Differential diagnosis between functional and organic intestinal disorders: Is there a role for non-invasive tests?

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Abstract

Abdominal pain and bowel habits alterations are common symptoms in the general population. The investigation to differentiate organic from functional bowel disorders represents a considerable burden both for patients and public health service. The selection of patients who should undergo endoscopic and/or radiological procedures is one of the key points of the diagnostic process, which should avoid the abuse of invasive and expensive tests as well as the underestimation of potentially harmful diseases. Over the coming years, clinicians and researchers will be challenged to develop strategies to increase the patient's compliance and to reduce the economic and social costs of the intestinal diseases.

INTRODUCTION

For the sake of simplicity, bowel diseases have been divided into organic (OBD) and functional (FBD) disorders. In the past, FBD was merely considered an "umbrella" for many clinical pictures where the term functional reflected an unknown etiology and/or pathogenesis and their existence was even denied by some physicians[1,2]. In the last years, the fast-growing insight into the pathogenesis of intestinal diseases has been narrowing the field of disturbances "not explained by structural or biochemical abnormalities", in parallel with the progress of diagnostic tools and the development of novel technologies. Recent evidences, such as the role of serotonin in visceral functions[3-5], the post-infective onset of irritable bowel syndrome (IBS)[6] or data about potential neuroendocrine dysfunctions[7] shed light on the phenomena underlying FBD. The "biopsychosocial model" focused on the complex interplay among genetics, environment, psychosocial and physiological factors, significantly contributed to clarify the true genesis of "functional" symptoms and to modify both treatment and clinical outcome[8]. However, while the new scenario of pathogenesis suggests an overlapping between morphologic and functional abnormalities, in clinical practice the distinction is maintained in prognostic terms, as "functional" identifies scarcely evolutive and virtually harmless conditions.

As the intestine reacts to different stimuli with a limited array of symptoms, the investigation to differentiate OBD and FBD represents a considerable burden for both the patients and public health service.

