PATHOPHYSOLOGY OF IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) affects approximately 20% of the Western population, and accounts for frequent absenteeism from work and impaired quality of life. It is charactererised by altered bowel habits and abdominal pain, in the absence of any other GI problems and diagnosis is based on the Rome criteria. The pathogenesis of IBS is poorly understood, although several factors including, psychosocial, gastrointestinal dysmotility, abnormal visceral hypersensitivity, and luminal factors have been noted in the literature.

Psychiatric disorders are recorded in 50-80% of patients with IBS in some studies, although a single disorder is not well defined. Anxiety, depression, somatization, and neurosis have all been recorded[1]. In patients with IBS, acute psychological attacks have been shown to significantly alter their gastrointestinal motility[2]. Drossman et al found that patients with IBS undergo more suffering from psychosocial distress than non-patients with IBS[3]. Osterberg et al, on the other hand, found that there were minute differences in psychological distresses between patients with IBS, and non-patients with IBS[4]. Thus, assorted studies have conclusions that vary from each other.

Altered gastrointestinal motility seems to be associated with the aetiology of IBS, but is not diagnostic. Serotonin (5-HT) has been studied for its role in regulating colonic motility in humans, but it is not yet known whether alterations in the colonic 5-HT system are involved in the pathophysiology of irritable bowel syndrome[5]. Lincoln et al established that the total indoleamine (5-HT plus its metabolite 5-HIAA) concentration in the sigmoid colon in patients undergoing partial or total colectomy for treatment of idiopathic constipation, attributed to IBS, was considerably higher than in normal subjects[6]. In unstimulated conditions, the colonic myoelectrical and motor activity are normal, whereas under stimulated conditions, IBS patients shown more abnormalities than normal subjects[7]. Lanng et al, found that all investigations regarding motility disorders showed variation, supporting the general theory of IBS being a broad-spectrum motility disorder.

Similar to the gastrointestinal motor studies, visceral hyperalgesia to distension is predominant in IBS patients compared to healthy subjects. The visceral hyperalgesia is concerned with mechanoreceptor-activated stimuli, as opposed to intestinal mucosal electrical stimulation[8]. The mechanism of visceral hypersensitivity is still unclear, although several propositions have been noted in the literature. The hypersensitivity experienced in IBS is confined to visceral innervation, without somatic involvement[9].

Luminal factors such as infectious agents or specific dietary components have been shown to be associated with IBS. Studies have shown that approximately 25% of patients develop chronic bowel disturbances resembling IBS following an episode of infectious diarrhoea. Whether this is a factor for all patients or only some patients, remains controversial. The inflammation that occurs during the infection may play a role in the pathogenesis of post-infectious IBS (PI-IBS)[10]. Specific dietary components, such as diary products, have been shown to be associated with IBS. Bohmer et al, showed that 24.3% of IBS patients had lactose malabsorption in comparison to only 5.7% of controls[11]. A Danish study from 1973 showed that 20% of patients with IBS also complained from lactose intolerance while the prevalence in

Denmark was only 3%[12]. Vesa et al, showed a similar finding[13]. All of this evidence suggests luminal factors also have a role in the pathophysiology of IBS.

Irritable bowel syndrome is the commonest functional gastrointestinal disorder, yet is a poorly understood condition. Part of the reason for this is the heterogenous nature of the disorder, which consists of a complex pattern of pathophysiological factors that interact and produce the clinical features attributable to IBS. Further research into the aetiological factors of IBS is warranted, such that specific targets for treatment can be established.

Article 1: Miwa J, Echizen H, Mastsueda K, Umeda N. Patients with constipation-predominant irritable bowel syndrome (IBS) may have elevated serotonin concentrations in colonic mucosa as compared with diarrhoea-predominant patients and subjects with normal bowel habits. *Digestion.* 2001;63:188-194.

This study compares the mucosal serotonin (5-HT) concentrations obtained from the various parts of the colon of constipation-predominant IBS patients with those obtained from diarrheoa-predominant IBS patients and control patients with normal bowel habits. This study is unique in that no other similar study has been performed on constipation-predominant symptoms, although several other studies have focussed on 5-HT as a role player in the regulation of colonic motility..

This study involved 15 patients diagnosed with IBS (6 men & 9 women, age range 25-35 years) with 7 of 15 patients (4 men & 3 women, age range 29-62 years) classified as diarrhoea-predominant type, and 8 of 15 patients (2 men & 6 women, age range 25-65 years) classified as constipation-predominant type. The control group consisted of 7 subjects with normal bowel habits (6 men & 1 woman, age range 43-66 years). The diagnosis of IBS was based on a questionnaire, which had questions relating to the symptoms of IBS according to the Rome I criteria. Organic disease was ruled out, by ultrasonography and colonoscopic examination. There is no evidence regarding where the IBS patients enrolled in this study came from. Benign colonic polyps < 5mm and diverticuli that were found were not part of the exclusion criteria. The authors do not mention in which groups these people belonged to. The diagnosis of IBS based on symptom criteria allows one limitation to the study, as other reliable biological markers such as colonic transit time, colonic manometry etc, could have been used. The control group was selected from persons who had normal bowel habits and who underwent a colonoscopic examination to discount malignancy subsequent to a positive faecal occult blood test and other reasons. The authors do not mention what the other reasons were. None of the patients or control subjects had abnormal haematological or biochemical tests.

