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Conceptual Paper

The Variable Portability- Irritable Bowel Syndrome

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Preface

Irritable bowel syndrome is a frequent, chronic disorder of the gastrointestinal tract which characteristically delineates abdominal pain or discomfort and altered bowel motility and is essentially devoid of associated causes or adjunctive disease processes. Irritable bowel syndrome is a functional bowel disorder defined by onset of clinical symptoms in the absence of organic disease. Currently, Rome III and Rome IV criterion are employed in the discernment and categorization of irritable bowel syndrome [1].

Development and continuance of irritable bowel syndrome is multifactorial. Therapeutic approach is focused upon reducing the emergence of typical symptomatology and contemporary pharmacotherapy is suboptimal. Nevertheless, the disorder can be appropriately managed with administration of diverse medications and non-pharmaceutical agents.

Diagnosis of irritable bowel syndrome is one of exclusion and therapeutic intervention is contingent to emerging symptoms. Treatment of irritable bowel requires a tailored approach for optimal results [1,2].

Disease characteristics

An estimated 12% subjects mandate a therapeutic intervention, a disease prevalence of around 10% to 15% is exemplified and the essentially global condition is preponderant in South America. Disease incidence declines with enhancing age. Incidence of irritable bowel syndrome is variable internationally on account of heterogeneity of prevalence assessment, employment of diverse methodologies and instruments, varied diagnostic criterion and diversifying population and culture.

Subjects implicated with irritable bowel syndrome demonstrate a diminished productivity, inferior quality of life with enhanced percentage of comorbidities although the mortality rate is not impacted [1,2].

Irritable bowel syndrome depicts a female predominance with a female to male ratio of 1.5 - 2:1, particularly within Caucasians.

Irritable bowel syndrome delineates a specific pattern of disease emergence which is designated as irritable bowel syndrome with diarrhoea (IBS-D), irritable bowel syndrome with constipation (IBS-C), irritable bowel syndrome with a mixed bowel pattern (IBS-M) and irritable bowel syndrome un-subtyped (IBS-U). Europeans exemplify a disease configuration with predominant constipation or a mixed pattern [1,2].

Disease pathogenesis

Of obscure aetiology, irritable bowel syndrome demonstrates a broad, multifactorial origin. Physiological and psychological factors can be delineated in the aetiology and perpetuation of symptoms of irritable bowel syndrome. Contributing features include aberrant gut motility, visceral sensations, brain- gut interaction and psychosocial distress.

A singular, inciting factor is usually implicated in cogent instances although the entire spectrum of disease- specific symptoms may not be relatable to the disorder. Specific genetic predispositions, environmental interactions, familial susceptibility and psychosocial stressors are incriminated [3,4].

Immune activation of altered gastrointestinal system, intestinal and colonic microbiome can be contemplated to be concurrent to the emergence of irritable bowel syndrome. Biological dysregulation is observed and neuro-hormonal pathways require further enunciation. Proposed mechanisms which contribute to disease symptomatology incorporate gastrointestinal dysmotility, inflammation, visceral hypersensitivity and modifications of intestinal microbiota. Dietary patterns and exposure to stress within early life can incur the disorder.

Environmental factors incriminated in disease occurrence are observed to be stressors in early life, intolerance to pertinent foodstuffs, administration of antibiotics and appearance of enteric infection. Symptoms of irritable bowel syndrome are concomitant to consumption of food. Nevertheless, a distinctive food allergen is minimally implicated in the genesis of the disorder [3,4].

Post-traumatic stress disorder (PTSD), amplification of life stressors, self-observed anxiety and depression can augment probable occurrence of irritable bowel syndrome. Consequently, the brain- gut axis (BGA) is implicated. Aforesaid axis is comprised of central nervous system, enteric nervous system and autonomic nervous system. Additionally, endocrine, neural and neuro-immune pathways can facilitate a bi-directional communication occurring within central nervous system and gastrointestinal tract. Subjects can demonstrate a disturbance of brain-gut axis along with the central nervous system, autonomic functions and involvement of peripheral factors, peptides and hormones [4,5].

Typical clinical representation of irritable bowel syndrome with pain, psychological co- morbidities and altered gastrointestinal motility can ensue on account of modifications of the brain-gut axis although cogent mechanisms remain undefined.

Precise mechanism of symptom initiation remains obscure. Major constituents of stress response system such as autonomic nervous system and hypothalamic- pituitary- adrenal axis necessitate assessment [4,5].