The selection of patients who should undergo endoscopic and/or radiological procedures is one of the key points of the diagnostic process, which should avoid the abuse of invasive and expensive tests as well as the underestimation of potentially dangerous diseases. In particular, we should take into account the high prevalence and increasing incidence of colo-rectal cancer which, at an early stage, can be successfully treated by endoscopic resection. Nevertheless, colonoscopy is not advisable in all patients with abdominal complaints in the absence of "red flag" features (age > 45 years, anaemia, bleeding, fever, weight loss, etc.) (Figure 1). Chronic or recurrent abdominal pain and bowel habit alterations are common symptoms in the general population. Because a wide range of etiologies may underlie these symptoms, they do not allow a differential diagnosis between OBD (neoplasm, infectious enteritis, Crohn's disease, celiac disease, etc.) and FBD. Moreover, patients may present overlapping syndromes as OBD and FBD , are not mutually exclusive and can be present in the same patient. FBD, mainly IBS, which affect 5%-20% of general population, are the most common intestinal disorders in both primary and secondary care[9-11]. Most patients are diagnosed and treated by general practitioners (GPs) and only those unresponsive to conventional treatment[10,12] are eventually referred to a gastroenterologist[9,13].
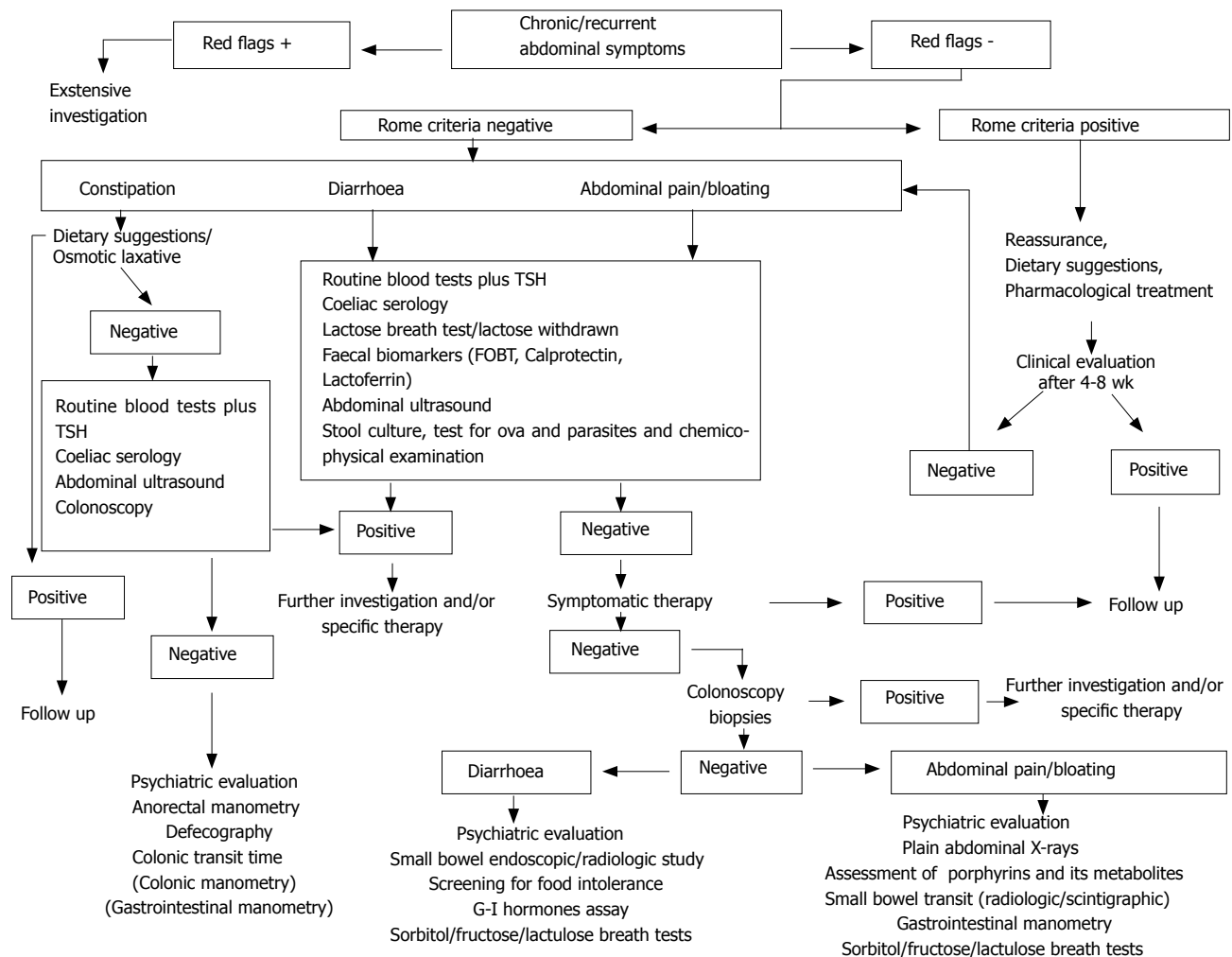
In order to improve the positive identification of

Figure 1 Suggested approach to the diagnosis of chronic abdominal symptoms.

patients affected with FBD, the Rome classification system has been developed. Although these guidelines have raised controversies about duration, frequency, severity and terminology itself of symptoms, they have created a common language for FBD and are now considered the gold standard. Unfortunately, Rome criteria have been developed by and for specialists working in the secondary care setting; they are ignored by many GPs and considered by others, as well as by many specialists, too complex and time-consuming and/or restrictive, suitable only for the tertiary care setting and for research purposes[14]. Therefore, many GPs and gastroenterologists are confident of making a correct diagnosis based on their personal criteria[14,15] and, in the absence of any biological or instrumental marker, FBD is still an exclusive diagnosis which often require extensive investigation. The recent Rome Ⅲ criteria appear to be simpler and less restrictive and hopefully will help the diagnosis of FBD on clinical basis[16].