There is systematic bias in this study. There is no reference to how the subjects were enrolled to fill in the questionnaire. The control group has a gender and age imbalance compared to the other groups, which could have influenced the level of outcomes. Using questionnaires introduces the possibility of misunderstandings by the subjects. The positive faecal occult blood tests for the control subjects suggest potential pathology from the beginning, therefore influencing the results. The article does not state whether the clinicians involved in colonoscopic investigations or outcome appraiser were blind to the groupings of the patients. Assuming there was no blind assessment, it is a potential source of bias.

The study design involved measuring the concentrations of 5-HT and 5-HIAA by obtaining colonic mucosal specimens via endoscopic biopsy to determine whether different clinical manifestations of IBS involved different disposition of 5-HT. The methods of obtaining the specimen and 5-HT / 5-HIAA assays were described in detail. Colonoscopic procedures were similar for all IBS patients. The authors acknowledge the possibility of the data being biased as a result of the colonoscopic procedures, although top control was maintained. The homogenisation procedures were exactly the same for all specimens, and the utmost standards were maintained in

order not to lose 5-HT / 5-HIAA as a result of degradation. Though the study does provide evidence that there is a significantly higher concentration of 5-HT in constipation-predominant IBS patients as opposed to diarrhoea-predominant IBS patients and control subjects, it does not provide concrete evidence about any aetiologic effect of 5-HT on this type of IBS. The authors also recognize that the data does not clarify whether the cephalocaudal gradient in the mucosal 5-HT concentration in the colon was due to regional differences in the enterochromaffin (EC) cell density or to differences in the 5-HT disposition.

This study is an original in terms of serotonin concentrations in patients with IBS. An incidental finding was an increasing cephalocaudal gradient in serotonin concentrations across all the study groups, and it found that patients with constipation-predominant IBS had the highest serotonin concentrations in their colonic mucosa. This indicates the pathophysiological significance of serotonin in terms of IBS.

Article 2: Gastrointestinal dysfunction in a community sample of subjects with symptoms of irritable bowel syndrome. *Digestion.67:14, 2003.*

The aim of this study was to appraise any correlation linking gastrointestinal pathophysiology and IBS in patients with symptoms of IBS as opposed to control subjects with no abdominal complaints.

A cohort of 4581 men and women were formed, of which 4130 people were invited for a follow up study, as the remainder were lost due to death or other circumstance. The people invited were born in 1922, 1932, 1942, and 1952. There is no mention of why these birth years were chosen specifically. The subjects were asked to fill out a questionnaire focussing on the following symptoms: abdominal pain, distension, borborygmia, altered stool consistency, heartburn, acid regurgitation, nausea and vomiting. A written letter further invited only subjects born in 1932, 1942, and 1952 during 1996 / 1997 followed by immediate telephone contact, as the study was considered too strenuous for persons older than 70 years. The subjects were further interviewed to make sure they still suffered from IBS as defined by Kay and Jorgensen's study, published in 1996. Thirty-two of fifty-eight patients classified as having IBS, accepted to participate in the study. The control group was randomly selected from the cohort, of which there were 26 subjects. Factors such as: social status, smoking & drinking, cholecystectomy, antibodies to H. pylori, psychic vulnerability previously shown to be related with IBS was included as potential confounders.

Unlike previous studies on IBS that were performed using patients attending gastroenterology clinics, the IBS patients and control subjects in this study were chosen from a random unselected population, therefore minimising any bias. Using questionnaires to elicit specific symptoms may cause misunderstandings among subjects or dishonesty, but true subjects were later personally interviewed. Although specialists involved in barium enema procedures were blind to the patients' groupings, the authors do not mention whether this was true for all abdominal measurements. Assuming blindness was not maintained for all abdominal measurements, this introduces an inherent bias.

The study design involved performing gastroscopy, manometry of the oesophagus, 23-hour pH and pressure recordings of the oesophagus, lactose tolerance test, measurement of colonic transit time, barium enema and rectoscopy. Not all participants were subject to these tests, and there is no mention of why this was so. Oesophageal manometry and 23-hour pH and pressure recording procedures were described, but procedures such as gastroscopy, rectoscopy, barium enema, and measurement of colonic transit time were not adequately described. There is no mention of uniformity of these procedures, in terms of times undertaken. With respect to the barium enema procedure, the authors mention records of diverticuli, polyps, cancer, ectopia caeci, colon elongatum, stenosis of colon (< 50% of normal), and spasms were noted, but do not give exact numbers of patients with such abnormalities and to which groups they belonged to. The authors mention that all results obtained from the outlined procedures were classified normal and abnormal according to set criteria, established by other referenced studies. This study found that in subjects with IBS, there were increased prevalence of gastrointestinal dysmotility and hyperperception compared to control subjects with no abdominal complaints. In addition, this study found that IBS patients previously tolerant to lactose had a greater tendency to develop intolerance during the lactose test compared to control subjects. The authors acknowledge that the proportion of abnormalities found were significantly lower than what other studies have recorded, and associate this with the fact that this study was performed using an unselected population.

This study provides a firm insight into the association between gastrointestinal pathophysiology and IBS in subjects with symptoms. Understanding this pathophysiology will enable a better definition of IBS to be formed.

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