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Review Article

Irritable Bowel Syndrome (IBS): A Review

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Abstract: Nowadays irritable bowel syndrome is one of the most common functional gastrointestinal disorders (FGIDs) with global prevalence. It's described by a change in the habit of the bowel system. Pathophysiology of IBS is unclear, therefore; IBS becomes a specific subject for many researchers to investigate and discover some biomarkers associated with IBS. Symptoms are a confusion of abdominal pain and bloating which is demonstrated according to Rome criteria. In this mini-review, we conclude that IBS makes additional complications in patients such as reflux gastro esophagus, dysphagia, and factors related to IBS are varied including gender, food, family, and environment. Furthermore, food and lifestyle have a direct role in the pathophysiology of IBS patients. Finding additional signs and symptoms of IBS is essential for diagnosis because IBS is dependent on symptoms. IBS has a significant association with genetic variants. *SLC6A4* (solute carrier family 6, member 4) is a serotonin transporter gene that gained the most attention from various researchers, therefore IBS require further investigation and discussion to demonstrate some biomarkers and factors associated with them.

Keywords: Irritable bowel syndrome, Rome criteria, FGID, Abdominal pain, Bloating.

1. Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal (GI) disorder that is characterized by altered bowel habits associated with abdominal discomfort or pain without detectable structural and biochemical abnormalities, now IBS is a global health problem [1-3]. The comprehension of irritable bowel syndrome (IBS) has undergone rapid development with scientific progress, but it was historically recognized more than 150 years ago. In 1849, Cumming reported, "The bowels are at one time constipated, another lax, in the same person. How the disease has two such different symptoms I do not profess to explain" [4,5]. IBS is a common functional bowel disorder and is the most frequently diagnosed gastrointestinal condition. IBS generates a significant health burden, which can seriously affect the quality of life. Etiology is not well understood and there are many factors involved. It is important to understanding the pathogenesis of IBS because new drugs are starting to target the known IBS pathophysiological mechanisms [3-6].

In the pathogenesis of IBS altered gastrointestinal motility, visceral hypersensitivity, post-infectious reactivity, brain-gut interactions, alteration in fecal microflora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all of them were implicated. The perceived symptoms consist of abdominal pain or discomfort, bloating, diarrhea, and constipation. Health care has traditionally focused on the symptomatic treatment of these patient complaints [7]. Serotonin is primarily present in the intestinal enterochromaffin cells and is a significant regulator of the intestinal peristaltic reflex and sensory relays [8].

The abnormality of serotonin regulation in the IBS is supported by two lines of evidence. Serotonin release in plasma appears to be increased in diarrhoea-predominant IBS (IBS-D) and decreased in those with constipation-predominant IBS (IBS-C) [9]. Serotonin signaling defect was observed in both IBS and ulcerative colitis, with reduced normal mucosal serotonin and serotonin transporter immunoreactivity [10]. Research focused on molecular level has also begun with serotonin receptor agonists and antagonists. It is must be considered the role of psychosocial factors in IBS, as these factors influence treatment options and patient expectations. According to the technical review of the American Gastroenterology Association (AGA). In primary care practices, the

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number of IBS-related patients approached 12% and is by far the largest subgroup in gastroenterology clinics [11].

Functional GI disorders (FGID), functional dyspepsia (FD) and IBS have a prominent place in functional somatic syndromes along with chronic fatigue syndrome and fibromyalgia, with which they often overlap. Psychosocial factors are assumed to affect GI sensorimotor activity and/or the generation of symptoms in FGID. Mechanisms by which psychosocial factors can act on GI function or symptomatology have been partially clarified by modern epidemiological, psychophysiological and functional brain imaging research [12].

2. Epidemiology and Disease Burden

Typically, IBS incidence rates are not calculated and prevalence rates fluctuate internationally, both within and between countries. These differences were attributed to the heterogeneity of prevalence studies, includes differences in the use of instruments, procedures, diagnostic criteria, populations and cultures. 83 community-based studies of IBS prevalence have been analyzed from around the world, confirming the global predominance of women who are suffering from IBS. However, the global prevalence rate could not be estimated confidently due to the heterogeneity of the investigations. The combined prevalence rate for North America, Europe, Australia and New Zealand was reported as 8.1% [13]. Globally, the prevalence of IBS is 11.2% (95% CI, 9.8–12.8). The lowest prevalence of IBS is found in Southeast Asia (7.0%) and the highest in South America (21.0%) (Fig. 1) [14].

Unfortunately, the burden or adverse effects of IBS are more consistent than the variability of prevalence estimates. IBS is not associated with higher mortality rates, but it puts a significant burden on patients and community as a result of direct medical costs, loss of productivity, reduced quality of life [15]. In 2010 U.S. patients made a total of 2,403,751 physicians, emergency, and hospital OPDs visits for IBS [16]. In the US Indirect costs (e.g. loss of work and reduced productivity) of IBS were estimated at up to $20 billion per year, with an estimated annual cost of $9933 per patient in 2012 [17].

Numerous studies have documented the excessive usage of health care services by IBS patients, as well as the adverse effect of IBS on the quality of life of patients [18]. Despite increasing medical attention to IBS patients, many patients experience difficulties and problems with their healthcare needs [19].

3. Rome criteria

In 1978 the first diagnostic criteria based on symptoms for IBS was Manning Criteria developed by Manning and colleagues in Bristol. Basically, Manning Criteria was the foundation for Rome's symptom-based criteria for IBS [20]. In 1989, the first consensus-based diagnostic criteria for IBS were published [21].

