Gut motility and visceral perception in IBS patients

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SUMMARY
Although IBS is the most common functional disorder of alimentary tract in western countries, its pathogenesis is still not fully understood. It seems that multiple precipitating factors alter gut motility and visceral perception, resulting in specific motor function disorders. These disorders seem to differ between patients presenting with constipation and those presenting with diarrhea. The most common motility disorders found in IBS patients include the frequency of high amplitude propagating contractions (HAPC), the contractile activity of rectosigmoid, and the motor function changes after ingestion of food. The presence of a generalized alimentary tract motility disorder in IBS, suggests the presence of a systematic neuromuscular dysfunction. In two-thirds of patients, a disturbance in visceral perception and visceral hypersensitivity as a response to either normal, or abnormal stimuli, exists. Despites the fact that the actual mechanisms responsible for these disorders are, as yet, partially unknown, there is a body of evidence that a brain-gut axis dysfunction, further impaired by psychological stress, may be the leading cause of IBS.

Key words: Irritable bowel syndrome, gastrointestinal motility, visceral hypersensitivity, visceral perception

INTRODUCTION
IBS is the most common functional motility disorder a gastroenterologist will ever deal with. Despite intense research, the pathophysiology of the syndrome and the cause of the symptoms, are yet to be determined. No specific anatomic, functional or biochemical markers for IBS have been established. Consequently, conventional treatment in IBS still aims at symptomatic relief.

Several theories have been proposed for the pathogenesis of the syndrome. These theories must explain some of the clinical and epidemiological features of the disease. First, females are more commonly affected, and, although symptoms are common, few patients seek medical advice. Second, symptoms are intermittent and last for hours, days, or even months and years. Third, bowel symptoms usually coexist with symptoms in the upper gastrointestinal (GI) tract.

IBS seems to be a multifactorial disease, since different stimuli may produce identical symptoms, and identical stimuli may result in a totally different clinical picture in different patients. There is evidence that psychological factors, certain foods, drugs and hormones may lead to a disorder in bowel motility by affecting visceral perception and disturbing the function of nerve plexuses.

Current knowledge about the pathophysiology of the syndrome is based on the calculation and interpretation of several parameters of bowel neuromuscular function. Methods used include plain abdominal films after ingestion of radioopaque markers, or scintigraphy, to assess bowel transit time, manometry for the assessment of bowel motility, barostat, imaging techniques to detect brain areas stimulated after alteration in bowel motility, and newly developed central and enteral nervous system studies for the detection of specific drug receptors.
Patients. The bowel hypermotility or hypomotility observed in these patients is considered the cause of alteration in bowel transit time and, consequently, symptoms. As a result, stool consistency varies greatly and thus bowel habits may change with time.

**Colonic motility disorders**

Disorders of colonic motor function are considered the most important precipitating factors of IBS, since it is the increase in frequency and amplitude of colonic contractions that elicit abdominal pain. However, a direct relationship between massive bowel contraction and symptoms of IBS has not been yet established. Current knowledge about large bowel motility in IBS has been derived from manometric studies and assessment of rectosigmoidal motor activity using electromyography (Table 1). Most studies have failed to show strict differences between patients and healthy subjects.

**Electromyographic studies**

It has been suggested that patients with IBS and diarrhea, as well as those with IBS and constipation, have a slow wave (SW) frequency of 3 cpm in their large bowel, in contrast to healthy subjects who have a SW frequency of 6 cpm. This difference in SW frequency has not been confirmed by other studies, however. Furthermore, psychoneurotic patients may present with a similar pattern of colonic motility in the absence of IBS. These findings suggest that the disturbance in colonic SW is not pathognomonic and consequently diagnostic for IBS, and is not related the symptoms of the disease. There is some evidence that patients with IBS and constipation have an increased number of short acting action potentials, which is decreased in patients with IBS and diarrhea. On the contrary, patients with IBS and diarrhea have an increased number and frequency of long acting action potentials.

