Irritable bowel syndrome in developing countries – a disorder of civilization or colonization?

K.-A. GWEE

Associate Professor of Medicine, National University Hospital, National University of Singapore, Singapore

Abstract

While irritable bowel syndrome (IBS) is common in the West, early studies suggest that the prevalence is low in developing countries. However, recent studies point to increasing prevalence in newly developed Asian economies. The presentation appears to differ from the West, with a lack of female predominance, a greater frequency of upper abdominal pain and defecatory symptoms perceived as being less bothersome. This difference, together with the preoccupation with organic disease, could explain why we may be missing IBS in Asia and also why excess surgery has been observed in some Asian countries. While a recent study from China, consistent with western studies, support an important role for infection and inflammation, early studies from India reporting no association between amoebic infection and IBS appear to dispute this observation. To reconcile these seemingly contradictory observations, an hygiene hypothesis model is proposed. Exposure to a variety of microorganisms early in life could result in the colonization of the intestine with microflora that can respond more efficiently to an episode of gastroenteritis. Together with the changes with evolution of Asian economies such as westernization of the diet and increased psychosocial stress, it is proposed that loss of this internal protective effect, could give rise to a more uniform worldwide prevalence of IBS.

Keywords epidemiology, Asia, symptoms, gender, pathogenesis, hygiene hypothesis.
Based on a small study of 20 black patients with IBS, and in the absence of a population survey or controls, it was claimed that IBS was rare among rural blacks and that those few that presented to these physicians had been pursuing a westernized lifestyle. However, scientifically acceptable evidence to support an association either between IBS and low fibre diet, or between IBS and diverticular disease, is lacking. The other piece of evidence to suggest a low prevalence of IBS in developing countries was a study from Thailand involving 676 subjects from urban Bangkok, and 401 subjects from a rural province. In this study, Danivat et al., found a very low IBS prevalence of 4.4%, with no difference between urban and rural subjects. This study employed a questionnaire similar to the one used by Drossman et al., who, in an earlier study, found a prevalence of 22% in an American population.

Following that 1988 study, there has been a paucity of high quality studies from developing countries until the year 2000. Since then, several studies have been reported from newly developed Asian economies. By restricting the analysis to studies employing standard criteria, and with large population-based random representative samples involving at least 1000 subjects, certain trends could be identified. Among studies employing the current (Rome II) criteria, the prevalence of IBS in Asian countries ranged from 5.7% in South China to 8.6% in Singapore (see Fig. 1). One study from Shahrekord in Iran reported a prevalence of 5.8%. These prevalences are not too far from those reported from Australia (6.9%) and Europe (9.6%). However, the prevalence of IBS appears to be higher in some western countries, i.e., Canada, UK and Italy, where the prevalence was reported to be 12%. By the older Manning criteria, the prevalence rates reported from Asian countries were Beijing, China 7.3%, Mumbai, India 7.5%, Singapore 11% and South China 11.5%. Prevalence using Manning criteria from the west was Spain 10.3%, Norway 16.2%, USA 17%, and UK 22%. Thus, by the Manning criteria, current prevalence rates of IBS in the recently developed economies of Asia were generally lower but not too different from rates in western developed economies.

It is unclear whether the current prevalence of IBS in these Asian countries represents a ‘catching-up’ phase (theoretically attributed to industrialization and urbanization). The picture is possibly distorted by several studies which unfortunately had methodological limitations. Small studies from China and Japan with only about 230 subjects revealed high prevalence rates of 23 and 25%. Surveys of selected populations such as among medical students in Nigeria and Malaysia, and patients attending for medical checkups in Taiwan, and Korea also revealed high prevalence rates of 16–45%. On the other hand, two pairs of studies from the same institution in Singapore, provide support for a real increase in IBS prevalence. Singapore is an extremely small compact island city state with a population of 3–4 million people of Chinese, Malay and Indian origin. It has witnessed rapid industrialization and urbanization within a short span of time from 1960 to 2000 and now has one of the highest gross domestic product per capita in the world. To facilitate communication among the different races, English has been the main language of instruction and education from early times, and as such, the majority of its people are conversant in this language. In a random sample of 3000 households representative of the general population in age, gender, race and housing-type, the prevalence of IBS was 11% by the Manning criteria [by at least two of six symptoms]. Using the same criteria, an earlier population-based study conducted between 1993 and 1996 had estimated a prevalence of only 2.3%. It is possible that this study had underestimated the prevalence since a disproportionate random sampling procedure resulted in a sample size of only about 200 in each racial group. Moreover, the focus of the study was gastroesophageal reflux disease rather than IBS. Another pair of studies from Singapore suggests that at least part of the observed prevalence increase could be real. Two surveys, using identical criteria and methodology, were carried out 4 years apart in patients attending the same gastroenterology clinic. This showed an increase in the proportion of patients with functional gastrointestinal disorders from 49 to 62%, with concomitant threefold declines in both peptic ulcer disease, from 32 to 12%, and gastric cancer, from 3 to 1% (see Fig. 2).