Experts from the different anatomic regions established five anatomic domains (esophagus, gastroduodenal, bowel, biliary, and anorectal). Several disorders have been identified within each region and their clinical features, diagnosis (using symptom-based criteria), and treatment were categorized for each region. This classification system with diagnostic criteria for all of the FGIDs published in Gastroenterology International. A series of publications related to each anatomic domain were published over the next few years [22].

New criteria for 21 functional GI disorders, a validated questionnaire was created to use in epidemiologic surveys and clinical studies. This questionnaire was applied in the US House-holder study, the first national epidemiologic database on the prevalence, demographic factors, and health care seeking features of people with FGIDs [23].

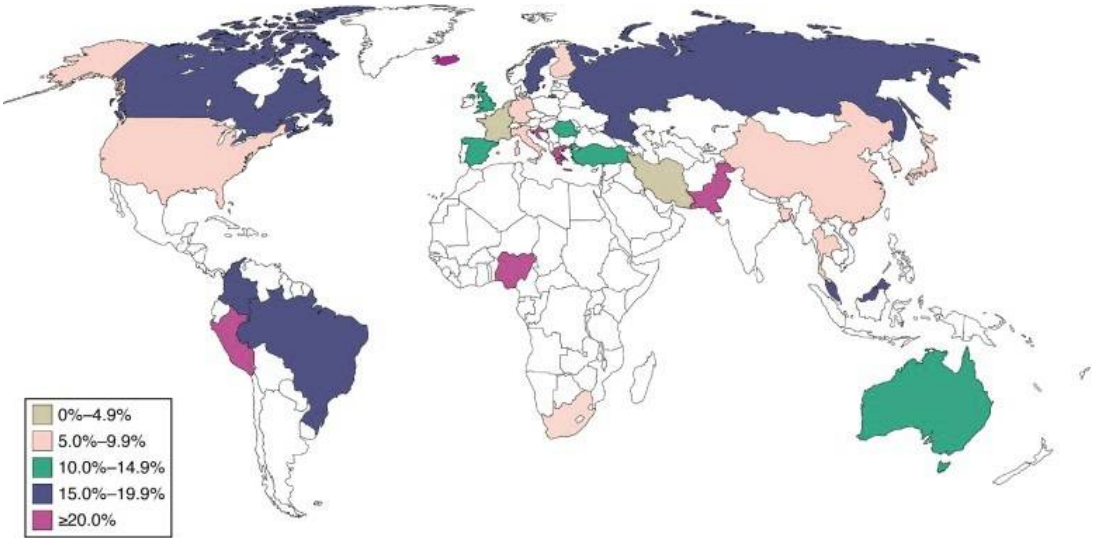

Fig. 1: Prevalence of IBS in world regions [14].

In 1994, A series of documents published in the early 1990s were eventually compiled into a book "The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment" and recognized as Rome I [24]. Rome I criteria was developed through expert consensus and using the Delphi approach. This is the first of the ongoing series of criteria for the standardization of IBS diagnostic criteria [25].

By the mid-1990s, the US Food and Drug Administration recommended the use of the IBS criteria to select patients for pharmaceutical studies, and the pharmaceutical industry took an interest in supporting the Rome Foundation's efforts. Then, by the late 1990s, 52 authors from 13 countries were recruited by the foundation to update the literature and produce the Rome II book [26]. In 1999, standardized symptom-based criteria were introduced for pediatric functional gastrointestinal disorders (FGIDs) with the publication of the Rome II criteria [27].

After Rome II publication, the number of studies conducted using the Rome criteria in clinical trials increased over the next 12–14 years. With the addition of several new chapters, Rome III was published in 2006. Rome III differed from Rome I and Rome II by the use of more evidence-based rather than consensus-based data [28]. It is classified into subtypes based on the consistency of the stool rather than the stool frequency, including IBS-C (constipation), IBS-D (diarrhoea), IBS-M (mixed) and IBS-U (unsubtyped) [29].

In May 2016 Rome III had been revised to Rome IV, with new chapters on multicultural differences, age-gender-women's health, the intestinal microenvironment, biopsychosocial issues, and centrally mediated disorders. One major change in the Rome IV criteria is that abdominal pain must be present in order to diagnose IBS [30].

IBS is defined in Rome IV as a functional bowel disorder in which chronic abdominal pain is related to defecation or changes in bowel habits. Usually, disordered bowel habits are present as abdominal bloating/distension symptoms (i.e., constipation, diarrhea or a mix of constipation and diarrhea). Symptoms onset should appear at least 6 months before diagnosis and symptoms should occur within the last 3 months [29].

4. Clinical manifestations

Symptoms include gastrointestinal and extraintestinal disorders with the primary (main) gastrointestinal syndrome that show chronic abdominal pain and altered bowel habits (Fig. 2) [31].

4.1 Chronic abdominal pain

Abdominal pain is generally characterized as a feeling of cramps of varying severity with occasional exacerbations. The pain is usually found in the lower abdomen, which is often experienced in the lower left quadrant [31].

4.2 Altered bowel habits

Patients with IBS frequently complain about altered bowel habits, this can be seen in the volume, frequency and consistency of the patient stools [31].

4.3 Diarrhea

In general, diarrhea is characterized as regular loose stools of small to moderate volume. Stools usually occur during the waking hours of the patients; often in the morning or after meals. Lower abdominal cramps (tenesmus) precede most bowel movements. Perceived urgency of defecation and often fecal incontinence, followed by an incomplete feeling of defecation.

