INFLAMMATION: A PATHOGENIC FACTOR IN THE IRRITABLE BOWEL SYNDROME

SIMONA GRAD[1], DAN L. DUMITRAȘCU[1], PIERO PORTINCASA[2]

[1]Clinica Medicală 2, UMF Iuliu Haţieganu Cluj Napoca Romania
[2]Clinica Medica "A. Murri", Dept Internal & Public Medicine, University Medical School, Bari, Italy

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Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by chronic abdominal pain or discomfort, associated with chance in bowel habits or with features of disordered defecation; in the absence of any organic cause [1]. It is the most commonly diagnosed gastrointestinal condition and comprises 25 to 50 percent of all referrals to gastroenterologists. IBS also accounts for a significant number of visits to primary care physicians and is the second highest cause of absenteeism after the common cold [2].

The pathophysiology of IBS remains uncertain. Hereditary and environmental factors are likely to have a role [3]. Many studies have reported abnormal gastrointestinal motility, visceral hypersensitivity, psychologic dysfunction, and emotional stress in patients with IBS. Despite intensive investigations, the results have often been conflicting and no physiologic or psychologic abnormality has been found to be specific for this disorder.

Microscopic inflammation - detailed immuno-histologic investigation has revealed mucosal immune system activation in a subset of patients with irritable bowel syndrome (mostly those with the diarrhea predominant type) [4,5]. Similar observations have been made in patients with presumed postinfectious IBS, suggesting a possible common link. A study in which full-thickness jejunal biopsies were obtained in 10 patients with severe IBS found an increase in lymphocyte infiltration in the myenteric plexus in nine patients and neuron degeneration in six patients [6]. The extent to which these observations might contribute to the pathogenesis of IBS in the general population remains unclear as only a small number of patients have been studied, most of whom were derived from tertiary referral centers. Other studies have demonstrated a correlation between abdominal pain in IBS and the presence of activated mast cells in proximity to colonic nerves [7,8].

The development of IBS following infectious enteritis has been suspected clinically based upon a history of an acute diarrheal illness preceding the onset of irritable bowel symptoms in some patients [9]. Presence of abnormal bacterial flora in the feces, signs of chronic inflammation in the intestinal mucosa, positive lactulose breath test and beneficial effect of probiotics and antibiotics serve as a proof of the bacterial etiology in postinfectious IBS [10]. Few controlled studies have investigated this topic in detail, but persistent IBS have been noted in approximately 10 to 30 percent of patients after acute bacterial infection [11-14].

The role of chronic inflammation in the pathophysiology of postinfectious IBS underlines in founding of lymphocitic infiltration in the intestinal mucosa and increased inflammatory components in intestinal mucosa and blood (cytokines, mastocytes and serotonin) [15].

Interleukin 8 is an important modulator of the inflammatory process. Its activity is inhibited by its natural antagonist IL 1 RA. The equilibrium between these two cytokines is the one who dictates the biological disponibility of the IL 8 and its contribution to the inflammation. The expression of IL 8 was enhanced during the acute infection and it continued to be increased in the patients who suffered from postinfectious IBS compared to patients who did not develop IBS and presented with decreased level of cytokines after the acute infection [16].

Enteroendocrine cells in patients with postinfectious IBS appear to secrete high levels of **serotonin**. These patients have postprandial increased serotonin levels compared to healthy individuals and patients with IBS with constipation who have normal levels of serotonin after meals [17].

Mastocites have a role in increasing intestinal mucosa permeability - a phenomenon that has been also reported in postinfectious IBS patients. The increased permeability implies a disruption of normal barrier, which allows bacteria to invade in lamina propria and provide a mechanism for chronic inflammation.

Assessing the presence and degree of intestinal inflammation objectively, simply, and reliably is a significant problem in gastroenterology. For assessing intestinal inflammation it can be used immunohistologic

Acceptat în data de: 04.10.2010
Adresa pentru corespondenţă: costinsimona_m@yahoo.com

exam and also **fecal calprotectin** and **fecal lactoferin** as a non-invasive methods.

