Irritable Bowel Syndrome

A traditional view of IBS

From “Irritable Bowel Syndrome (IBS), BetterHealth Channel from Victorian Government.

“Around one in five Australians experiences the unpleasant symptoms of irritable bowel syndrome (IBS) at some time. These include abdominal pain, mucus in the stools, and alternating diarrhoea and constipation. Other terms for irritable bowel syndrome include ‘spastic colon’ and ‘irritable colon.’

Some of the more common signs of irritable bowel syndrome include:
abdominal pain or cramping that is often relieved by passing wind or faeces

- alternating diarrhoea and constipation
- a sensation that the bowels are not fully emptied after passing a motion
- abdominal bloating
- mucus present in the stools
- nausea.

Irritable bowel syndrome can be subdivided into three major categories:

- Constipation-predominant – the person tends to alternate constipation with normal stools. Symptoms of abdominal cramping or aching are commonly triggered by eating.
- Diarrhoea-predominant – the person tends to experience diarrhoea first thing in the morning or after eating. The need to go to the toilet is typically urgent and cannot be delayed. Incontinence may be a problem.
- Alternating constipation and diarrhoea.

The underlying cause of irritable bowel syndrome is still unknown, but certain factors have been found to ‘trigger’ attacks in susceptible individuals. These include:

- Infection – an episode of gastroenteritis will often result in persistent bowel symptoms, long after the offending bacteria or virus has been eliminated. The cause of this is unknown, but may involve changes to nerve function in the bowel or changes in the normal bacterial population of the bowel. Up to 25 per cent of IBS may be due to this problem.
- Food intolerance – impaired absorption of the sugar lactose (found in dairy and many processed foods) is the most common dietary trigger for IBS. Other sugars believed to trigger IBS are fructose (present in many syrups) and sorbitol.
- General diet – low-fibre diets can exacerbate the constipation of constipation-predominant IBS. Some people find spicy or sugary foods cause problems. However, many experts are sceptical about the role of general diet, once specific food intolerances have been eliminated.
- Emotional stress – strong emotions, such as anxiety or stress, can affect the nerves of the bowel in susceptible people.
- Medication – certain types (such as antibiotics, antacids and painkillers) can lead to constipation or diarrhoea. (1)”

Current Research and its implications- the interactions of inflammatory and autonomic pathways and implications in the cause of other inflammatory disease

Recent studies indicate that the most important mechanisms in IBS include visceral sensitivity, abnormal gut motility and autonomous nervous system dysfunction. The interactions between these three mechanisms make bowel's function susceptible to many exogenous and endogenous factors like gastrointestinal flora, feeding and psychosocial factors. Recent data indicate that according to the above mechanisms, the influence of genetic factors and polymorphisms of human DNA in the development of IBS is equally important.(2)

Autonomic nervous system changes

“Most of IBS symptoms are directly related to specific abnormalities of ANS. The main characteristic of IBS patients is the increased activity of Sympathetic Nervous System (SNS) and the decreased activity of Parasympathetic Nervous System (PNS). There are differences between patients with diarrhoea and constipation as predominant symptoms and between men and women.

It is believed that vagal dysfunction is associated with constipation as a predominant symptom whereas adrenergic sympathetic dysfunction is associated with diarrhoea as a predominant symptom. Other studies reported that IBS diarrhoea-predominant patients were shown to have cortisol hyper-responsiveness unlike that of constipation-predominant IBS patients and controls. Other researchers observed elevated sympathetic dominance and vagal withdrawal during non-REM and REM sleep in diarrhoea-predominant IBS patients, but not in those with an alternating type of IBS. However, constipation-predominant IBS patients could not be distinguished from diarrhoea-predominant IBS patients or alternating type IBS with regard to autonomic nervous system. It is reported that there might be a continuum of autonomic dysfunction among these symptom-specific subgroups.” (2)

