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Short Communication

Clinical Considerations in Early/Transitional Inflammatory Bowel Disease: A Medical Anthropological View

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Abstract

Introduction: Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) are two gastrointestinal disorders with often overlapping gastrointestinal symptomatology consisting mainly of abdominal pain and altered bowel function. However, in early IBD the initial period consists of clinical manifestation of abdominal distress and of extra-digestive symptoms.

Methods: We performed a clinical characterization of 55 outpatients that suffered these symptoms.

Results: The previous diagnosis of these patients was IBS in 69.1% of the cases while 30.9% had no previous explicit diagnosis. No morphological changes were observed in upper or lower intestinal endoscopic and histopathological studies. Of these patients, 70.9% reported stressful life events in the past while the calprotectin fecal test exceeded 100µg/g in all the tested patients, indicating low grade intestinal inflammation. This "transitional disease" condition improved with anti-inflammatory treatment (i.e. oral mesalazine) leading to an inactivation of the symptomatology in 89% of the patients.

Conclusion: The data supports the notion that psychological distress favors a transitional or early IBD characterized by low grade inflammation. This early disease state improves with anti-inflammatory treatment.

ABBREVIATIONS

IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome

INTRODUCTION

Inflammatory bowel diseases (IBD), i.e. ulcerative colitis and Crohn's disease, are chronic multi-systemic disorders of increasing prevalence characterized by inflammation of the gastrointestinal tract. Its main symptoms are abdominal pain and discomfort and changes in bowel habits, as well as a high association with disorders of the psycho-neuro-immune sphere such as depression, arthropathies, and mucocutaneous complications, just to name a few [1-3]. The genetic background contributes importantly to IBD susceptibility pointing to several genes and cellular pathways involved in the normal maintenance of intestinal homeostasis [4]. Moreover, IBD patients often show psychiatric symptoms that are induced by exposure to psychological stress, also known to precipitate mood disorders [5,6]. Actually, the integration of these factors into a more holistic comprehension of IBD should be able to improve treatment strategies, thus interrupting worsening of symptoms and preventing the "natural" course of the disease, characterized by a gradual intensification of symptoms over years. In that respect, the diagnosis of IBD is often confused with Irritable bowel syndrome (IBS), a different pathologic chronic condition characterized by cramping, abdominal pain, bloating, gas, diarrhea or constipation without changes in the bowel tissue, as it may occur in the first stages of IBD, but lacking the extra-digestive symptoms that characterize IBD. Furthermore, the symptomatology of IBS remains with a stable grading over years [7]. Nevertheless, a frequent confusion between IBS and IBD occurs mainly during the early symptomatic period of IBD as has been analyzed previously by us [8]. We now present a study of 55 patients with a confusing symptomatology which had been diagnosed for a long time as IBS with an inefficacious outcome. When fecal calprotectin was used as a marker for low grade inflammation in these patients [9], it was positive (over 100µg/g). This fact was associated with the clinical symptomatology described above. Moreover, it was possible to treat them effectively with oral mesalazine, a standard anti-inflammatory treatment for IBD.

The hypothesis that we are proposing is that there is a new entity that can be confused with IBS but it is not entirely functional

in nature, because it has a subclinical intestinal inflammation that can be detected by the calprotectin test. Second, these patients intensify their symptoms along time in contraposition with IBS, that shows a stable evolution. Third, they suffer at the same time frequently extra-digestive symptoms related to autoimmune diseases. Fourth, without proper treatment, this entity may evolve to overt IBD.

MATERIALS AND METHODS

Clinical data from 55 patients who were attended between January 2012 to December 2016 at the Pontificia Universidad Católica de Chile Outpatient Clinic (Santiago de Chile) was collected. Patients had suffered for long periods, generally exceeding 5 years, abdominal discomfort and pain, diarrhea, and bloating. Fecal calprotectin was measured in 38 out of 55 patients by standard external laboratory procedures and considered as positive if its value was ≥ 100μg/g. We included 17 clinically characterized patients without the calprotectin test because at the beginning of our study, the test was not available. Furthermore, the following characteristics of the patients were assessed: time course of symptoms intensity, initiation of gastrointestinal symptoms, previous diagnosis, localization and type of pain, the presence of diarrhea, family history, emotional or psychiatric symptoms, weight loss or gain and extra-digestive symptoms such as dermatologic and rheumatologic symptoms. In a number of patients it was possible to feel a painful intestinal segment (ileum) at the lower abdominal quadrant. We also studied the medical and social biography of the patients.