Calprotectin is a zinc and calcium binding protein that is derived mostly from neutrophils and monocytes with antimicrobial and antiprolipherative activities [18]. It can be detected in tissue samples, body fluids, and stools, making it a potentially valuable marker of neutrophil activity [19]. Initial studies show that fecal calprotectin levels are increased in intestinal inflammation and may be useful for distinguishing inflammatory from noninflammatory causes of chronic diarrhea [20-22]. Other potential roles have also been proposed including in colorectal cancer screening [23-25] and monitoring of activity in inflammatory bowel disease. Normalization of fecal calprotectin seems to be a strong indicator of mucosal healing. Fecal calprotectin values can be used to evaluate the response to treatment, to screen asymptomatic patients [26], and to predict inflammatory bowel disease relapses [27]. Fecal calprotectin correlated closest with Simple Endoscopic Score for Crohn's disease (SES-CD), followed by CRP, blood leukocytes, and the Crohn's disease activity index (CDAI). Furthermore, fecal calprotectin was the only marker that reliably discriminated inactive from mild, moderate, and highly active disease, which underlines its usefulness for activity monitoring [28].

Calprotectin level of greater than 10 mg/L was most useful in the prediction of organic disease with a sensitivity of 89%, specificity of 79%. Elevations in calprotectin and lactoferrin are seen not only in IBD but in other organic gastrointestinal diseases such as diverticular disease, infectious enterocolitis, nonsteroidal antiinflammatory drug (NSAID) enteropathy, and cancer. Stool markers are appropriate, then, as a screening test to determine which patients with gastrointestinal symptoms require further invasive testing as opposed to those with likely IBS or functional disease. This is perhaps most useful in the pediatric patients in whom invasive testing is more difficult to perform; several studies suggest that calprotectin may be useful in this patient group [29].

With a cut off point of 30 mg/l fecal calprotectin has100% sensitivity and 97% specificity in discriminating between active Crohn's disease and irritable bowel syndrome [30].

Taking account this aspects, we assessed fecal calprotectin in patients with IBS and IBD and results were correlated with the presence of small intestinal bacterial overgrowth (SIBO). 40 patients with IBS (28F, 12M, mean age+/- SD= 43±15 yrs) diagnosed according to Rome III criteria were investigated by fecal calprotectine with a semiquantitative commercially available test (SOFAR, Italy). A group of 20 patients with inflammatory bowel disease (IBD) served as control group (15 ulcerative colitis, 3 Crohn, 2 nonspecific IBD) (12M, 8F, 47±13 yrs). IBS patients were tested for SIBO with the oral glucose and lactulose H2 breath test.

The results were that Calprotectin test was positive in all 20 IBD patients with 16/20 (80%) with severe inflammation. In IBS, calprotectin was mildly positive in 14/40 (35%) patients ($p<0.01$ vs. IBD). The prevalence of SIBO was significantly ($p<0.001$) greater in IBS patients with intestinal inflammation (71%) than IBS patients without intestinal inflammation (8%), as assessed by calprotectine test.

As a conclusion we can say that fecal calprotectin is a test which can differentiate between IBD and IBS patients. Small intestinal bacterial overgrowth is associated with mild intestinal inflammation in IBS, as suggested by calprotectine fecal test.

Fecal calprotectin has been proposed as a non-invasive surrogate marker of intestinal inflammation in inflammatory bowel disease. Close correlation between fecal calprotectin concentration and fecal leukocyte excretion quantified with (111) indium has been described. This fecal marker can be detected using simple and cheap techniques. Fecal calprotectin has a good diagnostic precision for separating organic and functional intestinal diseases. However, the specificity for the diagnosis of inflammatory bowel disease is lower than desirable, as several diseases other than inflammatory bowel disease, especially colorectal neoplasia and gastrointestinal infection, can also increase fecal calprotectin. High concentration of calprotectin in feces is a strong argument to carry out a colonoscopy in order to rule out the presence of inflammatory bowel disease or other organic pathologies. Parallelism between faecal calprotectin levels and inflammatory bowel disease activity has been confirmed, although this fecal marker appears to better reflect the disease activity in ulcerative colitis than in Crohn's disease. Fecal calprotectin's capacity to predict inflammatory bowel diseases relapse is promising. It has been suggested that, in inflammatory bowel disease patients receiving treatment, a normalization or decrease in fecal calprotectin concentrations is an accurate indicator of endoscopic healing. Greater fecal calprotectin concentration has been shown in asymptomatic first-degree relatives of patients with inflammatory bowel disease, suggesting that there is a high prevalence of subclinical intestinal inflammation in them [31].

References

1. Everhart JE, Renault PF. Irritable bowel syndrome in office based practice in the 1United States. Gastroenterology 1991; 100:998.

2. Schuster MM. Diagnostic evaluation of the irritable bowel syndrome. Gastroenterol Clin North Am 1991; 20:269.

3. Douglas A, Drossman MD, et al. Functional bowel disorders. Rome III The Functional Gastrointestinal Disorders 3rd Ediiton 2006; 9: 487-555.