The pathophysiology of irritable bowel syndrome (IBS) is complex and not fully understood, so Liu et al (6) studies whether visceral and somatic hypersensitivity, autonomic cardiovascular dysfunction, and low-grade inflammation of the gut wall are associated with diarrhoea-predominant IBS (D-IBS). They had a significantly higher systolic blood pressure and heart rate after a cold stimulus, indicative of autonomic cardiovascular dysfunction. They also had a significantly higher level of calprotectin. They also found significant correlations between visceral and somatic hypersensitivity, visceral hypersensitivity and autonomic cardiovascular dysfunction, and somatic hypersensitivity and autonomic cardiovascular dysfunction. (6)

Visceral Hypersensitivity

The latest data indicate that the main mechanism inducing abdominal pain is the visceral hypersensitivity.(2) There is evidence that interactions within the brain and gut axis (BGA) that involves both, the afferent- ascending and the efferent-descending pathways as well as the somatosensory cortex, insula, amygdala, anterior cingulate cortex and hippocampus are deranged in IBS showing both the activation and inactivation. (7)

Alterations in the bi-directional signalling between the enteric nervous system and the central nervous system and consequently between the brain and the gut may play a significant role in the pathophysiology of IBS. (7)

The primary afferent neuron terminals of enteric nervous system (ENS) which are localized in submucosal tunica of gastrointestinal tract (Meissner plexus) and between smooth muscle fibers (Auerbach plexus) transmit stimuli to central nervous system (CNS) through sympathetic and parasympathetic autonomic nervous system (SNS and PNS).

SNS transmits stimuli which are recognized as abdominal pain, whereas PNS transmits stimuli initiating a variety of reflexes. The pain stimuli through thalamus stimulate the cerebral cortex and permit the recognition of visceral pain. On the other hand, for the integration of visceral reflexes, the afferent stimuli through hypothalamus stimulate efferent neural fibers which through PNS stimulate or inhibit the contraction of smooth muscle fibers and the secretion of enterocytes in the gastrointestinal tract modifying the gut motility and secretion.

It is known that visceral sensitivity is regulated in many levels. Specifically this regulation is mediated at the level of enteric mucosa and submucosa, the level of spinal cord, the level of thalamus and the level of cerebral cortex.(2)

Visceral sensitivity at the level of enteric mucosa and submucosa

The presence of an injury in enteric mucosa leads to the release of chemical mediators like K^+, ATP and bradykinin but also inflammatory mediators like prostaglandin E_2. These substances can directly stimulate the afferent neuron terminals but also can induce the release of algogenic substances (histamine, serotonin (5HT), nerve growth factor (NGF) and prostaglandins). This cascade leads to the amplification of the stimulus which represents the visceral pain.

There is particular interest about the interactions between afferent neuron terminals and mast cells. The release of substance P from the neuron terminals induces the production and release of histamine and NGF from mast cells. Histamine amplifies the release of substance P, whereas NGF seems to be implicated in neuron terminal's plasticity. Recent data attribute the enhancement of neural sensitivity for algogenic stimuli to increased expression of sodium channels on primary afferent endings.(2)

Impact of Stress

Chronic life event stress is a powerful predictor of symptom intensity in irritable bowel syndrome. The psychophysiological responses to such chronic stress should include alterations in cardiosympathetic and abdominal parasympathetic function. Autonomic dysregulation, consistent with the effects of chronic stress is a feature of IBS. Studies by Leach et al (8) on patients with constipation predominant constipation IBS demonstrated enhanced cardiosympathetic, and attenuated abdominal parasympathetic tone. IBS patients with predominant diarrhoea also exhibit enhanced cardiosympathetic tone but no apparent attenuation in abdominal parasympathetic tone. They felt that the predominant alteration of bowel habit may be associated with subtle differences in the overall pattern of central and abdominal autonomic reactivity. (8)

Gut motility

The enteric nervous system (ENS), which is located in submucosa (Meisner plexus) and between smooth muscle fibres (Auerbach plexus) regulates the neuromuscular function of gastrointestinal (GI) tract. Sympathetic and parasympathetic autonomic nervous system (SANS and PANS) control the function of ENS, which is related to a variety of mediators and receptors, like serotonin and its receptors. Serotonin is implicated in a variety of reflexes, which regulate the gut motility and secretory efficiency. These reflexes are integrated both at the level of enteric mucosa, through ENS and at the levels of spinal cord and subthalamus through PANS. It seems that secreted serotonin stimulates afferent terminals leading to a reflective gut peristalsis. In other words, the stimulation of afferent terminals directly modifies the gut motility.

