

Irritable Bowel Syndrome: Do We Need More Answers to a Functional Gastrointestinal Disorder?

Opinion

It has been difficult to find a definition of functional gastrointestinal disorders (FGDs) that can be used in a clinical setting. This is due to the fact that FGDs are comprised by a heterogeneous group of chronic conditions with different symptoms that can be related to numerous organic diseases, but which lack the anatomical or biochemical anomalies that usually accompany them. As such, the usual tests carried out in a clinical setting will detect no anomaly and this complicates the patient-physician relationship. Altogether, FGD's are an important public health problem as they are common and disabling to a great proportion of patients and their medical and social cost is enormous [1].

Several functional lower gastrointestinal disorders have been identified, irritable bowel syndrome (IBS) is probably the most frequent and known of all of them. However, as stated before, there are several points that make this condition difficult to study and explain to the patient. Different studies have reported that almost 20% of the population suffer from IBS at some time of their life, and reported prevalence rates in the world vary between 5% and 25%. This variability is due to the use of different diagnostic criteria, population differences and study design like using convenience samples as opposed to population-based sampling [2,3]. In México, Dr. Schmulson's group has reported a prevalence of 16.0%, which is in agreement with a parallel study that was conducted in Central America (13.2%) and with a population-based study from South America (19.9%) [4].

Part of this variation in the reported prevalence of IBS has come from the changing definition of irritable bowel syndrome. Today, the diagnosis is based on symptoms (positive symptoms diagnosis using the Rome III criteria) that are present without an anatomical or biochemical abnormality, meaning that there is no available diagnostic test. In the past, it was considered an exclusion diagnosis, where that all possible diseases that shared the same symptoms had to be considered and ruled out. The clinical diagnosis based on symptoms has allowed to the physician to save time and health care cost. New biomarkers have been tested, but more accuracy is needed for these to be considered diagnostic tests in the clinical practice [3,5].

To complicate this situation, IBS has been divided into subtypes according to the stool pattern into constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M) and unclassified (IBS-U). Whereas this classification has been useful and practical for planning treatment regimes that treat patient symptoms, there is still no consensus as to whether they are different entities or whether they have a common underlying pathophysiological process [1].

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Oscar Teramoto Matsubara^{1*} and Teramoto Kimura SY²

¹Department of Gastroenterology, ABC Medical Center, Mexico

²Department of Physiology Anatomy and Genetics, Oxford University, UK

***Corresponding author:** Oscar Teramoto Matsubara, Department of Gastroenterology, ABC Medical Center, Mexico City, Mexico, Email: teramotomd@prodigy.net.mx

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A disease needs to be explained by its characteristics, and published study data regarding IBS in the past, attempted to explain causes, triggers, and possible underlying mechanisms. However, findings from these studies are complex, difficult to understand and somewhat confusing in the clinical setting and ultimately have no clinical relevance for the daily care of the patient. For example, genetic and familiar factors have been studied, but it is still not clinically useful because the results are complex and still do not identify anything that a clinician can apply in their practice [6]. First of all, these studies have studied over 60 genes that are related to the serotonin signaling pathways, control of immune activation, bile acid synthesis, neuropeptide activity, and intestinal secretion. Still, it seems that our understanding is incomplete as factors like mutations, RNA expression and epigenetic changes have not been fully explored [6].

In spite of the complexity of IBS, new findings over the last few years have resulted in three main hypotheses regarding the etiology and pathophysiology of IBS, which can begin to clarify the organic changes that can cause the disease.

These hypotheses are the following:

- Local changes in the gut, like altered peripheral regulation of gut function, in which motor regulation, and peripheral sensory and secretory mechanisms are altered;
- There are central and peripheral neural changes, today known as altered brain-gut-microbiota signaling, which may explain the visceral hypersensitivity; and
- Psychological distress that can partially be explained by changes in the cortisol and corticotropin release factor signaling.

Clinical research supports a major role of the brain in IBS symptoms, as well as psychosocial stressors play an important role in the first onset and perception of severity [5,7]. These

hypotheses may also help explain the differences between subtypes, and which might, in the future, allow us to understand each one as a different entity that can be diagnosed using biomarkers.

There are also external and internal factors that can trigger or perpetuate the disease. An example of external factors are gastrointestinal infections, which are known to be a risk factor for the development of the irritable bowel syndrome, now called post-infectious irritable bowel syndrome (PI-IBS). Gastrointestinal infections can lead to altered nerve signaling in the gut. Gut inflammation and changes in the microbiota have been described in patients with IBS and are also possible triggers of increased or decreased gut motility. However, all of these findings can be found in cases other than PI-IBS [8].

Gut microbiota are a key factor that has been researched because they play several key functions such as acting as a barrier, synthesizing vitamins, immune stimulation, metabolism of nutrients, and metabolism of drugs and toxins. For example, the microbiota consume nutrients necessary for survival of pathogens and produce molecules, which inhibit the growth of pathogenic flora, like lactic acid, bacteriocins and short chain fatty acids (SCFA). Changes in the normal intestinal microbiota have been recorded in many gastrointestinal disorders such as IBS, IBD and gastric and colon cancer. In the case of IBS, results have been reported showing decreased levels of lactobacilli and bifidobacteria, and increased levels of anaerobic bacteria such as streptococci and *Escherichia coli*, as well as increased ratios of Firmicutes, Bacteroidetes, and *Clostridium* species [8].

Although external factors seem to have a potential role to initiate and perpetuate the disease, there are internal changes that also play a role in the physiology of IBS. For example, in the IBS-D subtype, new findings related to bile acids have been shown to act as endogenous laxatives that stimulate gut motility (accelerated colonic transit time, frequent or loose bowel movements, and increased intestinal permeability). Low bile acid retention values, caused by bile acid malabsorption and/or overproduction, have

been shown in IBS-D and IBS-M, compared to healthy controls and patients with IBS-C [1].

In conclusion, a reasonable explanation of IBS has been reviewed to offer a deeper understanding of the research on IBS and the challenges faced to translate this knowledge into clinical practice. In the future, efforts should be made to propose an explanatory, easy model to explain, visualize, and understand. This will enable the patients' and clinicians' expectations to match the clinical practice. New research and findings are slowly but surely contribute to building that model from which clinicians can explain IBS to their patients in lay terms, and hopefully obtain a real curative treatment after all.

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