Clinical elucidation

Irritable bowel syndrome characteristically demonstrates symptoms such as abdominal pain or discomfort, altered gut motility exemplifying as constipation or diarrhoea or a combination of the two. Additionally, abdominal bloating, distension, symptoms incurred with food consumption, divergent localization of abdominal pain and variation of stool pattern within a varying time frame can ensue. Gastrointestinal distress is observed although an estimated 40% to 60% individuals encounter comorbid psychological disorders such as depression and anxiety. Somatization is enhanced, in contrast to subjects with gastrointestinal symptoms in the absence of irritable bowel syndrome. Quality of life is compromised [5,6].

Significant clinical features are constituted by disease onset beyond > 50 years of age, severe or progressive clinical symptoms, unexplained weight loss, nocturnal diarrhoea, rectal bleeding, iron deficiency anaemia, definitive family history of organic gastrointestinal diseases as enunciated with colon cancer, celiac disease or inflammatory bowel disease. History of recent travel and social interactions is mandated. Symptoms of irritable bowel disease and various gastrointestinal disorders can overlap in clinical practice. Clinical symptoms can be frequent in incriminated individuals below < 50 years [5,6].

Typical symptoms of irritable bowel syndrome are significantly enhanced in subjects with concurrent inflammatory bowel disease, whether active disease or disease in remission, with a comprehensive prevalence of around 40%, in contrast to individuals devoid of inflammatory bowel disease. Faecal calprotectin can be adopted as an initial investigation.

Dietary intolerance to wheat, lactose, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) is observed. Fructose malabsorption can be discerned [1,2].

Diagnostic criterion

The categorical Rome III criterion are required to diagnose and categorize irritable bowel syndrome. Discernment of irritable bowel syndrome necessitates the occurrence of clinical symptoms such as pain or abdominal discomfort exceeding six month duration with a reoccurrence for a minimal period of three days in a month for a duration of preceding three months and an association of two or more factors such as:

- Alleviation of abdominal pain or discomfort with defecation
- Disease onset accompanied by altered frequency of stool
- Disease onset associated with modifications in the configuration or appearance of stool [1,2].

Rome IV criterion delineates additional specific criterion such as disease chronicity exceeding six months and current expression of disease activity appearing within preceding three months. Frequency of symptoms necessitate an appearance for minimally one day per week, abdominal pain concurrent to defaecation and onset of abdominal pain is disassociated from alterations in stool configuration.

Rome IV criterion enunciates stool sub-type to be contingent to abnormal bowel motility, in contrast to stool sub-type concordant with bowel motility pervading on all days as exemplified in Rome III [1,2].

Histological elucidation

Intestinal mucosa delineates an influx of chronic inflammatory cells, mast cells and entero-endocrine cells along with demonstrable enteric nerves. Typically, diarrhoea pattern (IBS-D) displays an enhancement of mucosal T lymphocytes, in contrast to constipation pattern (IBS-C). Augmentation of quantifiable nerve fibres immune reactive to neuron specific enolase, substance P and 5- hydroxy-tryptamine (5-HT) can be exemplified. Nerve fibres circumscribing mast cells can be significantly elevated [5,6].

Differential diagnosis

Irritable bowel syndrome requires a segregation from various conditions demonstrating clinical symptoms of diarrhoea or constipation.

Distinction is necessitated from conditions such as celiac disease, microscopic colitis, inflammatory bowel disease as in Crohn's disease or ulcerative colitis, bile acid malabsorption, colorectal cancer and dys-synergic defaecation. Comprehensive prevalence of irritable bowel syndrome with concurrent microscopic colitis is at an estimated 33% [6,7].

Subjects with predominant diarrhoea (IBS-D) require a demarcation from lactose intolerance, caffeine and alcohol consumption, gastrointestinal infections such as giardia, entamoeba histolytica, human immune deficiency virus (HIV), inflammatory bowel disease, medication induced diarrhoea as cogitated with antibiotic administration, proton pump inhibitors, non-steroidal anti-inflammatory drugs, ACE inhibitors or chemotherapy, occurrence of celiac disease, various malignant disorders, colorectal cancer, hyperthyroidism, benign adrenal tumours as with vasoactive intestinal polypeptide adenoma (VIPoma) and ischaemic colitis [6,7].

Individuals with predominant constipation (IBS-C) require a differentiation from conditions such as inadequate intake of dietary fibre, immobile status, Parkinson's disease, multiple sclerosis, spinal injury, diabetes mellitus, hypothyroidism, hypercalcemia, medication-induced constipation as elucidated with opiates, calcium channel blockers, anti-depressants, clonidine, emergence of diverse malignant disorders, bowel obstruction, endometriosis and diverticular disease of the bowel. Mandated investigations are contingent to history pertinent to indicated disease [7,8].