The stimulated primary afferent neuron terminals synapse in the myenteric plexus (Auerbach plexus) with ascending and descending inter-neurons, thus inducing excitation and inhibition locally. Ascending inter-neurons activate excitatory motor neurons by releasing substance P and acetylcholine (Ach) onto myocytes resulting in circular muscle contraction. Descending cholinergic neurons stimulate inhibitory motor neurons releasing nitric oxide (NO), vasoactive intestinal peptide (VIP) and adenosine triphosphate (ATP) leading to circular muscle relaxation. The resulting peristaltic reflex is largely responsible for the bolus movement from proximal to distal sites within GI tract.(2)

Impact of diet:

Acute hypersensitivity reactions are rare causes of IBS. Patients often present with atopic conditions, such as eczema, asthma, angioedema, while they respond well to elimination diets. Those hypersensitivity reactions are mediated by degranulation of mast cells. The degranulation of mast cells leads to the production of local and systemic mediators, including histamine, which act upon adjacent smooth muscle cells and nerve endings.

Lactose intolerance, as well as intolerance to sorbitol or fructose, has been implicated in IBS. It is likely that the specific enzyme deficiency is not the cause of IBS, but that the hypersensitive guts of patients with IBS show exaggerated responses to the gaseous and fluid distention caused by incomplete absorption of carbohydrate.(2) There are so many food types that can trigger IBS symptoms, that the FODMAP diet used to treat the lactose/sorbitol/fructose intolerance is simply inadequate. Lectins is a common intolerance discussed separately, and often responsible for arthritic pain. Migratory arthritis is another disease that may reflect food intolerance.

Post Infectious Irritable Bowel Syndrome

Post infectious IBS (PI IBS) represents a subtype of IBS. It affects 6-17% of IBS patients, who had undergone a previous episode of infectious gastroenteritis. While most patients rapidly recover from bacterial gastroenteritis, about a quarter show persistent disturbance of bowel habit at 6 months and most commonly increased stool frequency. Recovery from PI IBS may be slow, with approximately 50% of patients manifesting symptoms at 5 years. (2)

Clinical features include bloating, loose and watery stools, urgency for defaecation and the passage of mucus per rectum. There are indications that an episode of acute gastroenteritis is capable to induce small intestine sensitization and symptoms of IBS, only if there are other factors mainly psychosocial, which can stimulate through psychical, neuronal and endocrinal mechanisms, the presence of mast cells and other inflammatory cells in the gastrointestinal tract.

Small Intestine Bacterial Overgrowth Syndrome

About 65-84% of IBS patients present with small intestine bacterial overgrowth, that is, presence of more than 10^5 cfu/ml of bacteria, resembles the bacterial composition of the colon, in the proximal small bowel. It has been documented that in pathological cases of small intestine bacterial overgrowth, there are excessive bacterial counts in the proximal small bowel, commonly with bacterial species including *Streptococci*, *Bacteroides*, *Escherichia*, and *Lactobacilli*.(2)

Bacterial overgrowth implies abnormal colonization of the upper gastrointestinal tract, arising from failure of specific defense mechanisms restricting colonization under physiological conditions. These defense mechanisms are the gastric acid barrier and the intestinal clearance. *H. pylori* induced-gastritis is the main cause of acquired failure of the gastric acid barrier. Failure of intestinal clearance may come as a result of impaired intestinal peristalsis, in case of myopathic,

neuropathic, autoimmune, infectious, metabolic, endocrine or neoplastic diseases. Anatomical abnormalities that alter luminal flow may as well cause failure of intestinal clearance. This may be the result of gastrointestinal surgery, intestinal diverticula, or fistula. The bacterial content of oral cavity, host's general condition, immunological disorders and bad nutrition play important role in the development of bacterial over- growth syndrome.(2)

Inflammatory activation

Low grade inflammation has been implicated as one of the underlying mechanisms of IBS. Variations in the circulating pro-inflammatory interleukin-6 (IL-6) levels and IL-6 gene polymorphisms have been demonstrated in IBS. Basasharti et al found levels of pro-inflammatory interleukins 2,6 and 8 have been found to be elevated in IBS, especially in the post-infectious IBS (against non-post-infectious IBS) and reduction of anti-inflammatory IL-10 in both. (3).