**Manometric studies**

During manometric studies, a significant decrease in the frequency of giant propagating and an increase in the number of segmental non-propagating contractions has been shown in patients with constipation type-IBS (IBS-CONST), in relation to healthy subjects. These giant propagating contractions are closely related to incidents of abdominal pain. In patients with diarrhea type-IBS (IBS-DIARR), there is a lower index of rectosigmoidal motility compared to healthy subjects.

**Scintigraphic measurements of colonic transit**

During scintigraphic evaluation of colonic motility, a selective increase in right colon transit time was found in patients with IBS-DIARR. This finding is not specific for the diagnosis of IBS, since increase in right colon transit time is encountered in almost any patient with diarrhea. On the other hand, there is a decrease in colonic transit time in patients with IBS-CONST, but this motility pattern is also present in patients with idiopathic constipation.

**Response to normal and abnormal stimuli**

Another type of motility disorder in IBS is the abnormal motor response of the large bowel to normal stimuli.

**Response to food consumption**

It is already known that in half of the IBS patients, symptoms appear or are aggravated after food ingestion. Normally, ingestion of food promotes colonic motility. Large bowel contractions ultimately result in defecation within 30 to 60 minutes. In IBS patients, the urge to defecate may appear earlier and may be accompanied by abdominal pain or diarrhea. There are food ingredients however, that produce hypomotility, increase in transit time and constipation. These findings suggest the presence of an abnormal motor response to food ingestion.

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**Table 1. Changes of gastrointestinal motility in IBS**

<table>
<thead>
<tr>
<th>In animal models, psychological and somatic stress result in an increase in large bowel contractility</th>
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<tbody>
<tr>
<td><strong>Diarrhea-type IBS</strong></td>
</tr>
<tr>
<td>• there is increase in contractility after food ingestion</td>
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<tr>
<td>• there is an increase number of propagating contractions</td>
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<tr>
<td>• total intestinal transit time is reduced</td>
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<tr>
<td>• rapid evacuation of intestinal contents especially in the area of ascending and transverse colon</td>
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<tr>
<td><strong>Constipation-type IBS</strong></td>
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<tr>
<td>• reduced number of propagating contractions of the colon</td>
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<tr>
<td>• in patients with idiopathic constipation and normal anorectal function: acceleration of transit time, rapid evacuation of ascending and transverse colon</td>
</tr>
<tr>
<td>• normal colon and rectal compliance and tone</td>
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<tr>
<td><strong>IBS with pain</strong></td>
</tr>
<tr>
<td>• contractions aggregated in the area of jejunum and ileus</td>
</tr>
<tr>
<td>• giant propagating contractions during abdominal pain, not pathognomonic for IBS</td>
</tr>
<tr>
<td>• sensitivity disorders that accompany motility disturbances during fasting</td>
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In healthy subjects, the frequency of action potentials begin to increase 10 min after a meal and gradually decrease to fasting levels within 50 min. The frequency and amplitude of contractions begins to increase 20-30 min after a meal and gradually decrease to fasting levels within 60 min. There may be another increase in contraction frequency and amplitude 80 min after food consumption. In IBS patients an increase in recto-sigmoidal phasic contractions within even 180 min after meal consumption has been found during manometric studies. The effect of food ingestion on colonic motor activity depends on caloric contents and especially fat-related calories, as fat is a strong promoter of colonic motility.

In contrast to healthy subjects, IBS patients have increased rectosigmoidal motor function during sham meals, suggesting that there is probably a cephalic phase in gastrocolic reflex. Patients with IBS-CONST have contractions of higher amplitude than patients with IBS-DIARR, after food ingestion. Furthermore, in patients with IBS-DIARR, there is an increase in rectal tone after food consumption, while in IBS patients with constipation, rectal tone is decreased. These differences, however, are not statistically significant if compared with healthy subjects. Patients who present with symptoms after food ingestion, comprise a specific subgroup of IBS patients and may benefit from administration of drugs that affect GI motility.