**Epidemiology of IBS in developing countries**

**Gender distribution** In the west, IBS is more prevalent amongst women, both in clinic-based series as well as population-based surveys. However, early studies of IBS patients attending specialist clinics in India consistently reported a two- to fourfold predominance of men over women. As these were patients attending for medical care, cultural factors and easier access to medical services favouring men in a male-dominant society was suggested as a possible reason for...
the predominance of male IBS patients in India. However, in a recent large population-based survey involving over 2000 adults in a major Indian city, a male predominance was recorded, with a sex-adjusted prevalence of 7.9% in men and 6.9% in women. Similarly the prevalence of IBS was almost equal between men and women from a rural community in Bangladesh. Studies of predominantly Chinese populations in China, Hong Kong, Taiwan and Singapore, reported no female predominance (see Table 1).

Studies from Korea, involving both rural as well as urban communities have also not found female predominance. In Japan, the gender distribution appears to be similar to western communities. A lack of female predominance was also observed in a study from Iran. Men and women were just as likely to have consulted for their IBS in Bangladesh (35% vs. 35%) and in Japan (30% vs. 23%). Another area of study suggests a difference in gender-related risks between East and West. In a prospective study, from the UK which had examined equal numbers of male and female patients with acute gastroenteritis, 77% of women developed IBS, compared with only 36% of

Table 1 Gender distribution of IBS subjects by Rome criteria in population-based surveys

<table>
<thead>
<tr>
<th>Country</th>
<th>Female to male ratio</th>
</tr>
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<tbody>
<tr>
<td>Spain 2001</td>
<td>2.42</td>
</tr>
<tr>
<td>Australia 2000</td>
<td>2.01</td>
</tr>
<tr>
<td>Canada 2003</td>
<td>1.75</td>
</tr>
<tr>
<td>Japan 2004</td>
<td>1.73</td>
</tr>
<tr>
<td>Bangladesh 2001</td>
<td>1.35</td>
</tr>
<tr>
<td>China 2004</td>
<td>1.25</td>
</tr>
<tr>
<td>Singapore 2004</td>
<td>1.21</td>
</tr>
<tr>
<td>Taiwan 2003</td>
<td>1.05</td>
</tr>
<tr>
<td>Norway 2004</td>
<td>1.04</td>
</tr>
<tr>
<td>HK 2002</td>
<td>0.99</td>
</tr>
<tr>
<td>Iran 2003</td>
<td>0.93</td>
</tr>
<tr>
<td>India 2001</td>
<td>0.85</td>
</tr>
<tr>
<td>Korea 2001</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Figure 1 World map of IBS prevalence year 2000–2004 by Rome 2 criteria with Manning criteria in parenthesis where available.

Figure 2 Increase in proportion of functional causes of chronic upper abdominal pain in patients presenting to a gastroenterology clinic between 1984 and 1995.
men.\textsuperscript{37} In contrast, a recent study from China found similar risks for men and women.\textsuperscript{38} Apparent differences in gender distribution may arise from the use of different diagnostic criteria. The Manning criteria appear to be less sensitive for diagnosing IBS in men compared with Rome criteria.\textsuperscript{39,40} However, no strong female preponderance was observed even in Singapore and China when the female-friendly Manning criteria were applied while striking female preponderance was observed in Spain and Canada with the Rome II criteria.\textsuperscript{10,11,19,20}

Recently sex-related differences in IBS has received attention because of growing evidence suggesting that men and women may differ in their responses to new pharmacological agents targeting serotonin receptors. While it has long been recognized that hormonal changes can influence bowel functions in women, research addressing masculine factors that may possibly be protective against IBS are awaited. Luteinizing hormone and possibly testosterone levels appear to be reduced in male IBS patients.\textsuperscript{41} Lower male-trait scores were also observed, although no difference in prevalence of homosexuality was found between male IBS patients and controls.\textsuperscript{42} These observations raise the intriguing possibility that the investigation of masculine factors could provide leads not only to help us better understand the pathogenesis, but also discover new treatments and prognostic markers. It is possible that the recruitment of men for future clinical trials will benefit from the inclusion of Asian centres, given the difficulties encountered by western centres.