Investigative assay

Certain clinical symptoms can be designated as "alarm symptoms" and are categorized as weight loss, haematochezia and iron deficiency anaemia. In the absence of aforesaid features, routine diagnostic investigations may not be mandated.

With the occurrence of atypical symptoms of irritable bowel syndrome or appearance of "alarm symptoms", a comprehensive blood count, comprehensive metabolic panel, inflammatory markers such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and thyroid stimulating hormone (TSH) require evaluation [7,8].

With predominant diarrhoea (IBS-D), faecal leukocytes and infective agents such as *Clostridium difficile, Giardia, Cryptosporidium* necessitate assessment.

A cogent history with age of implicated subject, family history, dietary practices, physical and especially anorectal examination, complete blood count, faecal calprotectin, celiac disease serology and assessment of emerging "alarm symptoms" is mandated [7,8].

Haematological biomarkers composed of cytokines, nerve growth factor, autoantibodies, antibodies and serological biomarkers along with genetic expression and psychological parameters can be evaluated. Colonic transit time, faecal bile acids, anti- cytolethal distending toxin B and anti- vinculin antibodies can be employed for discerning individuals with predominant diarrhoea (IBS-D) besides assaying faecal dysbiosis to characterize irritable bowel syndrome. However, biomarkers are yet to be accepted as a gold standard for categorization of irritable bowel syndrome [7,8].

Assays for celiac disease is imperative and a tissue transglutaminase or TTG-IgA can be ordered.

Colonoscopy or upper gastrointestinal endoscopy is beneficial in instances with family history of inflammatory bowel disease, appearance of "alarm symptoms" and concurrent colon cancer. Tissue biopsy from a randomly selected site is recommended and can be obtained with colonoscopy in instances with predominant diarrhoea (IBS-D).

Variations of central processing systems of brain-gut axis can be visualized with neuroimaging techniques. Irritable bowel syndrome exhibits a divergence of the brain structure, connectivity and consequent functional response [8,9].

Therapeutic options

Irritable bowel syndrome is a disorder contingent to the appearance of typical clinical symptoms. Thus, therapy is aimed at alleviating specific symptoms such as pain, cramps, abdominal bloating, diarrhoea or constipation.

Constipation is managed with supplementation of appropriate dietary fibres. Laxatives are beneficial.

Diarrhoea can be alleviated with medications such as loperamide. Probiotic intake can be advantageous. Moderate enhancement of physical activity can decimate severity of symptoms related to irritable bowel syndrome on account of augmentation of colonic transit time [8,9].

Consumption of food can be concurrent with typical symptoms of the condition. Specific foods such as wheat, onion, fruits, vegetables, sorbitol and pertinent dairy products incorporate short chain, inadequately absorbed, preponderantly fermentable carbohydrates or FODMAPs. Aforesaid food products are associated with enhancement of gastrointestinal symptoms as cogitated in individuals with irritable bowel syndrome. Diets with minimal quantities of FODMAPs can alleviate abdominal pain and bowel symptoms.

Subjects demonstrating chronic and constant abdominal symptoms can be treated with minimal doses of tricyclic antidepressants (TCAs) or serotonin reuptake inhibitors (SSRI).

Alternative treatment modalities as enunciated with cognitive behavioural therapy, interpersonal psychotherapy and hypnotherapy can be advantageous [1,2].

Alteration of intestinal microbiota with therapeutic administration of probiotics can be employed to relieve symptoms of irritable bowel syndrome such as abdominal pain, abdominal distension and flatulence. Faecal microbiota transplantation (FMT) is contemplated as a contemporary and beneficial therapy for rejuvenating native microbiota.

Adoption of specific manoeuvers such as yoga, acupuncture, electro- acupuncture and moxibustion can aid in decimating symptoms related to irritable bowel syndrome [8,9].

Irritable bowel syndrome as a condition displays a superior prognosis and the diagnosis is consistent on further monitoring.