RESULTS AND DISCUSSION

Of the patients, 16 were males and 39 females. At the time of evaluation, the medium age was 38.5 ± 2.1 years (mean ± SEM), ranging between 17 and 77 years. The patients were suffering their symptomatology for 9.6 ± 1.5 years before the present evaluation. Interestingly, the gastrointestinal symptoms began in 50.9% of the patients during childhood or early adolescence. In turn, the symptoms of 49.1% of patients began in the adulthood, at an age ranging between 19 and 51 years with a mean age of 33.3 + 10.0 years. Finally, 48.8% of the patients aggravated during the last year. Their previous diagnosis was IBS in 69.1% of the cases while 30.9% had no previous explicit diagnosis. The main symptoms consisted of episodes of abdominal pain (96.4%); colic pain (50.9%), diarrhea and bloating (78.2% and 72.7% respectively), while 10.9% presented vomiting. This was accompanied by extra-digestive symptoms (Table 1) consisting in unexplained lassitude, somnolence and discomfort and the presence of psychiatric symptoms characteristic of mood disorders (i.e. depressed mood and anxiety) in addition to arthritis or arthralgia. Dermatologic signs were also assessed in these patients. Regarding the family history, 28 patients (58.3%) had close relatives, including siblings and parents and their siblings, suffering immunologic diseases such as psoriasis, rosacea, IBD or lupus erithematosus (Table 2). Stressful life events in the past history, that might contribute to trigger or worsen the disease, occurred in 70.9% of the cases.

In 38 patients out of the 55 patients, fecal calprotectin was measured and positive results (i.e. over 100 μg/g, and with an upper limit of 600μg/g) were obtained in all of them while in the remaining patients, as we explained before, it was not available. Of 55 patients, 49 improved at least partially few days after initiation of the therapy with oral mesalazine. In the non-responder group, a later development of Crohn´s Disease was confirmed for 5 patients. In them, the morphologic intestinal damage was confirmed by colonoscopy and/or CT scan. Thus, the early appearance of gastrointestinal symptoms together with the presence of inflammation and psychiatric signs, possibly precipitated by early stressful life events, may lead to the expression of IBD (Figure 1). If these continuing inter-related events leading to morphological intestinal alterations are not stopped timely, classic Crohn's Disease may develop in these patients.

IBD and IBS often occur with overlapping symptoms according to Rome III criteria. However, the evolution of the symptoms in IBD distinctively increases over years, leading to the potential morphologic expression of the disease. As a matter of fact, we may remind that over 60 years ago Gustav von Bergmann stated that in chronic diseases, functional symptoms preceded morphological manifestations [10]. In such a way, the existence of occult or low grade inflammation has been reported consistently to be a salient feature of IBD. This is reflected in the fecal calprotectin test, with a recommended cutoff value of 100μg/g and exclusion criteria of 30μg/g [7,9,11]. Interestingly, inflammation is a recognized common pathophysiological feature in depression as well as in IBD [12], and thus, the co-morbidity of depression with IBD is not surprising and has been clearly established over years [13]. However, important and unresolved controversies regarding this co-morbid relationship remain. One of the most challenging questions under discussion is whether depression and anxiety precede the onset of IBD. As it has recently been described, a large

Table 1: Extra-digestive manifestations of patients.

Extra Digestive Manifestations		
	Patients	**Percentage**
Lassitude	33	0.6
Anxiety - Depression	32	0.588
Rough Elbow	18	0.327
Arthralgia	18	0.327
Arthritis	11	0.2
Oral Aphtous	12	0.218
Rosacea	10	0.182
Clubbing	11	0.218
Psoriasis	2	0.036

Table 2: Immune Diseases in Relatives.