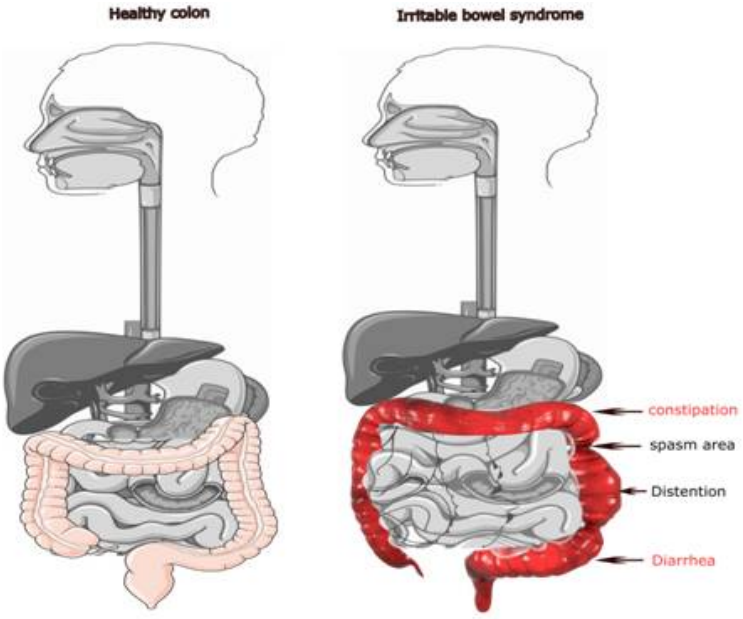

Fig. 2: Changes in large intestine structure in patients with IBS.

About half of IBS patients complain that there was a mucosal discharge along with their stools. IBS is not associated with large volume diarrhea, bloody stools, nocturnal diarrhea and greasy stools. A patient subgroup experiences an acute viral or bacterial gastroenteritis known as postinfectious IBS [31].

4.4 Constipation

Stools are hard and can be described as pellet-shaped. Feeling of incomplete evacuation experiences by the patients, even if the rectum is completely empty. This can result in a long time spent in the bathroom [31].

4.5 Upper gastrointestinal symptoms

Upper GI symptoms include gastroesophageal reflux, dysphagia, early satiety, intermittent dyspepsia, nausea, and non-cardiac chest pain. Patients often complain of abdominal bloating and increased gas production in the form of flatulence or belching [32].

4.6 Extra-intestinal syndrome

Symptoms include reduced sexual activity, dysmenorrhea, dyspareunia, and a rise in urinating frequency and urgency. Hypertension, asthma, or fibromyalgia are more common in patients [33,34].

5. Factors affecting irritable bowel syndrome

5.1 Gender Role

Gender appears to play a significant role in IBS. Two-thirds of IBS patients are female, with an estimated prevalence of 14% to 24% among women. There is a significant clinical association between IBS and other female predominance functional pain syndromes such as fibromyalgia, chronic fatigue syndrome, interstitial cystitis, and migraine headaches with aura. The impact of gender differences in IBS also extends to differences among IBS patients. Recently, interest in gender differences within the IBS patient population has been renewed because of the demonstration of novel pharmacological therapies for IBS (5-HT_3 antagonist and 5-HT_4 agonist) may show higher efficacy in treating symptoms in female patients. Evidence is also available to support gender differences in IBS physiologic responses and clinical symptoms that may be partly responsible for the heterogeneous responses seen in most IBS studies. Modulating factors that may influence clinical presentation and physiologic responses, which may differ in men and women, include biobehavioral stress response, gender role, hormonal factors, and psychological symptoms [35].

Researchers compared the symptoms of GI in both men and women with IBS. Women were found to have more symptoms of nausea, constipation, and bloating, while men with IBS reported more diarrhea [36,37,38]. In addition, women were more likely to experience viscerosensory and somatosensory extracolonic symptoms (urinary urgency, alterations in taste, muscle stiffness, aching) compared to men [36]. No differences in abdominal pain severity were reported between men and women. Taub *et al.*, used factor analysis and suggesting that the same bowel symptoms (loose stools with the onset of pain, more frequent stools with the onset of pain, pain relieved by defecation, and postprandial exacerbation) would cluster together in men and women. Such symptoms were more common in women than men [39].

Toner *et al.*, provided insight into gender-related variations in how symptoms could be experienced and interpreted. They offer an alternative concept of gender role, defined as generalizations of appropriate male and female characteristics associated with masculinity and femininity. It has been suggested that there are several common gender role concerns or themes among women with IBS including shame and bodily functions, bloating and physical appearance, and pleasing others, assertion, and anger. Women with IBS usually experience feelings of shame associated with losing control of bodily functions. Women are taught that bodily functions are something to be kept private and secret. One important implication of such teachings is that bowel functioning becomes a source of shame and embarrassment more so than it does for men. Women often score higher on indices of bloating and constipation. Bloating as a physical disorder that creates a fatty appearance is a cause of physical pain and psychological distress in women with IBS [40,41].

A research conducted in an outpatient clinic using interpretive approaches found that women were affected by how IBS affects their relationship roles as partners and mothers, as well as their job decrement. On the other hand, men have been affected by how IBS interrupts masculinity development through the label 'female health concern' attached to the condition and the ways symptoms make them feel vulnerable and incapable of doing anything, thereby stopping them from being able to help their families reliably. A more gender-based approach in clinical settings would also improve awareness among patients with IBS [42].

Women with IBS suffer more often from constipation than men with IBS, except during times of menstruation when the levels of ovarian hormones are low. It's also recognized that women have slower GI transits than men. Colonic transit times in women are delayed when they have higher levels of ovarian hormones. Not enough work has been carried out into the role of male hormones in IBS. Androgens were reported to be protective against chronic pain disorders in humans and testosterone showed an analgesic effect in experimental pain models. Differences in levels of androgen, receptors and sites of action can play a role in the gender differences in both IBS and development of chronic pain disorders. Recent research found that middle-aged people with IBS tend to have lower luteinizing hormone levels than healthy men and that IBS symptomatology tends to be inversely related to

testosterone. Furthermore, it suggests that high concentration of sex hormone-binding globulin (SHBG) can play a role in IBS production [43].

