Irritable bowel syndrome: Diagnosis and pathogenesis

Magdy El-Salhy

Magdy El-Salhy, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, 5416 Stord, Norway
Magdy El-Salhy, Section for Gastroenterology, Institute of Medicine, University of Bergen, 5029 Bergen, Norway
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Correspondence to: Magdy El-Salhy, Professor, Consultant Gastroenterologist, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Tysevegen 64, 5416 Stord, Norway, magdy.el-salhy@helse-fonna.no
Telephone: +47-5-3491000 Fax: +47-5-3491001
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Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that considerably reduces the quality of life. It further represents an economic burden on society due to the high consumption of healthcare resources and the non-productivity of IBS patients. The diagnosis of IBS is based on symptom assessment and the Rome III criteria. A combination of the Rome III criteria, a physical examination, blood tests, gastrosopy and colonoscopy with biopsies is believed to be necessary for diagnosis. Duodenal chromogranin A cell density is a promising biomarker for the diagnosis of IBS. The pathogenesis of IBS seems to be multifactorial, with the following factors playing a central role in the pathogenesis of IBS: heritability and genetics, dietary/intestinal microbiota, low-grade inflammation, and disturbances in the neuroendocrine system (NES) of the gut. Duodenal chromogranin A cell density is a promising biomarker for the diagnosis of IBS. The pathogenesis of IBS seems to be multifactorial, with the following factors playing a central role in the pathogenesis of IBS: heritability and genetics, dietary/intestinal microbiota, low-grade inflammation, and disturbances in the neuroendocrine system (NES) of the gut. One hypothesis proposes that the cause of IBS is an altered NES, which would cause abnormal GI motility, secretions and sensation. All of these abnormalities are characteristic of IBS. Alterations in the NES could be the result of one or more of the following: genetic factors, dietary intake, intestinal flora, or low-grade inflammation. Post-infectious IBS (PI-IBS) and inflammatory bowel disease-associated IBS (IBD-IBS) represent a considerable subset of IBS cases. Patients with PI- and IBD-IBS exhibit low-grade mucosal inflammation, as well as abnormalities in the NES of the gut.

INTRODUCTION

Irritable bowel syndrome (IBS) affects as many as 5%-20% of individuals worldwide (Figure 1)[1-31]. The annual incidence of IBS is between 196 and 260 per 100 000 [32,33], with IBS occurring more often in women than in men, and being more commonly diagnosed in patients younger than 50 years of age[14,34-44]. IBS symptoms range from diarrhoea to constipation, or a combination of the two, with abdominal pain or discomfort existing alongside abdominal distension[45]. The degree of symptoms varies in different patients from tolerable to severe, and the time pattern and discomfort varies immensely from patient to patient[14,34-44]. Some patients complain of daily symptoms, while others report intermittent symptoms at intervals of weeks or months. IBS is not known to be associated with the development of serious disease or with excess mortality[46,47]. However, IBS causes a reduced quality of life with the same degree of impairment as major chronic diseases, such as diabetes, congestive heart failure, renal insufficiency and hepatic cirrhosis[48-50]. Although a minority (10%-50%) of IBS patients seek healthcare, they generate a substantial workload in both primary and secondary care[49-53]. The annual costs in the United States, both direct and indirect,
for the management of patients with IBS are estimated at 15-30 billion USD[57,58].

The treatment options for IBS have included pharmacological symptomatic relief of symptoms such as pain, diarrhoea or constipation. Evidence of the long-term benefit of pharmacological agents has been sparse, and new agents that have proven to be effective have raised issues concerning safety[36,75]. Alternative therapies, such as cognitive behavioural therapy and gut-directed hypnotherapy, have been used with good results[58]. Other non-pharmacological approaches have been also tried with proven effects on symptoms and the quality of life in patients with IBS[59].

The present review is an attempt to give an update on the diagnosis and pathogenesis of IBS, and to discuss some controversial issues in both the diagnosis and pathogenesis of IBS.

