel syndrome? Am J Gastroenterol 1992; 87:1407-9.

24. Quigley E, Fried M, Gwee KA et al. Irritable bowel syndrome: A global perspective. WGO–practice Guideline 2009; 4:1-20.

25. Dunlop SP, Jenkins D, Neal KR et al. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in post infectious IBS. Gastroenterology 2003 Dec;125(6):1651-9.