Response to external stimulating factors

IBS patients seem to have similar responses after intravenous administration of cholecystokinin, cholinomimetics, or corticotropin releasing factor (CRF), after intraluminal administration of deoxycholic acid, or after rectal distension with a balloon. The increase of CRF during stress may be the reason why GI motility is disturbed in such conditions. Rectal distension results in greater increase in rectosigmoidal motility index in IBS-DIARR, in relation to patients with IBS-CONST. In both instances, however, rectosigmoidal the motility index is significantly higher than in healthy subjects. The increase in colonic motility related to the aforementioned stimuli is followed by events of abdominal pain, e.g. abdominal pain caused from distension of rectosigmoid during endoscopy.

Motility disorders of small intestine

Manometric studies

A decrease in duration of all MMC phases has been found in IBS-CONST, while in patients with IBS-DIARR there is a decrease in time between two consecutive MMCs. During the period between meals, there seems to be an increase in the frequency of minute rhythm, and an increase in long acting propagating contractions of ileus. Furthermore, discrete clustered contractions in the area of the duodenum and ileum have been found in patients with IBS and in the higher frequency compared to healthy subjects. These contractions are separated from each other by prolonged periods of resting. Abdominal pain and discomfort usually follow these contractions. In IBS patients of both groups, there is a decrease in duration of fed pattern.

Transit time studies

Results of several studies suggest that mouth-cecum and total GI transit times are decreased in IBS-DIARR, in relation to healthy subjects. However, these findings have not been confirmed by other studies. A delay in evacuation of ileal contents has been detected in IBS-CONST, and abdominal distension during scintigraphy, suggesting a discrete disturbance in end-ileum motility. However, a similar motility pattern has been found in patients with idiopathic constipation.

Response to external stimuli

Intravenous administration of cholecystokinin results in high amplitude contractions in the ileum of IBS-DIARR, while minute rhythm is detected after administration of anticholinergic agents (e.g. neostigmine) in IBS patients of both groups. This motility pattern has also been described in healthy subjects.

Motility disorders of upper GI tract

Spontaneous isolated or simultaneous contractions of the esophageal body have been described in IBS patients. The lower esophageal sphincter is generally hypotonic, in contrast with the upper esophageal sphincter, which functions normally. A high incidence of gastric rhythm disorders (dysrhythmias) has also been reported in these patients. According to previous reports, gallbladder contractility is impaired in IBS patients with diarrhea in relation to these with constipation. Although gallbladder volume during fasting and after food ingestion is increased in IBS patients, the incidence of cholelithiasis is similar to that observed in healthy subjects.

Motility disorders of other systems

Motility disorders of the bladder have been described in 30% of IBS patients and in 10% of healthy subjects. Airway hypersensitivity following metacholine inhalation
sustains the presence of a generalized autonomous nerve or smooth muscle dysfunction in IBS.\textsuperscript{42}

**DISORDERED VISCERAL PERCEPTION**

Currently, it is widely accepted that visceral hypersensitivity or increased visceral perception, is a common and predominant pathophysiologic mechanism, responsible for triggering the motility disturbances and abdominal pain, in patients with functional GI disorders. It is present in two-thirds of IBS patients who have abdominal symptoms following exposure to a stimulus. In contrast to normal subjects, these patients seem to be sensitive to stress, to abnormal events or even to normal intrinsic stimuli during digestion such as intestinal gases and foods with increased fat or fiber content. There are data suggesting that pain or flatulence can be induced by normal contractions because of the disordered filtering mechanism of such stimuli.\textsuperscript{43} Visceral hypersensitivity is the only mechanism which can explain the clinical and epidemiologic features of IBS.

**Visceral perception in IBS**

In Cook et al’s study,\textsuperscript{44} IBS patients were shown different description of abdominal pain compared to healthy subjects. Less sensitivity to low intensity non-painful stimuli and a higher threshold for painful stimuli were also found in IBS patients. On the other hand, several studies have shown that IBS patients, particularly those with diarrhea, are more sensitive to rectal distension with a balloon.\textsuperscript{24,48} Increased sensitivity (decreased tolerance) to rectal distension independently of the motility pattern elicited by this manipulation was found in IBS patients in a well designed trial by Whitehead and colleagues.\textsuperscript{45} This kind of visceral hypersensitivity was related neither to psychiatric disorders, nor to a generalised decrease in somatic pain threshold. This study shows for the first time, that there is a subgroup of IBS patients in whom the main pathogenetic mechanism for the syndrome is an increase in rectosigmoidal sensitivity (Table 2).