Immune Diseases in Relatives		
	Patients	**Percentage**
Psoriasis	16	0.29
IBD	4	0.073
Arthritis	3	0.055
Lupus erythematosus	3	0.055
Thyroiditis	2	0.036

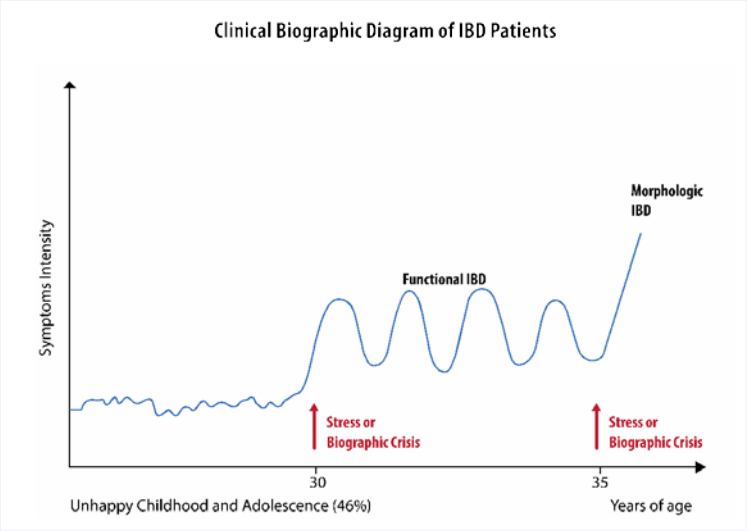

Figure 1 IBD appears to be an ailment that develops along the life of patients with a genetic susceptibility. We believe that the main trigger to express the disease is psychological stress, often associated to biographical crisis. After this evolution, that may last years, classic IBD with morphological alterations is expressed.

proportion of adults develop depression before the onset of IBD [14,15], although a bidirectional risk cannot be excluded. Most of the IBD studies are complicated by the methodology used in the diagnosis of psychiatric disorders. Most frequently, as in the present report, depressive symptoms but not the disorders itself and/or their possible subtypes are assessed, while standardized psychiatric evaluation, including grading of symptoms according to structured interviews, are often lacking. A further complexity in our country is that psychiatric patients remain under diagnosed, especially when depression and anxiety develop in response to child abuse and neglect, including sexual abuse, a fact that frequently remains unknown. The difficulty to trace these facts adds to the difficult accessibility of primary health care systems to include standardized psychiatric evaluations, a fact that is explained by the cost and the specialized professionals implicated in a precise psychiatric diagnosis.

In 2012, we reported that the diagnosis of Cohn's Disease occurs with an excessive delay, attributable to some of the above mentioned difficulties [8]. To facilitate an earlier diagnosis we propose that risks to acquire IBD rests on a genetic susceptibility background [4], which in turn is determinant to shape personality traits, vulnerability and innate resilience to external stressors. During the very early stages of IBD, the digestive symptomatology cannot be distinguished from IBS [11]. However, early life stress, as well as other external events will gradually favor the development of inflammatory disorders that include the gastrointestinal tract [16]. We propose that at the early stages of IBS/IBD, called transitional disease by us, low grade bowel inflammation is indicative of a probable future development towards classic IBD, a transition that can be favored by further stressful life events. This might be stopped or delayed by the use of drugs targeting inflammation, such as oral mesalazine. In contrast, lately treated or non-treated patients may progress to classic IBD, the symptoms of which may be precipitated or augmented by further stressful life events while its treatment remains often unsatisfactory [17].

Finally, first we may say that, according of what is depicted in Figure 1, IBD can be inserted in what has been defined as a biographic disease [18,19]; second, we must remind that the first definition of what is now called Crohn disease, was one of a local ileal inflammation [20], that then has evolved to an extended and complex psychoneuroimmunology ailment [5].

CONCLUSION

1. - In IBD, a long lasting functional symptomatology precedes morphologic gastrointestinal manifestations.
2. - In clinical practice, the consideration of a stressful life event together with low grade enteric inflammation is helpful for an earlier diagnosis of IBD.
3. – Mesalazine is a useful therapeutic tool in what we have called transitional inflammatory bowel disease (early IBD).
4. - IBD appears to be inserted in the patient's biography.

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ETHICAL CONSIDERATIONS

The present retrospective study was approved by the Ethics Committee of the Pontificia Universidad Católica de Chile.

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