	Rome III Criterion	Rome IV Criterion
Diagnostic Timeframe	Symptom onset > 6 months. Symptom activity in preceding 3 months Symptom frequency at least 3 days/ month	Symptom onset > 6 months Symptom activity in preceding 3 months Symptom frequency at least 1 day/ month
Symptom description	Abdominal pain or discomfort	Abdominal pain
Symptom association (two or more)	Improvement with defaecation, onset associated with change in form and/or frequency of stool	Related to defaecation, associated with change in form and/or frequency of stool
Predominant stool pattern (IBS-C, IBS-D, IBS-M, IBS-U)	Stool type based on bowel movement on all days	Stool type based on days of abnormal bowel movement
Categorization of stool	Bristol Stool Form Scale	Bristol Stool Form Scale

Table 1: *Diagnostic Criterion of Irritable Bowel Syndrome [1].*

Abdominal Pain	Bowel Subtype IBS-C	Bowel Subtype IBS-D
Antispasmodics	Chloride channel activators	Opioid agonists
Peppermint oil	Polyethylene glycol	Antibiotics (Rifaximin)
Selective serotonin reuptake inhibitors (SSRIs)	Psyllium	Bile salt sequestrants
Tricyclic antidepressants	Guanylate cyclase C agonists	Probiotics
		Mixed opioid agonists- antagonists/ 5-HT3 antagonists

Table 2: *Therapies for Irritable Bowel Syndrome [1].*

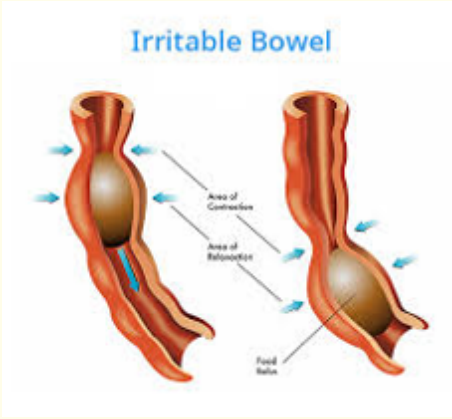

Figure 1: *Irritable bowel syndrome with zones of muscular spasm, intestinal dilatation and colonic motility [10].*

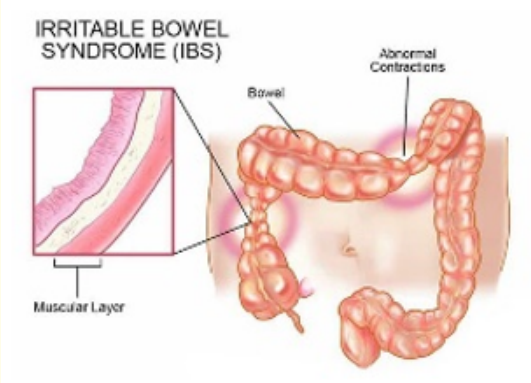

Figure 2: *Irritable bowel syndrome with colonic dilatation, muscular spasm and aberrant gut motility [11].*

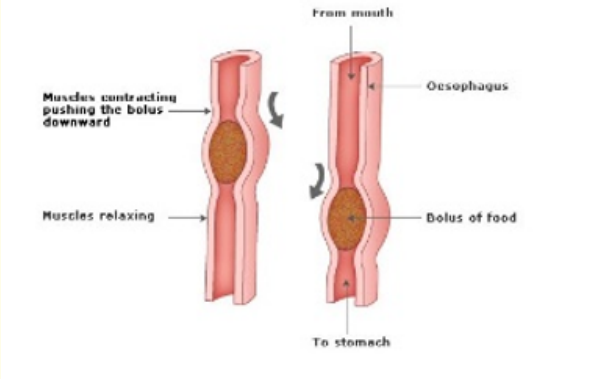

Figure 3: *Irritable bowel syndrome with gastrointestinal dilatation, muscular spasm and anomalous colonic transit [12].*

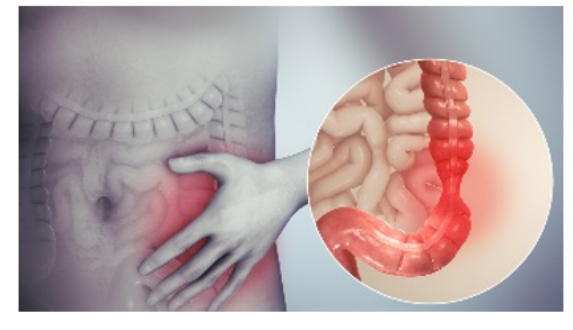

Figure 4: *Irritable bowel syndrome with abdominal cramps, flatulence, abnormal colonic transit and intestinal dilatation with contractions [13].*