### Education and social status

The Asian studies appear to have in common a greater prevalence of IBS in the better educated and possibly more affluent classes of their society. In Beijing, South China, and Singapore there was a progressively higher prevalence up the education ladder.\textsuperscript{10,11,15} An interesting further observation in the Singapore study was that after multivariate analysis, IBS was no longer associated with education, but living in landed property remained a significant risk factor. The authors speculate that affluence and westernized lifestyle and dietary habits could be involved. In contrast, data from the USA, show a greater reporting frequency for functional bowel disorders in the lower household income group.\textsuperscript{43} Studies have consistently observed a strong correlation between childhood and adult social class as well as educational attainment and mid-life social class.\textsuperscript{44} It may well be that psychosocial stressors operating at both ends of the wealth spectrum account for these observations. However, it is interesting that two studies from westernized societies have implicated affluent childhood living conditions as a risk factor for adult IBS.\textsuperscript{44,45} Childhood socioeconomic disadvantage is generally linked with poorer adult health.\textsuperscript{43} Therefore, alternative explanations involving dietary choices and childhood exposure to infections need to be considered (see discussion under Pathogenetic Mechanisms).

### Symptom patterns – the diagnostic challenge

Several recent studies have highlighted the risks of unnecessary surgery in IBS. Studies from the USA, UK and Europe report excess rates of cholecystectomy, appendicectomy, hysterectomy and even back surgery.\textsuperscript{46,47} In an editorial, Talley highlighted the potential consequences of unnecessary surgery.\textsuperscript{48} Based on statistics from studies in the USA population, an estimated 8\% of IBS patients will undergo unnecessary cholecystectomy in a lifetime. This would result in 770 fatal and 38,000 non-fatal surgical complications. IBS patients in Asia also appear to be at risk of unnecessary surgery. IBS subjects had twice the rates of their non-IBS subjects for cholecystectomy in Taiwan and for abdominal surgery in Singapore.\textsuperscript{10,26} Hesitation to diagnose IBS could contribute to this risk. In a recent study from Hong Kong, only 21\% of patients with IBS criteria were told by their western trained medical practitioners that they were suffering from IBS.\textsuperscript{9} While some of this hesitation may be due to a pre-occupation with organic diseases, several observations suggest that the pattern of IBS symptoms in Asia could differ from those taught in western-biased textbooks.

### Site of pain

In contrast to western patients who present more frequently with lower abdominal pain, IBS patients in Asia appear to present more commonly with upper abdominal pain. In three early Indian studies, more than half of their patients complained of upper abdominal pain, whereas in western series the majority of patients presented with lower abdominal pain and only about a quarter complain of pain predominantly in the upper abdomen.\textsuperscript{32–34,49,50} For example, in a gastroenterology clinic in rural India, 16 of 88 (32\%) patients presented with pain in the epigastrium, whereas in a clinic in Bristol, UK, only one of 104 patients pointed to the epigastrium.\textsuperscript{34,50} (see Fig. 3). Similarly, in recent community studies from Singapore and Bangladesh, more than half of IBS subjects reported pain in the upper abdomen, whereas in a community study from the USA only one-third reported upper abdominal pain.\textsuperscript{2,10,36}
Perception of bowel habit In the Singapore study, when subjects were asked to describe their bowel pattern in the preceding 3 months, 77% of those with IBS criteria thought they had a normal bowel habit. And yet, when they were asked specific questions relating to defecatory symptoms, 50% had symptoms of chronic constipation, 25% had symptoms of chronic diarrhoea, while 4% had an alternating bowel pattern. Therefore, it appears that, in this population, the defecatory and stool disturbances may have been relatively mild and the subjects were more bothered by abdominal pain and discomfort. The importance of this is that if a patient with abdominal pain is simply asked whether there is a problem with the bowels, the diagnosis may be missed in a substantial majority. If doctors fail to recognize IBS, patients may be referred for irrelevant investigations leading to unwarranted surgery by doctors unfamiliar with IBS. Thus, it is important not only for doctors in developing countries to recognize the rising prevalence of, but also to recognize the symptom patterns peculiar to, IBS in their communities. In the west, cholecystectomy rates for non-acute indications have risen with the introduction of laparoscopic surgery. In 1987, a study from Malaysia reported a high prevalence of asymptomatic gallstones of 11.8% in men and 13.7% in women. The probability of a person with asymptomatic gallstones undergoing cholecystectomy was 0.01%, approximately fivefold less than that in the UK. Thus, with increasing affluence, the cost from unnecessary surgery in IBS patients is set to rise dramatically.