The use of rectosigmoid sensitivity as a biological marker of IBS has been suggested by some authors\textsuperscript{45} but it can not be accepted, because: a) the prevalence of rectosigmoid hypersensitivity varies greatly in different studies, between 20 and 80 per cent, and can be induced only with repetitive stimuli, rather than with a simple distension area.\textsuperscript{24,45,47,48} b) there is no correlation between rectal perception threshold and severity of pain two weeks before the test and only poor correlation during rectal distension.\textsuperscript{49} In IBS patients with rectal symptoms, such as incomplete defecation, significant rectal sensitivity to distension was not found, c) the changes in sensitivity thresholds can not be an indicator for response to treatment,\textsuperscript{50} d) in cases of rectosigmoid hypersensitivity reflex contractions simultaneously with rectal balloon distention were recorded 5 cm above the balloon.\textsuperscript{24,45,47,48} This observation means that there may be a motility component to increased visceral perception,\textsuperscript{24} e) the presence of rectal hypersensitivity does not affect the diagnosis and medical treatment of IBS.

There also seems to be an increase in visceral perception in other than rectosigmoid GI areas. Visceral hypersensitivity has been detected after distension of the central colon,\textsuperscript{54,55} and the small bowel.\textsuperscript{56} There is an equal distribution between jejunum and ileum.\textsuperscript{57} Some IBS patients have gastric and duodenal hypersensitivity as well, which may be the leading cause of the symptoms of functional dyspepsia present in 40\% of IBS patients.\textsuperscript{58,59}

The repeated stimulation of rectosigmoid in IBS patients results in rectal “hyperalgesia”, that is, an excessive sensation of pain following application of a stimulus, and rectal “alodynia”, that is, the elicitation of pain by a stimulus that was previously not painful.\textsuperscript{60} Since these effects are absent in healthy subjects, it has been suggested that IBS patients may have specific receptors in their sigmoid colon, responsible for visceral hypersensitivity.

IBS patients may also present with various symptoms that are neither relevant to their primary disease, nor can be explained by any pathology. The term “somatization” has been used for this phenomenon, which includes a variety of symptoms (Table 3).

The overlapping of perception and pain thresholds

<table>
<thead>
<tr>
<th>Table 2. Increased visceral perception in IBS</th>
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<tbody>
<tr>
<td><strong>Diarrhea-type IBS</strong></td>
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<tr>
<td>• lower thresholds for the perception of gases, feces, discomfort and urge to defecate with graded rectal balloon distention which induces increased rectal contractility\textsuperscript{24,48}</td>
</tr>
<tr>
<td><strong>Constipation-type IBS</strong></td>
</tr>
<tr>
<td>• reduced rectal sensitivity (discomfort with increased distention volumes)</td>
</tr>
<tr>
<td>• sigmoidal hypersensitivity?\textsuperscript{51}</td>
</tr>
<tr>
<td>• normal or high threshold for painful somatic stimuli\textsuperscript{44}</td>
</tr>
<tr>
<td><strong>IBS with pain</strong></td>
</tr>
<tr>
<td>• increased visceral perception as a result of rectosigmoidal, ileal and anal distension</td>
</tr>
<tr>
<td>• normal intestinal compliance</td>
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</table>

\textsuperscript{44} Cook et al
\textsuperscript{45} Whitehead and colleagues
\textsuperscript{47} 24,45,47,48
\textsuperscript{49} 24,45,47,48
Substance P released from the ends of sensory fibers activates the degranulation of mastocytes, resulting in the release of histamine which provokes the further release of substances P and NGF from end fibers. These substances affect the development and function of sensory neurons.64,65

In cases of inflammation, prostaglandins released by neutrophiles and macrophages stimulate a number of receptors, resulting in ATP formation and release of nor-adrenaline. ATP and nor-adrenaline released from sympathetic neurons then stimulate end nerve fibers, and may elicit pain.63,66