5.2 Stress and Psychological Factors

Psychological disorders (anxiety and depression) are common comorbidities in IBS and stress was associated with exacerbations of IBS symptoms (Fig. 3). Some patients report avoiding social activities in order to prevent embarrassment due to postprandial exacerbation of symptoms (flatulence and distension) and lack of access to toilets, which leads to social isolation [44].

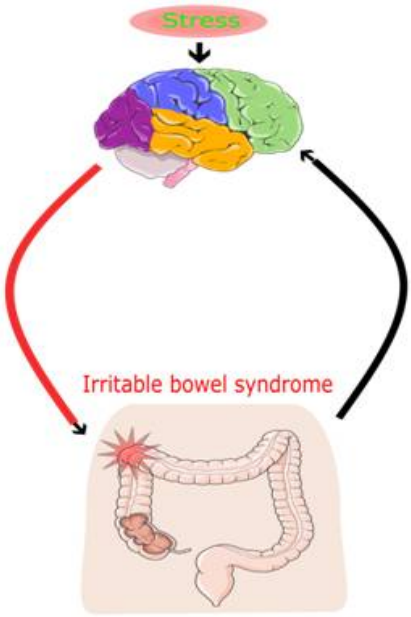

Fig. 3: Relationship between stress and Irritable bowel syndrome.

Corticotrophin-releasing hormone (CRH) mediates the stress response of the gut-brain axis and colonic motility has been shown to increase and promote inflammation through increased intestinal permeability in IBS patients [45]. Other effects of CRH on the intestines that can contribute to IBS symptoms include changes in the intestinal microbiota, altered secretions, visceral sensitivity, and mucosal blood flow [46]. CRH plays a stimulatory role in the stress response by activating CRHR1, while the specific actions of urocortin 2 and urocortin 3 on CRHR2 may be important to reduce stress response. Therefore, dysfunction of CRH signaling is considered to be related to the pathophysiology of IBS [47].

5.3 Diet

Food is considered to have a major role in IBS. There are several pathways that may link food intolerance to symptoms of IBS e.g. osmotic and fermentation effects, changes in neurohormonal or intestinal immune function, changes in intestinal microbiome or permeability. Food is a mixture of many different constituents, many of which may affect the function and sensation of the intestine [48].

There is a consensus that food and lifestyle recommendations will be the first-line solution to IBS dietary management. Any health care professional provides healthy eating and lifestyle advice in IBS dietary management. Several studies reported irregular eating habits in IBS patients may affect colonic motility and therefore contribute to IBS symptoms. Generally, recommendations are based on regular eating habits and limit the consumption of possible dietary causes such as alcohol, caffeine, spicy foods, and fat. Also includes adequate hydration and daily physical activity. Second-line IBS dietary management solution includes advanced dietary manipulations to reduce symptoms, like low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet. FODMAPs are not absorbed into the colon, where they increase luminal water by osmotic activity and cause gas production because of fermentation by colonic bacteria, which can lead to luminal distension and GI symptoms in IBS patients [49].

Recent studies of low FODMAP diets showed promising preliminary data in reducing GI symptoms. Research showed that low FODMAP diet has reduced the frequency of GI symptoms in 30 subjects (10 IBS-D, 13 IBS-C, 5 IBS-M, 2 IBS-U), specifically, reducing abdominal pain, bloating, and flatulence [50]. In a non-randomized observational study of 90 patients with IBS, almost 75% reported symptom relief, a low FODMAP diet improved abdominal pain/discomfort, bloating, constipation, and bowel urgency [51]. However, a recent study compared traditional dietary advice (regular eating habits, reduced intake of coffee/alcohol) to a low FODMAP dietary recommendation for IBS. Determined that the severity of the symptoms had decreased in both groups with no significant difference [52].

5.4 Socioeconomic, family and environmental factors

Like some other health problems, IBS has a wide distribution of socio-economic factors. The prevalence of IBS among people with a lower household income was significantly higher [53]. Decreased IBS prevalence has been reported according to income and education from the lowest to the highest groups [54]. Another study also showed that unemployed people were more susceptible to IBS than working people [55]. Despite the well-defined diverse IBS distribution, the determinants of this diversity according to socio-economic status have not been recognized and described using specific inequality indices [56].

The pathogenesis of IBS is based on a biopsychosocial model [57]. The biopsychosocial model was first suggested by George Engel in 1977 takes into account the relationship between biological, psychological, and social factors. This model suggests that there is an underlying biologic predisposition for IBS

that may be affected by environmental factors and psychological stressors, which contribute to the development of disease, patient perception of illness, and effect on treatment outcomes. Various studies have shown that stress may result in the release of stress-related hormones that affect the function of colonic sensorimotor (corticotropin-releasing factor [CRF] and inflammatory mediators [interleukin (IL)-1]). This leads to inflammation and alteration of GI motility and sensation [58].

The best known environmental cause of IBS is bacterial gastroenteritis. Many studies support the view that IBS may occur in some patients after exposure to acute gastroenteritis (postinfectious IBS) [57], with an incidence that varies from 3.6% to 36.2%, compared to 0.3% to 10.2% in controls. Risk factors for the development of PI-IBS include longer duration of illness, severe diarrhea, prolonged fever, younger age, and psychological comorbidities (including anxiety and depression). In patients with PI-IBS, pathophysiological changes include increased EC cells in the rectal mucosa, increased intraepithelial lymphocytes, and increased postprandial serotonin levels [44]. Several bacterial pathogens, including *Campylobacter*, *Shigella*, *Salmonella* and *E. coli* 0157:H7 have been involved in the development of PI-IBS [59].