4. Chadwick VS, Chen W, Shu D, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 2002; 122:1778.

5. Liebregts T, Adam B, Bredack C, et al. Immune activation in

patients with irritable bowel syndrome. Gastroenterology 2007; 132:913.
6. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002; 123:1972.
7. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004; 126:693.
8. Guilarte, M, Santos, J, de Torres, I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. Gut 2007; 56:203.
9. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: Postal survey of patients. BMJ 1997; 314:779.
10. Valentina Tzaneva, Razvan Dadu, Dan Dumitraşcu. Postinfectious Irritable bowel syndrome. Current topics in neurogastroenterology. Editura Medicală Universitară " Iuliu Haţieganu" Cluj Napoca 2007; 125:137.
11. Marshall JK, Thabane M, Garg AX, et al. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. Gastroenterology 2006; 131:445.
12. Marshall JK, Thabane M, Borgaonkar MR, James, C. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. Clin Gastroenterol Hepatol 2007; 5:457.
13. Tornblom H, Holmvall P, Svenungsson B, Lindberg G. Gastrointestinal symptoms after infectious diarrhea: a five-year follow-up in a Swedish cohort of adults. Clin Gastroenterol Hepatol 2007; 5:461.
14. Ruigomez A, Garcia Rodriguez LA, Panes J. Risk of irritable bowel syndrome after an episode of bacterial gastroenteritis in general practice: influence of comorbidities. Clin Gastroenterol Hepatol 2007; 5:465.
15. Spiller RC. Post infectious functional gastrointestinal disorders. The proceeding of 7th International symposium on functional gastrointestinal disorders. 2007; 95-100.
16. Gwee KA, Collins SM, Read NW et al. Increased rectal mucosal expression of interleukin 1β in recently aquired post-infectious irritable bowel syndrome. Gut 2003;52:523-526.
17. Wheatcroft J, Walkelin D, Smith A et all Enterocromafin cell hyperplasia and decreased serotonin transporter in a mouse model of post infectious bowel dysfunction. Neurogastroenterol Motil 2005;17:863-70
18. Paduchova Z, Durackova Z. Fecal calprotectin as a promising marker of inflammatory diseases. Bratisl Lek Listy. 2009;110(10):598-602.
19. Poullis A, Foster R, Mendall MA, Fagerhol MK. Emerging role of calprotectin in gastroenterology. J Gastroenterol Hepatol 2003; 18:756.
20. Carroccio A, Iacono G, Cottone M, et al. Diagnostic accuracy of fecal calprotectin assay in distinguishing organic causes of chronic diarrhea from irritable bowel syndrome: a prospective study in adults and children. Clin Chem 2003; 49:861.
21. Delgado-Aros S, Cremonini F. Role of fecal calprotectin test in the work-up of IBS patients. Gastroenterology 2003; 124:1164.
22. Limburg PJ, Ahlquist DA, Sandborn WJ, et al. Fecal calprotectin levels predict colorectal inflammation among patients with chronic diarrhea referred for colonoscopy. Am J Gastroenterol 2000; 95:2831.
23. Kristinsson J, Nygaard K, Aadland E, et al. Screening of first degree relatives of patients operated for colorectal cancer: evaluation of fecal calprotectin vs. hemoccult II. Digestion 2001; 64:104.
24. Kristinsson J, Armbruster CH, Ugstad M, et al. Fecal excretion of calprotectin in colorectal cancer: relationship to tumor characteristics. Scand J Gastroenterol 2001; 36:202.
25. Limburg PJ, Devens ME, Harrington JJ, et al. Prospective evaluation of fecal calprotectin as a screening biomarker for colorectal neoplasia. Am J Gastroenterol 2003; 98:2299.
26. Erbayrak M, Turkay C, Eraslan E. et al..The role of fecal calprotectin in investigating inflammatory bowel diseases. Clinics (Sao Paulo). 2009; 64,:421-5.
27. Kallel L, Ayadi I, Matri S, et al. Fecal calprotectin is a predictive marker of relapse in Crohn's disease involving the colon: a prospective study. Eur J Gastroenterol Hepatol. 2010;22:340-5.
28. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol. 2010 ;105:162-9.
29. Tibble J, Bjarnason I. Non-invasive investigation of inflammatory bowel disease. World J Gastroenterol 2001; 7:460-465.
30. Tibble J, Teahon K, Thjodleifsson B, et al. A simple method for assessing intestinal inflammation in Crohn's disease. Gut. 2000;47:506-13.
31. Gisbert JP, McNicholl AG.Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. Dig Liver Dis. 2009;41:56-66.