Furthermore, nerve remodelling during the inflammation process, may result in chronic hypersensitivity in intestinal submucosa,67 by altering threshold of sensitivity. Several studies in animal models have shown that submucosal nerves are under continuous remodeling,68 and that this process is up or down regulated by locally acting immune cells.63,69

In conclusion, afferent sensory neurons may be stimulated by inflammatory mediators released under the regulation of the immune system. In inflamed tissue, there are high levels of these substances which are possi-

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**Table 3. Symptoms in IBS patients attributed to somatization**
- pain located to the chest, back or pelvis
- fatigue
- insomnia
- muscle pain, cramps
- headache, dizziness
- inability to focus
- dysmenorrhea, dyspareunia
- decrease in libido
- disordered functioning of the bladder

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Pathophysiology of visceral hypersensitivity in IBS

Pathophysiologic mechanisms of visceral hypersensitivity in IBS are currently under extensive research.

**Central process of stimuli**

According to results of the initial studies investigating the stimulation of specific brain areas after painful rectal distention using PET, IBS patients were found to have more diffuse abdominal perception of the distention than healthy subjects.52,61 This finding could be explained by disordered central process of the stimulus. However, more recent studies using fMRI failed to confirm these findings.62 It can thus be concluded that, since the brain cortex is normally stimulated following intestinal stimulation, the disorder responsible for visceral hypersensitivity must be located somewhere in the peripheral nerve pathways (peripheral mechanoreceptors, afferent visceral fibers, posterior horns of the spinal cord etc.).

**Sensitization of mechanoreceptors and afferent nerve fibers**

Local tissue damage or application of a stimulus result in the release of chemical (K+, H+, bradykinine) and/or inflammatory (prostaglandin) mediators, that instantly stimulate the end nerve fibers.63 These mediators provoke the release of “pain” mediators from other cells and efferent fibers (histamine, serotonin, nerve growth factor (NGF) and prostanoids), resulting in the sensitization of the end efferent fibers and the increased response to painful stimuli. Prostaglandins and derivatives of arachidonic acid increase the sensitivity of end fibers to bradykinine and other pain mediators and the second-

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**Table 4. Peripheral pain mediators**

Agents acting on the level of peripheral receptors
- PEG2
- PGI2
- ATP, adenosine
- Bradykinin
- Serotonin
- Low pH
- Calcitonin-gene related peptide (CGRP)
- Substance P
- Eicosanoids

Agents acting indirectly on immune cells
- Noradrenalin
- Interleukine 1, 6, and 8
- TNF-a
- Nerve growth factor (NGF)
- Bradykinin
- Leukotriene B4
- Phenylalanine
- Substance P, VIP
- Complement factors (C5a)
ibly responsible for chronic inflammation-related local pain. Table 4 shows some of the substances that are responsible for visceral hypersensitivity.

**Sensitization at the level of posterior horns of the spinal cord**

The peripheral damage of first class sensory neurons results in stimulation of posterior horn of the spinal cord. It has been suggested that visceral hypersensitivity is the result of prolonged stimulation of this area. Excluding animal models, to date, there is no evidence that there is a cross-reaction between visceral and somatic afferent fibers via posterior horn neurons. Moreover, only 40% of Crohn’s disease patients have rectal hypersensitivity. It can, therefore, be suggested that hyperstimulation of posterior horn neurons is either not enough to promote visceral hypersensitivity, or there are efferent inhibitory nerve fibers that produce a down-regulation of sensory pathways.

The mediators responsible for stimulation at the level of the spinal cord are NO and NMDA (N-methyl-D-aspartate) acting substances. Their action, in conjunction with brain cortex stimulation, results in hyperalgesia and alodinia after the initial stimulus passes. Substitution with brain cortex stimulation, results in hyperalgesia and alodynia after the initial stimulus passes. Sensitization at the level of posterior horns of the spinal cord are NO and NMDA (N-methyl-D-aspartate) acting substances. Their action, in conjunction with brain cortex stimulation, results in hyperalgesia and alodinia after the initial stimulus passes.

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