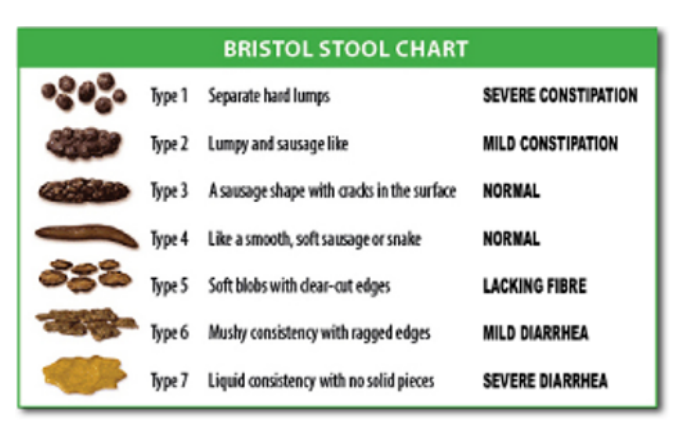

Figure 5: *Irritable bowel syndrome demonstrating varieties of stool formation as per the Bristol stool form scale [13].*

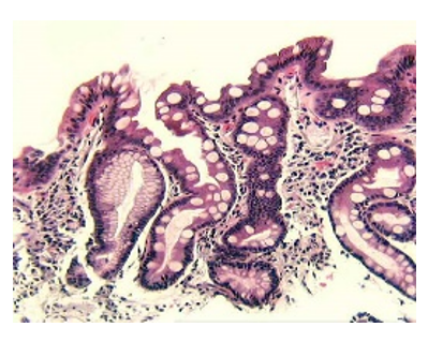

Figure 6: *Irritable bowel syndrome with demonstrable goblet cells, tortuous villi, inflammation within the lamina propria and a lack of brush border [14].*

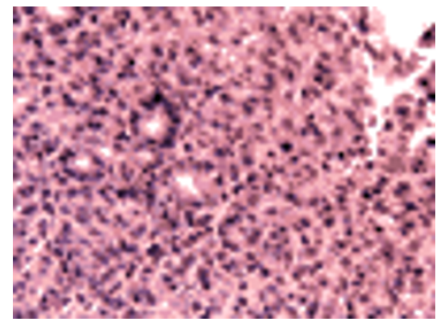

Figure 7: *Irritable bowel syndrome depicting a cluster of dysplastic epithelial glands intermixed with a chronic inflammatory exudate [14].*

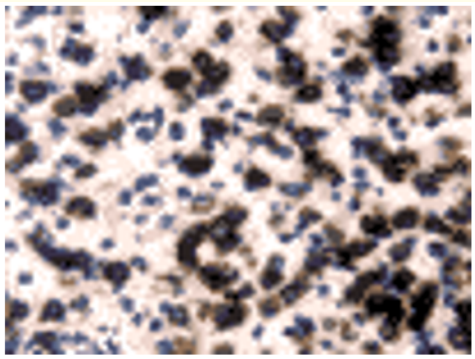

Figure 8: *Irritable bowel syndrome demonstrating immune reactivity to pan-keratin [14].*

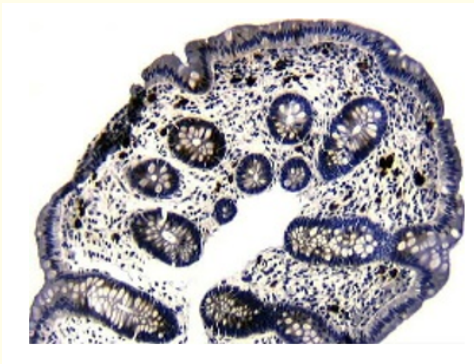

Figure 9: *Irritable bowel syndrome with immune reactivity to carcino-embryonic antigen (CEA) [14].*

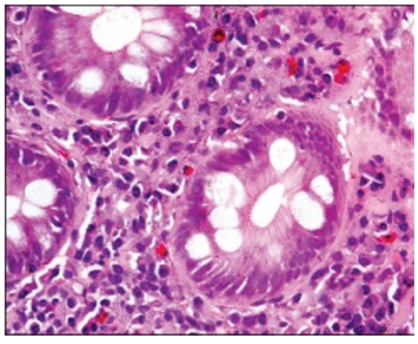

Figure 10: *Irritable bowel syndrome concurrent with infectious aetiology and an increase in the mast cells [15].*

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10. Image 1 Courtesy: Galus Australis.
11. Image 2 Courtesy: Wickenburg Community Hospital.
12. Image 3 Courtesy: Medium.com.
13. Image 4 and 5 Courtesy: Wikipedia.
14. Image 6, 7, 8 and 9 Courtesy: UPMC.
15. Image 10 Courtesy: Indian Journal of Pathology and Microbiology.

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