Other possible environmental risk factors for IBS include childhood exposure to violence or sexual abuse, and a higher childhood socioeconomic environment [60]. Pathophysiological relationships between childhood abuse and IBS show subsequent alterations in norepinephrine and serotonin levels as well as dysregulation of the HPA system. Subsequently, these changes may affect intestinal motility and distort pain recognition [61].

IBS strongly aggregates in families. The strength of the association varies somewhat depending on the relationship with the proband. However, the lack of association in spouses supports either a possible genetic etiology or a shared household environmental exposure as an underlying cause of IBS. Twin studies and abdominal symptoms support the concept that IBS may be a complex disorder with genetic and environmental contributors [62].

6. The genetic construction of IBS

Twin studies showed that IBS is twice prevalent in monozygotic twins than in dizygotic twins. IBS may be associated with selected gene polymorphisms, including those in IL-10, G-protein GNb3, alpha-adrenoceptor, and serotonin reuptake transporter (SERT) [58].

Twin and family studies have demonstrated a heritable component of IBS, while heritability estimates varied between 0 and 57% [63]. Recently, however, the Swedish national survey, which included more than 50,000 cases, has shown increased IBS risk, among first-, second- and third-degree relatives, clearly indicates that there is a genetic component exists [64]. In IBS, genetic risk spans from complex polygenic conditions with the combination of common genetic variants to cases with rare single gene abnormalities [65]. Subsets of patients may be present where highly penetrant genetic variability accounts for most of the phenotype in the individual genes [66].

Specific "candidate" genes have been evaluated by a number of investigators. Based on the biological plausibility the protein product of the candidate gene may play a role in the pathophysiology of the disease. Polymorphisms are common genetic variation within these genes that are believed to be responsible for the development of the disease. The gene that has received the greatest attention from different researchers is the serotonin transporter gene (*SLC6A4*, solute carrier family 6, member 4). Serotonin transporter is a protein on the presynaptic terminal which is responsible for reuptake of serotonin from the synaptic cleft. 5-HTTLPR (serotonin transporter-linked polymorphic region) is the most studied genetic polymorphism is in the promoter region of the serotonin transporter gene (Fig. 4). Researchers evaluated this polymorphism in U.S., Turkish and Korean patients; however, this polymorphism was not found to be more common in cases than controls [67].

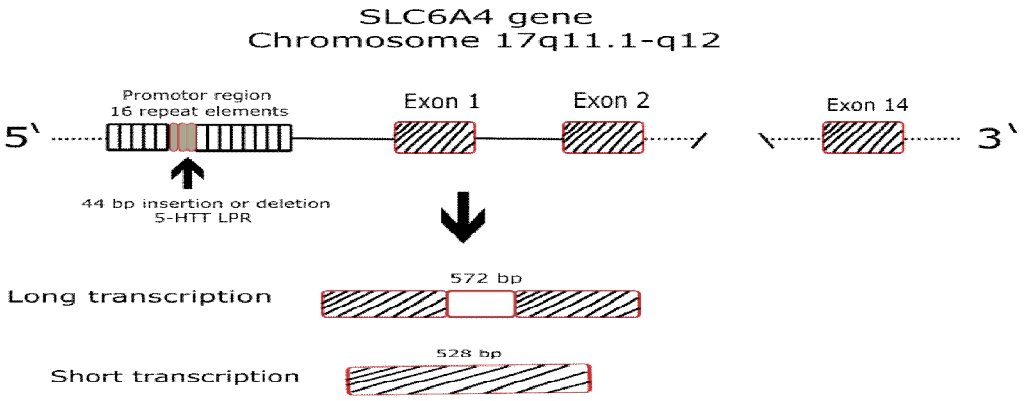

Fig. 4: The serotonin transporter gene (*SLC6A4*) contains the 5-HTTLPR polymorphism that results in a 44 base pair (bp) insertion/deletion of repeat elements 6–8 in the promoter region. This polymorphism results in a long and short transcript with functional differences [67].

A meta-analysis also concluded that 5-HTTLPR polymorphism is not associated with IBS or its subtypes [68]. Additionally, two studies have shown that this polymorphism can predict the response to therapy. In particular, the LL genotype was associated with better treatment response to alosetron, a 5-HT_3 (5-hydroxytryptamine receptor 3) receptor antagonist [69], and the S allele was associated to predicting the response to tegaserod therapy among constipated-predominant IBS patients in an allele dose-dependent manner [70].

7. Pathogenesis of the IBS

Irritable bowel syndrome is a chronic heterogeneous multifactorial (genetic, physiological, psychosocial and environment) gastrointestinal (GI) disorder [15]. IBS is characterized by abdominal pain and changes in the form of stool which cannot be explained by structural abnormalities. Its prevalence varies from 9 to 23% of the world population. Pathogenesis and pathophysiology of IBS are complex and incompletely understood. Biopsychosocial definition suggests that the disorder is a result of psychosocial factors and has been altered at various levels of gut physiology interactions. Some aetiological factors have already been identified. Disruption of brain-gut mutual communication, leading to visceral hypersensitivity is one of the most important. Genetic and epigenetic factors are also involved. Chronic stress can predispose and worsen the symptoms of IBS. Both quantitative and qualitative disorders are observed in the gut microbiota. The symptoms of IBS are often related to the consumption of a specific type of food product. The role of previous GI infection is shown in diarrhoea type of IBS. Recent studies have shown that visceral hypersensitivity can be secondary to immune cell activation and low-grade inflammation in IBS patients. Abdominal pain, change in bowel habits, somatic and psychiatric comorbidities are clinical symptoms of IBS [71]. Other factors contributing to the development of IBS may include genetic predisposition and environmental interactions, such as family susceptibility and psychosocial stressors [72].