**DIAGNOSIS**

There is currently no biochemical, histopathological or radiological diagnostic test for IBS, with the diagnosis of IBS being based mainly on symptom assessment. Over the last few years, Rome working parties have generated detailed, accurate, and clinically useful definitions of the syndrome. As a result, the Rome criteria (I, II and III) have been established (Table 1)[59,60]. In addition to these criteria, warning symptoms or red flags, such as age over 50 years, a short history of symptoms, nocturnal symptoms, weight loss, rectal bleeding, anaemia, and the presence of markers for inflammation or infections, should be excluded. IBS patients are sub-grouped on the basis of differences in the predominant bowel pattern as diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C), or a mixture of both diarrhoea and constipation (IBS-M), and un-subtyped IBS in patients with an insufficient abnormality of stool consistency to meet the criteria for IBS C, D or M (Table 2). It has been reported that around one third of patients have IBS-D, one third have IBS-C, and the remainder have IBS-M[61-63]. The division of IBS patients into subtypes is useful for clinical practice and symptomatic treatment, but it is common for IBS patients to switch from one subtype to another over time. These patients are known as “alternators”. More than 75% of IBS patients change to either of the other 2 subtypes at least once over a 1-year period[60].

The majority of gastroenterologists believe that a symptom-based diagnosis, such as that based on the Rome III criteria, without red flags is enough for the diagnosis of IBS and that no further investigations are needed. The use of red flags in combination with Rome criteria has been found to be highly specific, but not particularly sensitive[64]. The American College of Gastroenterology Task Force does not recommend routine colonoscopy in patients younger than 50 years of age without any associated alarming symptoms[60]. The guidelines of the of the British Society of Gastroenterology go further, however, by recommending an examination of the colon earlier if there is a first degree relative affected by colorectal cancer who is younger than 45 years, or two first degree relatives of any age [65]. The British Society Of Gastroenterology also recommended further investigations in IBS-D due to the overlap with other diarrhoea diseases, such as coeliac and inflammatory bowel disease (IBDs)[60]. These recommendations seem to be suitable for detecting and diagnosing colorectal cancer in this group of patients, but not in other organic gastrointestinal (GI) diseases. It is rather difficult to clinically distinguish IBS from adult-onset coeliac disease (CD)[67-73], as the breadth of the spectrum of symptoms associated with IBS results in a potential for overlap of IBS and CD symptomatologies. The situation is further complicated by the fact that the abdominal symptoms of both IBS and CD patients are triggered by the ingestion of wheat products. In CD patients, this is due to a gluten allergy, while in IBS the effect is attributed to the long sugar polymer fructan in the wheat[74]. The prevalence of CD in IBS varies in different studies and varies from 0.04% to 4.7%[72,73,75,76]. Regardless of the number of CD patients among patients diagnosed with IBS, I believe that IBS patients from all subtypes should be routinely screened for CD, which is in line with current opinions in the field[60,64].

Distinguishing IBD from IBS, especially with mild disease activity, can be difficult[87]. Furthermore,
IBS-like symptoms are frequently reported before the diagnosis of IBD\textsuperscript{87-90}. Microscopic colitis (MC) and IBS have similar symptoms and a normal endoscopic appearance\textsuperscript{91-101}, and the diagnostic overlap between IBS, IBD and MC is important because of a potentially different treatment for each disorder. The prevalence of IBD in patients that fulfilled the Rome criteria without alarming symptoms varies between 0.4% and 1.9%\textsuperscript{96-100}, and MC from 0.7% to 1.5%\textsuperscript{90-97}. It is conceivable, therefore, to conclude that symptom-based diagnosis of IBS may lead to a number of other GI disorders that require quite different management than IBS being missed. Sigmoidoscopy in IBS patients might be insufficient, however, as a considerable number of MC patients may not be identified without mucosal biopsies from the right colon\textsuperscript{101}. Moreover, performing a sigmoidoscopy would not exclude Crohn’s disease lesions in the terminal ileum, making ileocolonoscopy preferred, especially in IBS-D patients. This seems, at first sight, to add more economic burden to healthcare, which is already suffering from a lack of resources. IBS patients are already consuming a large amount of healthcare resources. However, performing an ileocolonoscopy would reassure IBS patients and prevent them from seeking a new examination, which would not increase the economic burden of this patient group on society, but instead use the existing resources effectively.