When FBD is suspected, the clinical criteria can be combined with a number of non-invasive diagnostic tools. Unfortunately serological biomarkers of inflammation such as erythrocyte sedimentation rate, C-reactive protein, white cell count, platelet count, are not sufficiently sensitive or sufficiently specific because they do not directly reflect the level of local inflammation[17-19]. The faecal occult blood test is of little use in detecting inflammatory bowel diseases (IBD) and has a low sensitivity for the diagnosis of colon cancer, especially at an early stage[20,21]. Therefore, in recent years considerable effort has been devoted to find alternative solutions. The latest knowledge about the pathogenesis of FBD (infection, food allergy or intolerance)[22-24], have focused attention on the role of microscopic inflammation, bacterial overgrowth, altered immunity and even more subtle alterations, whose effects are detectable in non-invasive manner, by analysing stools, breath samples and blood.

FAECAL MARKERS

Neutrophil-derived proteins

Faecal neutrophil-derived proteins (mainly calprotectin and lactoferrin) assessment is receiving increasing attention as promising tools to differentiate OBD and FBD; although their clinical use needs definitive confirmation especially in the work-up of FBD, they could be the putative ideal test for non-invasive assessment of intestinal inflammation[25-27].

Calprotectin is a 36-kDa calcium and zinc binding protein that accounts for about 60% of total proteins in the cytosol fraction of neutrophil granulocytes[28,29]. An

increase in faecal calprotectin levels in IBD, colorectal cancer and non-steroidal anti-inflammatory drugs enteropathy has been reported[30-33]. In a study of Dolwani, faecal calprotectin was superior to small bowel barium follow-up in identifying patients with organic diseases[34]. In Crohn's disease (CD) and ulcerative colitis (UC), its levels closely correlated with the faecal excretion of ^{111}In-labelled leukocytes, which is considered to be the gold standard for measuring intestinal inflammation[35] and recently it has been reported that a high faecal calprotectin concentration may identify those IBD patients in remission who are at risk of early relapse[36,37]. Calprotectin has a high negative predictive value for intestinal inflammation. It has low specificity for intestinal pathology but, at a cut-off of 30 mg/L (150 μg/g of faeces by the new method), it showed a sensitivity of 100% in discriminating between active Crohn's disease and IBS[27]. The combined use of presence/absence of alarm features, Rome criteria and calprotectin test proved to be a non-invasive, effective mean of screening patients for organic intestinal disease[38].

Lactoferrin is an iron-binding protein contained in organic fluid, intestinal mucus and in neutrophils. Similarly to calprotectin, faecal lactoferrin proved to be a simple, sensitive marker of intestinal inflammation[25,39,40].

DNA

The molecular genetics of colorectal cancer provided the basis for the analysis of faecal DNA[41]. Colonoscopy is the best tool for the diagnosis of colorectal cancer but it cannot be proposed for a systematic screening of the entire population > 50 years of age. The recent availability of faecal-based, multi-target DNA panel has allowed a better sensitivity than faecal occult blood test for the detection of colorectal cancer[21]. This panel consists of different mutations (*K-ras* gene, *APC* gene, *p53* gene), markers of microsatellite-instability and markers of disordered apoptosis, clearly involved in the progression of colorectal cancer. Although the performance of faecal DNA testing is not comparable to colonoscopy, it is simple and non-invasive, therefore its use at frequent intervals might compensate for the lower diagnostic accuracy[21].

Pancreatic elastase

Chronic pancreatitis is a frequent cause of abdominal pain and diarrhoea whose diagnosis often requires complex and expensive procedures. The assessment of pancreatic elastase on stools seems to offer a better performance than previous non-invasive tests (i.e. serology, Pancreolauryl test, faecal tests for pancreatic enzyme) with a high sensitivity for moderate and severe pancreatic insufficiency[42,43]; this faecal test, like faecal neutrophil-derived protein assessment, is easy to perform, requires a single stool sample and offers a great advantage in terms of patient's compliance. Although most authors reported poor sensitivity for mild disease, its use has been recommended as a first choice test in patients with chronic diarrhoea of putative pancreatic origin[44].