IBS is known to be aggregated in families and to affect several generations, but not in a manner consistent with a major Mendelian effect. Relatives of an IBS individual are two to three times the risk of having IBS. In addition, IBS was clearly associated with childhood events such as nasogastric tube placement, poor nutrition, abuse, and other stressors [63]. A large proportion of IBS patients report the onset of symptoms following acute gastroenteritis [73].

After viral, bacterial, protozoa and nematode infections, the post-infectious (PI)-IBS was reported, with the incidence of PI-IBS varies between 7% and 31%, although the largest studies indicate that this is around 10% [74]. Recent findings indicate that some people are genetically predisposed to developing PI-IBS, with some individuals showing an increased pro-inflammatory and/or decreased anti-inflammatory cytokine response to infection [75].

8. Diagnosis

There is no biochemical, histopathological or radiological diagnostic test for IBS is currently available. The diagnosis of IBS is mainly based on symptom assessment and Rome criteria. Over the last few years, the Rome organization has provided detailed, accurate and clinically useful descriptions of the syndrome [74]. The Rome criteria are extensively used in clinical studies. Most primary care physicians have no knowledge of diagnostic criteria for IBS and about one-third of secondary care doctors do not use them in practice [76].

Patients with IBS are sub-grouped based on 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 unsubtyped IBS in patients with an insufficient abnormality of stool consistency to meet the IBS C, D or M criteria. It has been reported that about one-third of patients had IBS-D, one-third had IBS-C and the remainder had IBS-M [77]. Dividing IBS patients into subtypes is useful for clinical practice and symptomatic treatment. In IBS patients it is common to switch from one subtype to another over time. Such patients are known as 'alternators'. Over 75% of patients with IBS change to one of the other 2 subtypes at least once over a 1-year period [74,78].

It must be noted that there are many other conditions associated with IBS. At least half of the patients with IBS can be identified as depressed, anxious, or hypochondriacal. Fibromyalgia also occurs between 20% and 50% of IBS patients. In addition, IBS is common in many chronic pain disorders, present in 51% of patients with chronic fatigue syndrome, 64% with temporomandibular joint disorder, and 50% with chronic pelvic pain. Lifetimes rates of IBS are higher in patients with these syndromes. Patients with these co-morbidities usually have more severe IBS [76].

There is still no gold standard for the diagnosis of IBS. Therefore, clinicians and researchers depended on different criteria (Manning, Kruis, and Rome) that have been developed over the years. Although none of them proved perfect [29].

8.1 Clinical features

Apart from the symptoms included in the diagnostic criteria, there are other clinical characteristics that support an IBS diagnosis, but none of them are mandatory for the diagnosis of IBS. A recent study found variations in the consistency and frequency of stools or an unpredictable bowel pattern (irregularly irregular) may be used to properly distinguish IBS-D from organic gastrointestinal disease [79]. In addition, an abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week), excessive strain during

defaecation, urgency, feelings of incomplete evacuation and mucus with bowel movements support diagnosis of IBS but are nonspecific [80]. The same applies to postprandial worsening or exacerbation of symptoms, which is common in IBS [81] but also seen in other gastrointestinal diseases. The existence of other functional gastrointestinal diagnoses (e.g. functional dyspepsia) [82], also numerous functional non-gastrointestinal symptoms and syndromes (e.g. chronic fatigue, fibromyalgia, uro-gynaecological symptoms, muscle and joint pain and sleep disturbances) and psychological comorbidity (e.g. anxiety and depression), are all common and support the diagnosis of IBS [83,84].

8.2 Physical examination

In order to reassure patients and exclude another organic cause of the symptoms, physical examination must be a part of the diagnosis. An abdominal examination rarely shows a specific diagnosis because abdominal tenderness is observed in various diseases, but the absence of objective findings on a physical examination was found to support an IBS diagnosis [85]. In physical examination digital rectal examination is an important and valuable tool for identifying patients with dyssynergic defaecation, because it is important to exclude constipated patients as well as rectal cancer. Perianal inspection should also be included in the examination to exclude perianal fistulas and other related anal pathology [84].

8.3 Laboratory tests

From the current literature, it is not clear which laboratory test to suggest when diagnosing patients with IBS symptoms. Based on the totality of evidence, routine serological screening for coeliac disease is recommended in patients with IBS-D and IBS-M [86], even though that was not confirmed by a large multicenter, observational cohort study [87]. However, few studies have assessed the usefulness of laboratory tests. A recent systematic review has shown that C-reactive protein (CRP) levels of ≤0.5 mg per dl or faecal calprotectin levels of ≤40 µg per g essentially exclude IBD in IBS-symptomatic patients [88]. A thyroid profile may be included if there is a high clinical suspicion of thyroid disease, serological test for coeliac disease in patients with non-constipated IBS may be recommended. If an inflammatory process is suspected, a faecal calprotectin measurement may be included. Stool analyzes for gastrointestinal infections may be suggested if diarrhoea is prevalent and difficult to treat, particularly in regions where infectious diarrhoea is common [89].

9. General treatment access

IBS is a chronic, recurrent condition with a wide variety of symptoms. Therefore, the main objective of the treatment is to reduce the symptoms of abdominal pain, altered bowel transit (diarrhea or constipation) and any related symptoms such as bloating and fecal incontinence. The treatment approach should be individualized and depends on the symptom intensity and the degree of other comorbid conditions [90].