Several biomarkers for the diagnosis of IBS have been considered, but only gut transit measured by radio-isotope markers meets the criteria for reproducibility and availability\textsuperscript{102}. However, radio-isotope tests themselves are expensive and of limited availability\textsuperscript{102}. It has been reported that the chromogranin A-containing cell density is low in the duodenum of IBS patients (Figure 2)\textsuperscript{103,104}. As chromogranin A is a general marker for endocrine cells\textsuperscript{105,106}, this finding indicates a general reduction in small intestinal endocrine cells in these patients. It has been proposed that the quantification of duodenal chromogranin A cell density could be used as a histopathological marker for the diagnosis of IBS\textsuperscript{103,104}. Receiver-operator characteristic curves for chromogranin A cell density in the duodenum is given in Figure 3. The sensitivity and specificity at the cutoff \(< 31 \text{cells/mm}^2\) in the duodenum are 91% and 89%, respectively. Screening of IBS patients for CD is now widely accepted. Thus, gastroscopy with duodenal biopsies can be used for excluding or confirming CD instead of blood tests, and the same biopsies can be used for the diagnosis of IBS. The duodenal endocrine cell types affected and their role in the pathogenesis of IBS is discussed in the next section.

**PATHOGENESIS**

Patients with IBS typically present with GI complaints for which physicians can find no organic cause. It is natural and understandable to make comparisons with hysteria, which is also predominant in women. Hysteria has been replaced in modern psychiatry by somatisation disorders and conversion disorders. The notion that IBS is a psychiatric disorder is deeply rooted in clinical practice.
This situation was not improved by the huge number of publications on a selected group of IBS patients, which show that IBS patients are more likely to be psychiatrically ill and sexually or physically abused than the general population\[107-121]. Many patients with IBS ignore their symptoms and regard them as a normal part of everyday life. IBS patients with anxiety, depression, somatisation or hypochondria are more liable to seek healthcare than other IBS patients. Unless this is borne in mind, incorrect conclusions can be drawn. A hospital-based case-control study showed that patients with IBS have a comparable health-related quality of life, level of psychological distress and occurrence of recent stressful life events to age-matched IBD patients\[122]. These findings are interesting as IBD patients receive effective treatment and are treated with sympathy, understanding and support by their doctors as well as society. In contrast, IBS patients are offered non-effective treatments, are treated with mistrust and neglect by their doctors, feel that they are labelled as hypochondriacs and believe that they receive no support from society. It could be expected that IBS patients would be more anxious and depressed than IBD patients, but this is not the case. Two percent of patients diagnosed with IBS among the adult residents of Olmsted County, Minnesota, United States, were found to suffer from depression compared to the 16.2% incidence of depression in the entire population of the United States\[122,123]. In conclusion, there is no convincing evidence to show that psychological factors play a role in the onset and/or progression of IBS\[66].

The pathogenesis of IBS appears to be multifactorial. There is evidence to show that the following factors play a central role in the pathogenesis of IBS: heritability and genetics, environment and social learning, dietary or intestinal microbiota, low-grade inflammation and disturbances in the neuroendocrine system (NES) of the gut.

**Heritability and genetics**

Up to 33% of patients with IBS had a family history of IBS compared to 2% of the controls\[124]. In a study of a family cluster from Olmsted County, United States, a significant association was reported between having a first degree family member with bowel symptoms and presenting with IBS. In contrast, those who reported having a spouse with bowel symptoms were no more likely to present with IBS than the general population\[125]. It was further shown that the prevalence of IBS was 17% in the relatives of patients compared to 7% in the relatives of spouses\[126]. Another study showed that patients with IBS were more likely to present a family history of IBS than controls (33.9% and 12.6%, respectively). Moreover, 21.1% of IBS non-consultant patients reported a family history of IBS, in comparison with 12.6% of the control subjects\[127].