The higher IL-6 levels in IBS and more specifically in IBS-D suggests a pro-inflammatory phenotype in these patients, while this phenomenon is not supported by the polymorphism of IL-6 (-G174C). Increased IL-6 in IBS might be an acquired phenomenon or mediated by other genotypes.(9)

Zonulin and Leaky Gut Syndrome

Leaky gut, or “intestinal permeability,” is a condition in which the lining of the small intestine becomes damaged, causing undigested food particles, toxic waste products and bacteria to “leak” through the intestines and flood the blood stream. The foreign substances entering the blood can cause an autoimmune response in the body including inflammatory and allergic reactions such as migraines, irritable bowel, eczema, chronic fatigue, food allergies, rheumatoid arthritis and more.

“Zonulin works like the traffic conductor or the gatekeeper of our body's tissues," says author Alessio Fasano.(4) “Zonulin is a protein, synthesized in intestinal and liver cells, that reversibly regulates intestinal permeability. Zonulin modulates the permeability of tight junctions between cells of the wall of the digestive tract. It was discovered in 2000 by Alessio Fasano and his team at the University of Maryland School of Medicine. The classic symptom of cholera is profuse, watery, debilitating diarrhea. One of the bacterial toxins associated with cholera, called zonula occludens toxin, rapidly and reversibly opens the tight junctions between intestinal cells, temporarily causing leaky gut. Dr. Fasano and his colleagues found that cells in the human intestine produce a protein that is almost identical to the zonula occludens toxin, and they named it zonulin. Dr. Fasano’s group then isolated zonulin from human intestines and found it to increase intestinal permeability in primates.(5)

“When leaky gut is present, the spaces between the cells open up too much allowing larger protein molecules to get into the bloodstream where an immunologic reaction can take place. Once that happens, the body is primed to react to those proteins each and every time they appear. It can also cause inflammation as the immune system struggles to deal with the incoming toxins from the gut, overloading the liver’s ability to filter the toxins.(4)”

Several autoimmune, inflammatory, and neoplastic diseases have been associated with elevated levels of zonulin or evidence of increased intestinal permeability. These include celiac disease, type 1 diabetes, and juvenile nonalcoholic fatty liver disease (NASH). In addition, evidence is accumulating to support an association with multiple sclerosis, rheumatoid arthritis, asthma, and inflammatory bowel disease.(5)

“Coeliac disease offered Dr. Fasano and his team a unique model for understanding the dynamic interaction between zonulin and the immune system. Coeliac disease is a genetic disorder that affects one out of every 300 people in Europe, but its prevalence in the United States is not fully known. People

who suffer from the disorder are unable to eat foods that contain the protein gluten, which is found in wheat and other grains. The gluten sets off a reaction that can cause diarrhoea, abdominal pain, malabsorption of nutrients, and other gastrointestinal problems. “(4)

Coeliac disease can be easily treated by avoiding foods with gluten. With coeliac disease, the body reacts to gluten by creating antibodies that attack the intestine and cause severe damage over time. Unlike other autoimmune disorders, scientists also know that coeliac disease is triggered by a specific antigen, which is the protein gluten. Coeliac disease is also known to cause increased permeability of the intestine. In addition, many people who suffer from coeliac disease also suffer from other autoimmune disorders.

Conclusion

While the pathogenesis of IBS is not fully understood, it is certainly not a psychosomatic disease, although stress plays a significant role in its symptoms. It creates inflammatory and autonomic changes that can have far-reaching importance in a person’s health. When treating other diseases its importance cannot be ignored, and treating this is an integral part of any management strategy.

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