If these experimental data are confirmed in large controlled studies, the routine use of faecal tests might contribute to the selection of patients with abdominal complaints both in the first diagnosis and in the follow-up avoiding invasive and expensive procedures.

BREATH TESTS

Breath analysis is a simple and safe alternative to invasive tests to investigate digestive functions. Exhaled hydrogen (H_2) and carbon (C) can be employed to assess malabsorption, gastrointestinal motility and *H pylori* infection. H_2 in humans is produced only by bacterial fermentation of carbohydrates[45]. This process has been related to the onset of symptoms such as diarrhoea, bloating and abdominal pain[46,47]. Different hydrogen breath tests are currently used to detect carbohydrate malabsorption. Lactose, fructose, sorbitol are the most commonly tested carbohydrates, although their role in symptoms of FBD is controversial, and the prevalence of lactose, fructose and sorbitol malabsorption in IBS patients is not different from healthy subjects[48].

Small intestinal bacterial overgrowth (SIBO) is a malabsorption syndrome characterized by more than 105 colonic type bacterial/mL of jejunal juice described in case of structural bowel alterations (surgical blind loop, stenosis, etc), motility disturbances (pseudo-obstruction, diabetic autonomic neuropathy, sclerodermia) and also present in chronic diseases (liver cirrhosis, chronic pancreatitis, chronic renal failure)[49]. Recent data also indicate that an altered gut flora may play a pathogenic role both in IBS and IBD[50,51]. It has been shown that eradication of SIBO eliminates IBS symptoms in 48% of patients[52]. Although jejunal culture is considered the gold standard for the diagnosis of SIBO, some drawbacks limit its widespread use; thus, glucose and lactulose breath tests are commonly employed. Breath tests based on the excretion of CO_2 subsequently measured by a mass spectrometer have been developed; they employ a variety of ^{13}C substrates to investigate the exocrine pancreatic function (^{13}C triolein, ^{13}C mixed chain triglyceride)[53], gastric emptying (^{13}C octanoate)[54], as well as in the diagnosis of *H pylori* infection (^{13}C urea)[55].

The simplicity and the safety of breath tests encouraged a widespread use, but the data on their low diagnostic accuracy should be taken into account and their use on regular basis cannot be recommended in clinical practice[56].

SERUM

Recent literature highlighted that approximately 4% of patients diagnosed as IBS are affected with celiac disease[57]. Altered bowel habits and abdominal pain, the clinical hallmark of IBS, are common in celiac patients, and serological assessment for anti-endomysial and anti-transglutaminase antibodies should be performed as a first level test when IBS is suspected. Many patients suffering from abdominal pain and/or bowel habit changes perceive their symptoms as related to some form of dietary intolerance and show a good response to an exclusive diet. Nevertheless, any attempt to correlate food-specific IgE production and chronic abdominal symptoms has been disappointing[24,58]. Although it has been reported

that sometimes IgE-mediated reactivity can present with chronic abdominal complaints, the measurement of food-specific IgE antibody concentrations to ascertain food intolerance in FBD is not justified and should be discouraged[59]. Preliminary data showed that high titres of food-specific IgG4 antibodies are present in IBS patients suggesting a diagnostic role in those cases of IBS who could benefit mostly by an exclusive diet[60]. Their clinical follow-up and further research are needed to clarify the importance of these findings and their role in clinical practice.

CONCLUSION

Likely the near future will lead to a deep revision of the concept of "functional disorder". The striking progress in our knowledge of the molecular basis of diseases is identifying new models for FBD pathogenesis, which tend to be less "functional" and more "organic".

These new evidences will have a relevant effect on the clinical management of intestinal diseases. We are not far from the time when the development of minimally or non-invasive techniques will allow an accurate diagnosis, a serial monitoring and a "real time" adjustment of therapy.

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