In twin studies, a higher rate of IBS was reported in monozygotic twins than in dizygotic twins (33.3% vs...
13.3%). Moreover, 56.9% of the variance was attributed to additive genetic factors, indicating a substantial genetic component in IBS\(^\[128-132\]\). In contrast, a study performed on British twin pairs did not show any significance in the rates of IBS between monozygotic and dizygotic twins\(^\[133\]\).

The serotonin transporter (\(\text{SERT}\)) gene encoding the SERT protein is located on chromosome 17q11.1-q12. A functional polymorphism is the insertion or a deletion of 44 base pairs in the \(\text{SERT}\)-gene-linked polymorphic region\(^\[134\]\). An association was reported between a functional polymorphism in the \(\text{SERT}\) gene and diarrhoea-predominant IBS\(^\[135,136\]\). Individuals with a long allele genotype of the \(\text{SERT}\) gene have been shown to be vulnerable to developing IBS with constipation\(^\[137\]\). Other studies, however, did not show such association between \(\text{SERT}\)-gene polymorphism and IBS\(^\[138\]\). A polymorphism in the CCK1 receptor \(\text{CCK1R}\) gene (779T>C) has also been found to be associated with IBS\(^\[139\]\).

**Environment and social learning**

Parental modelling and the reinforcement of illness behaviour can contribute to the causes of IBS\(^\[140-144\]\). Having a mother with IBS has been shown to account for as much variance as having an identical set of genes as a co-twin who has IBS. This suggests that the contribution of social learning to IBS is at least as great as the contribution of heredity\(^\[144\]\).

**Dietary and intestinal flora**

Patients with IBS believe that their diet has a significant influence on their symptoms and they are interested in finding out which foods they should avoid\(^\[145-148\]\). About 60% of IBS patients report a worsening of symptoms following food ingestion: 28% within 15 min after eating and 93% within 5 h\(^\[148\]\). Many IBS patients report specific foods as triggers, most commonly implicating milk and dairy products, wheat products, onion, peas and beans, fruits, milk and dairy products. Polyols are used in low calorie food products. Galactans and fructans are present in common dietary constituents, such as wheat, rye, garlic, onions, legumes, cabbage, artichokes, leeks, asparagus, lentils, inulin, soj; Brussels sprouts and broccoli\(^\[137\]\).

A deficiency in dietary fibre was widely believed to be the primary cause of IBS\(^\[144\]\). Although increasing the amount of dietary fibre continues to be a standard recommendation for patients with IBS, clinical practice has shown that increased fibre intake in these patients increases abdominal pain, bloating and distension. IBS patients assigned to the fibre treatment showed persistent symptoms or no improvement in symptoms after treatment compared to patients taking the placebo or a low-fibre diet. Other studies have shown that whilst a water-insoluble fibre intake did not improve IBS symptoms, soluble-fibre intake was effective in improving overall IBS symptoms\(^\[135,136\]\). It is noteworthy that the role of FODMAPs and fibre on IBS symptoms is associated with intestinal flora. The presence of bacteria that break down FODMAPs and fibre and produce gas, such as \(\text{Clostridia spp.}\), can cause distension of the large intestine with abdominal discomfort or pain.

Most bacteria in the GI tract exist in the colon. The colon of each individual contains between 300 and 500 different species of bacteria\(^\[1\]\), and each person has his own unique intestinal flora. The intestinal flora is affected by several factors, such as diet, climate changes, stress, illness, aging and antibiotic treatment\(^\[1\]\). The intestinal flora in IBS patients has been found to differ considerably from that of healthy controls, as IBS patients have fewer \(\text{Lactobacillus}\) and \(\text{Bifidobacterium spp.}\), than healthy subjects\(^\[157\]\). These bacteria bind to epithelial cells and inhibit pathogen binding as well as enhancing barrier functioning\(^\[158\]\). Furthermore, these bacterial species do not produce gas upon fermenting carbohydrates, which is an effect that would be amplified as they also inhibit the \(\text{Clostridia spp.}\). Probiotics alter colonic fermentation and stabilise the colonic microbiota, and several studies on probiotics have shown improvements in flatulence and abdominal distension, with a reduction in the composite IBS symptom score\(^\[158-160\]\).