In the primary care setting, most IBS patients are treated successfully. These patients usually show mild symptoms and respond well to changes in diet and lifestyle, education and the reassurance of their disease. Gut-directed medical treatment (anticholinergics, antispasmodics and newer IBS-specific agents) is most commonly used in patients with mild to serious symptoms and is occasionally accompanied by low dose tricyclic antidepressants (TCAs) and/or other psychiatric medicines [91,92].

It is necessary to set realistic and consistent treatment objectives in all cases of IBS [90]. Patients should know that a single medication is not likely to cure all symptoms. At that time, patience, and "trial and error" use of drugs will be needed. In addition, doctors will inform patients about their diagnosis and ensure that this disease is a real medical disorder [93].

9.1 Pharmacotherapy

Therapy may include stool softeners and laxatives in IBS-C and antidiarrheals (e.g., opiate, or opioid analogs such as loperamide, codeine, diphenoxylate) in IBS-D for mild symptoms and for severe cases, stronger opiates, such as morphine and oxycodone [94]. Medication that affects serotonin (5-HT) receptor in the intestines may help to reduce symptoms. On the other hand, many patients with IBS-D report that SSRI type medications exacerbate spasms and diarrhea. This is believed to be due to the large number of serotonin receptors found in the gut [8]. Some antipsychotic drugs (clozapine and olanzapine) may also provide relief due to the serotonergic properties of these agents, they act on the same receptors as other drugs in this specific category [95]. Reduced diarrhea and reduced abdominal cramps, and improved general well-being may be the benefits. If nausea is present, that may also respond to 5-HT_3 antagonists due to their antiemetic properties [96]. Patients who are not responding adequately to dietary fiber, osmotic laxatives such as polyethylene glycol, sorbitol, and lactulose can help to avoid "cathartic colon" that has been associated with stimulant laxatives [97].

Antispasmodic medicines (e.g., anticholinergic such as dicyclomine and hyoscyamine) may benefit patients, especially those with cramps or diarrhea. The Cochrane Collaboration meta-analysis concluded that if seven patients are treated with antispasmodic drugs, one patient would benefit [98]. Mebeverine hydrochloride (musculotropic antispasmodic) is a sodium channel antagonist with a direct effect on the smooth muscle of GI tract, relieving spasm without affecting normal gut motility. Pinaverium bromide (an antispasmodic) is a GI-selective calcium channel antagonist that selectively acts on the GI tract, by inhibiting the influx of calcium into

intestinal smooth muscle cells. Both antispasmodics are suggested for the treatment of IBS [99].

Proton pump inhibitors (PPIs) are often used to suppress production of stomach acid and can induce bacterial overgrowth leading to symptoms of IBS. Discontinuation of PPIs may lead to an improvement in IBS symptoms [100].

Low-dose tricyclic antidepressants (TCAs) are also used for severe diarrhea-predominant IBS because patients are constipating and can relieve anxiety and pain. However, global IBS symptoms are not alleviated by TCAs [101,102]. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressant seem to be effective in IBS due to their serotonergic effect, especially constipation-predominant patients. Serotonin agonists (Tegaserod), a selective 5-HT_4 agonist is used to relieve IBS constipation in women and chronic idiopathic constipation in men [103,104]. Evidence is conflicting as some meta-analysis reported benefits of antidepressants in IBS, whereas others have not [105].

Preliminary research on the efficacy of fecal microbiota transplant in the treatment of IBS was very favorable with a cure rate between 36% and 60% with remission of the main IBS symptoms that persists at 9 months and 19 months of follow-up [106,107]. There is increasing evidence that mesalazine an aminosalicylate drug with anti-inflammatory properties is effective in the treatment of IBS [108].

It has been proposed that small intestinal bacterial overgrowth (SIBO) is common in IBS patients. Pimentel and colleagues used lactulose breath tests (LBT) to show that 78% of IBS patients had SIBO and a seven-day course of neomycin has been associated with a significant reduction in symptoms [109,110]. However, these results are controversial, as both the accuracy of the LBT and its ability to gauge treatment response has been questioned [111,112,113]. Recently, Posserud and colleagues carried out a study using jejunal aspirates culture to detect SIBO [114]. Compared to placebo higher bacterial counts were found in IBS patients (43% *vs* 12%), but this result was not related to small intestinal motility. Additionally, there was no difference between IBS patients and healthy controls using a standard SIBO definition (> 10^5 bacteria / mL) [115]. Non-absorbable antibiotic Rifaximin can be useful in the effective treatment of abdominal bloating and flatulence [116].

H1-antihistamines and mast cell stabilizers have also been shown to be effective in reducing pain associated with visceral hypersensitivity in IBS [117].

9.2 Non-pharmaceutical therapy

9.2.1 Probiotics

A complex ecosystem of microorganisms colonizes the human gastrointestinal tract [118]. Probiotics are live strains of strictly selected microorganisms that confer a health benefit on the host when administered in adequate amounts [119].

Probiotics may help to restore alterations in the intestinal flora both qualitative (i.e. depleted bifidobacteria species) and quantitative (i.e. small intestinal bacterial overgrowth). Most frequently studied probiotics are lactobacilli and bifidobacteria [115].