**Low-grade inflammation**

In a subset of IBS patients GI symptoms appear following gastroenteritis, with about 25% of patients showing IBS-D symptoms 6 mo post-infection and approximately 10% developing persistent symptoms\(^\[161-164\]\). Post-infectious (PI)-IBS has been reported after viral, bacterial, protozoa and nematode infections\(^\[163\]\), with the incidence of PI-IBS varying between 7% and 31%, although the largest studies suggest this number is about 10%\(^\[161-164\]\). One study showed that 6% to 17% of sporadic (un-
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selected) IBS patients believed that their symptoms began with an infection[166]. Following infection, the initial inflammatory response shows an increase in CD3 lymphocytes, CD8 intraepithelial lymphocytes and calprotectin-positive macrophages[166]. These changes rapidly decrease in most subjects but a small number with persistent symptoms fail to show this decline[166]. Furthermore, the number of serotonin cells was shown to increase in subjects with persistent symptoms[166]. There are several pieces of evidence showing that inflammation and immune cells affect the NES of the gut, which controls and regulates GI motility and sensitivity[166]. Thus, serotonin secretion by enterochromaffin (EC) cells can be enhanced or attenuated by the secretory products of immune cells such as CD4+T[167]. Furthermore, serotonin modulates the immune response[168]. The EC cells are in contact with or very close to CD3+ and CD20+ lymphocytes, and several serotonergic receptors have been characterised in lymphocytes, monocytes, macrophages and dendritic cells[168]. Moreover, immune cells in the small and large intestine show receptors for substance P and vasoactive intestinal polypeptide[169].

IBS occurs in 32%-46% of patients with ulcerative colitis (UC) and in 42%-60% of Crohn's disease patients who are in remission[170-174]. Faecal calprotectin has been found to be significantly elevated in UC and Crohn's disease patients with criteria for IBS, compared to those without IBS-type symptoms, indicating the presence of occult inflammation[175].

Abnormalities in the NEC of the gut in IBS

The NES of the gut consists of two parts: endocrine cells scattered among the epithelial cells of the mucosa facing the gut lumen, and peptidergic, serotonergic and nitric oxide-containing nerves of the enteric nervous system (ENS) in the gut wall (Figure 4A)[176]. This system regulates several functions of the GI tract, such as motility, secretion, absorption, microcirculation in the gut, local immune defence and cell proliferation[177]. This regulatory system includes a large number of neuroendocrine peptides/amines, which exert their effects via a number of actions: an endocrine mode of action, by circulating in the blood to reach distant targets, an autocrine/paracrine mode, which is a local action, and via synaptic signalling or via neuroendocrine means, which involve the release from synapses into the circulating blood. The different parts of this system interact and integrate with each other and with afferent and efferent nerve fibres of the central nervous system, in particular the autonomic nervous system. There are at least 14 different populations of endocrine or paracrine cells in the GI tract[176]. The ENS comprises a large variety of neurotransmitters and associated receptors. Almost every known neurotransmitter can be found in the ENS, and most of the receptors associated with these neurotransmitters are also expressed there[177].

In the stomach of patients with IBS, the density of ghrelin-immunoreactive cells in the oxyntic mucosa was found to be significantly lower in IBS-constipation patients and significantly higher in IBS-diarrhoea patients compared to healthy controls[178]. However, the levels of total or active ghrelin in plasma and stomach tissue extracts from IBS patients did not differ from those of healthy subjects[179,180]. Ghrelin is a 28-amino acid peptide hormone that was originally isolated from the stomach[178]. Ghrelin mostly originates from endocrine cells in the oxyntic mucosa of the stomach, but small amounts are expressed in the small intestine, large intestine and in the arcuate nucleus of the hypothalamus[177]. Ghrelin has several functions, including a role in regulating growth hormone (GH) release from the pituitary, where it acts synergistically with the GH-releasing hormone[178,179]. Ghrelin also increases appetite and feeding and plays a major role in energy metabolism[178,180]. Furthermore, this hormone has been found to accelerate gastric and
small and large intestinal motility\cite{181, 192}, as well as having anti-inflammatory actions and protecting the gut against a wide range of insults. The density of neuropeptide-expressing cells is altered in the small intestine of IBS patients. Thus, the density of cells expressing gastric inhibitory polypeptide and somatostatin is decreased in patients with both diarrhoea- and constipation-predominant IBS subtypes\cite{193}. The densities of secretin and cholecystokinin (CCK)-expressing cells are decreased in the diarrhoea-predominant subtype, but not in the constipation-predominant subtype. Serotonin cell density has also been found to be unchanged in the duodenum of IBS patients, regardless of the subtype\cite{193}, which is interesting as serotonin cells were previously reported to be affected in the small intestine of IBS patients\cite{194, 196}. These peptides all play important roles in secretion and gastric motility. In the large intestine, serotonin and polypeptide YY (PYY) cell densities have been found to be low in both IBS-constipation and IBS-diarrhoea patients (Figure 5)\cite{197}. Furthermore, the mucosal 5-HT concentration has also been reported to be low in IBS patients\cite{197}, which is in line with current observations. In PI-IBS, the number of CCK and serotonin cells has been reported to be increased in the small intestine\cite{198}, and serotonin and PYY cell numbers were found to be increased in the large intestine\cite{199, 202}.

**HYPOTHESIS**

As described above, abnormalities in the neuroendocrine peptides/amines of the gut have been reported. These abnormalities could cause disturbances in digestion, GI motility and visceral hypersensitivity. These abnormalities appear to contribute to symptom development and could play a central role in the pathogenesis of IBS. Genetic differences have been found between IBS patients and healthy subjects in genes controlling the serotonin signalling system and CCK. Moreover, differences in the diet, intestinal flora and inflammation affect the NES of the gut. The release of different gut hormones depends on the composition and quantity of ingested food, as the food content of FODMAPs and fibre, intestinal flora and the subsequent fermentation can increase intestinal osmotic pressure. This change in intestinal pressure can stimulate hormonal release, such as the release of serotonin. Likewise, inflammation and the release of secretory products from immune cells effects hormonal release and the proliferation of gut endocrine cells.

Therefore, it is feasible to hypothesise that the cause of IBS is an altered NES (Figure 4B). An altered NES would cause abnormal GI motility, secretion and sensation, all of which are characteristic of IBS\cite{203, 204}. The alteration in NES could be a result of one or more of the following: genetic factors, dietary intake, intestinal flora or low-grade inflammation.

**CONCLUSION**

The diagnosis of IBS is based on symptom assessment and the Rome III criteria. Whereas the latter has been...
widely used in scientific studies and in GI congresses in the past 10 years, it is not, however, used by most clinicians consulted by IBS patients. This is not because these clinicians are unaware of the Rome III criteria, but because of the reality in the clinic. IBS patients that seek advice from a doctor are worried and want to be investigated, and are rarely satisfied until this is done, so they will repeatedly seek healthcare until they are investigated. I believe, therefore, that the Rome III criteria should be combined with a physical examination, blood tests, gastroscopy, duodenal biopsies and colonoscopy with segmental biopsies. These examinations and tests, in addition to the Rome III criteria, would reassure the patient and exclude CD, IBD, MC and cancer. Furthermore, performing these examinations and tests would remove the pressure applied by some patients to perform these examinations repeatedly, as the need for further investigations can always be argued against if there are no new symptoms. Duodenal chromogranin A cell density also appears to be a promising biomarker for the diagnosis of IBS.

The pathogenesis of IBS appears to be multifactorial. There is evidence to suggest that the following factors play a central role in the pathogenesis of IBS: heritability and genetics, dietary and intestinal microbiota, low-grade inflammation and disturbances in the NEC of the gut. Several authors have tried to connect these factors in a logical cause-effect pattern, but it is my belief that the proposed hypothesis presented in this review is the most logical.

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