To date, trials on lactobacilli remain conflicting and no clear benefit has yet to be identified. However, some efficacy is shown by bifidobacteria, *Saccharomyces boulardii*, and other probiotic combinations. A systematic review of randomized clinical trials evaluating the efficacy, safety and tolerability of probiotics in IBS found that the global and specific IBS symptoms improved significantly only with *Bifidobacterium infantis* 35624 in appropriately designed studies. It has been shown that the probiotic strain *Bifidobacterium infantis* 35624 reduces pain, bloating and defecatory difficulty and normalizes stool habit in IBS patients [120] and probiotic strain *Bifidobacterium lactis* DN-173 010 accelerates gastrointestinal transit and increases stool frequency among constipated IBS patients [121]. In view of the limited clinical trials, the role of probiotics in IBS remains uncertain [120].

9.2.2 Psychological therapies

The lack of satisfactory treatment led to the development of a variety of psychological therapies for IBS. These therapies are based on biopsychosocial model described by Engel and applied to FGIDs by Drossman and colleagues. This model states that thoughts, emotions, and behaviours are proposed to be bi-directionally related to gut physiology and symptom manifestations in IBS [122].

In recent research, several psychological and central processing mechanisms have been identified that contribute to brain-gut dysregulation, including visceral hypersensitivity, central processing deficits, and visceral anxiety. These central processes contribute to the development and maintenance of IBS and psychological treatments targeting these cognitive processes. Psychological treatments are considered to be important for IBS patients with moderate to severe symptoms or those with comorbid psychological factors who didn't respond to initial pharmacotherapy [123].

According to current NICE/NHS guidelines, physicians should recommend referral for psychological treatment in patients who do not respond to pharmacotherapy for a period of 12 months and develop a continuing symptom profile (described as refractory IBS) [124].

Several psychotherapy modalities were examined, including cognitive-behavioral therapy (CBT), gut-directed hypnotherapy, psychodynamic psychotherapy, and mindfulness [123]. CBT is the most studied form of psychological therapy with both short-term and long-term efficacy associated with an overall improvement in symptoms of IBS [125]. A case-control study showed that gut-focused hypnotherapy reduces gastrointestinal symptoms, possibly through changes in cognitive

function, leading to a decrease in visceral sensitivity [126]. In a recent study, hypnotherapy was associated with decreased abdominal pain and improved symptoms and quality of life [127]. Despite this evidence, the utility of psychological interventions in IBS is limited by availability of expert therapists [128].

9.2.3 Exercise

Exercise is beneficial to health, however, limited data with conflicting results are available to relate physical activity to IBS. Previous studies have shown that moderate physical activity is associated with improved symptoms of IBS [129]. Physical activity in healthy individuals has been associated with improvement in gas transit and abdominal distension, symptoms often seen in IBS patients [130]. Medical conditions, including depression and fibromyalgia, which are associated with IBS, were suggested to be reduced with regular mild exercise [131]. A randomised controlled trial has also documented the beneficial role of physical activity in IBS management [132]. Findings from case-control studies have shown lower physical activity in IBS patients [133]. However, Omagari *et al.*, reported a high level of physical activity among patients with IBS compared to those without IBS [134].

Yoga practice has demonstrated effectiveness in reducing anxiety and symptoms of depression and improving quality of life [135,136]. Psychological factors seem to play an important role in the cause of IBS because a strong association of psychiatric disorders can be found in 94% of IBS patients. Headache, fibromyalgia, fatigue, and depression were frequently seen in individuals with IBS. Evidence supports the role of stress in IBS patients, particularly alterations in brain-gut interactions. It was believed that yoga addresses the brain-gut axis in the management of IBS with fewer side effects than conventional medical treatments [137].

9.2.4 Diet modification

Diet appears to play a significant role in people with IBS, with up to 84% of IBS patients reporting symptoms associated with food, especially for foods that contain fermentable carbohydrates and fats. Multiple mechanisms are suggested by which food may cause symptoms in IBS. These include primary effects, such as osmotic, chemical, mechanical, neuroendocrine, pro-, pre- and postbiotic. Secondary effects include fermentation by-products, alterations in intraluminal pH and effects on the microbiome [138].

There is no convincing evidence that patients with IBS are suffering from food allergy and intolerance, and there is no evidence that gluten causes non-coeliac gluten sensitivity (NCGS). Several studies have shown that IBS patients attribute exacerbations of their GI symptoms to the consumption of specific foods, including certain carbohydrates, fruits and vegetables, dairy products, beans, and legumes. Subsequently, some dietary manipulations in the treatment of IBS were investigated, including high-fiber diets, gluten-free diets, lactose-reduced diets, low-fat diets, and diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) [126].

Individual dietary guidance for intake of low FODMAPs (fermentable oligo-, di-, monosaccharides and polyols) diet and insoluble fibers should be recommended for IBS patients in combination with probiotics and daily exercise [127].

10. Conclusion

IBS is a chronic, often debilitating functional gastrointestinal disorder in which abdominal pain or discomfort is associated with defecation or change in bowel habits. Nowadays IBS is one of the most common disorders with a prevalence varying from 9-23% of the population worldwide. This range will continue to increase without a specific known cause for IBS development. However, several studies have shown that IBS has been associated with many factors, such as stress, environment, genetics and lifestyle. Altered gastrointestinal motility, visceral hypersensitivity, post-infectious reactivity, brain-gut interactions, alteration in fecal microflora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation all of them were involved in IBS pathogenesis. Treatment options for IBS may include both nonpharmacological and pharmacological approaches. Nonpharmacological treatment approaches are sufficient for the treatment of patients with mild IBS. Pharmacological treatment approaches are mainly symptomatic. IBS is a disorder that has a complex and multifactorial etiology. The most recent iteration of symptom-based criteria for diagnosis of IBS is the Rome IV diagnostic criteria. Despite several studies on its definition, pathophysiology, diagnostic criteria and management many questions remain unanswered in this area.

Conflict of interests

The authors of this review article have no actual conflicts of interest.

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