Pathogenetic mechanisms

Dietary factors Early investigators had largely attributed the high prevalence of IBS in western populations to a fibre deficient diet, and conversely a relatively low prevalence of IBS in African populations to a largely unrefined high residue diet in African villagers. At the time that this theory was propounded in the 1970s, there was no population-based epidemiology study from Africa. Since then, studies from Nigeria and Kenya suggest that the prevalence of IBS in black populations may not be as low as believed. Furthermore, formal dietary analyses of IBS patients have not only failed to convincingly demonstrate dietary fibre deficiency, but recent studies from UK even suggest that the majority of patients were worse off on bran fibre supplements. An interesting study from Iran comparing two very different populations from the same country observed that the prevalence of chronic constipation among industrial labourers was actually more than twice that of their pastoral nomad cousins. This was contradictory to expectations; it had actually been hypothesized that there would be more constipation among nomads given their living conditions where they had almost no access to fresh fruits and vegetables. The labourers as a group actually reported a higher level of fruit and vegetable consumption. The finding of this study not only casts further doubts on the fibre hypothesis, but points to another possible contributory factor, i.e., psychosocial stress, as the working conditions in the factory were reported to be harsh.

The two major food groups implicated in food challenge studies by IBS patients in the west are cereal grains and dairy products. These are now commonly promoted in Asian countries as elements of a healthy diet. Thus, ironically, IBS symptoms may manifest more obviously as Asians become more exposed to the very foods implicated by IBS sufferers in the west. Increasing consumption of milk and dairy products may also give rise to lactose intolerance which is often considered a differential diagnosis for IBS as it can produce symptoms indistinguishable from IBS. There is a high prevalence of lactase deficiency in many Asian countries ranging from 70% to nearly 100%. Yet, in Sri Lanka when 145 subjects with lactase deficiency were fed 50 g lactose, equivalent to four glasses of milk, only one-third reported symptoms. In Bangladesh lactose intolerance was reported by 12.6% of IBS subjects, no more than that reported among non-IBS subjects.

Postinfectious IBS An episode of infectious gastroenteritis is now recognized as a strong risk factor for the development of IBS. In the UK, infective gastroenteritis was reported to confer a 12-fold increased risk. In patients admitted to hospital for acute gastroenteritis, as many as 30% may develop IBS. Studies from Beijing also suggest that a history of dysentery predisposes to the development of IBS in China. In a recent cohort-controlled study, 8% of patients presenting to a major hospital in Beijing with dysentery...
developed IBS, whereas only 0.8% of family members not exposed to dysentery developed IBS. As with the western studies, it was also observed that a longer duration of diarrhoea was associated with a higher risk of developing IBS.

Prospective studies provide strong evidence that the development of postinfectious IBS (PI-IBS) involves an interactive multifactorial aetiological process. On the one hand, psychological factors such as major life event stress preceding the infectious episode and hypochondriasis were strong predictors for the development of IBS.\textsuperscript{37,60} On the other hand, increased expression of interleukin 1\(\beta\) mRNA in rectal biopsies and increased numbers of intraepithelial lymphocytes and T-lymphocytes in rectosigmoid biopsies provide evidence that the pathogenesis of PI-IBS is also underpinned by an inflammatory process.\textsuperscript{60–62} The study of PI-IBS from China observed a similar increase in these inflammatory markers.\textsuperscript{38} Interestingly, they also found increased numbers of mast cells in biopsies taken from the terminal ileum of both PI-IBS as well as non-postinfection IBS patients, compared with controls. Similarly, an earlier study from New Zealand had found increased numbers of mast cells in colonic biopsies from patients with IBS who had non-specific microscopic inflammation on conventional histology.\textsuperscript{63} What was particularly interesting in this study was the finding of immune activation in a group of IBS patients whose presentation was atypical for PI-IBS. These patients had an insidious onset, more chronic IBS symptoms, and their colonic biopsies were judged to be normal on conventional histology. The CD25 positive staining and numbers of intraepithelial lymphocytes were even more prominent than patients with a history suggestive of PI-IBS. These observations suggest the possibility that immune activation may extend beyond the postinfectious subset of IBS.\textsuperscript{64}

While these studies support an important role for infection in the development of IBS, earlier studies from India seem to dispute this. Although not specifically identified in latter day studies of PI-IBS, early studies had implicated amoebic dysentery in the development of IBS among British soldiers returning from India and Egypt at the end of World War II.\textsuperscript{49,65} Despite this, several studies suggest that exposure to amoeba did not predispose to IBS symptoms in India and other endemic countries.\textsuperscript{66–68} In a study from India, no differences in amoebic serology were observed between patients with IBS symptoms and asymptomatic controls, suggesting an absence of association with past infection.\textsuperscript{66} Several earlier studies had observed that chronic abdominal symptoms were found more often in people without amoeba in their stools than those with amoeba.\textsuperscript{66} Furthermore, if infection is an important risk factor, the prevalence of IBS in developing countries should be higher rather than lower, than in developed western countries.

**Hypothesis on the cause of increasing IBS prevalence in developing countries**

To reconcile these seemingly contradictory observations, the author proposes an hygiene hypothesis model. As Collins has pointed out, with the widening scope for an inflammatory process in IBS, the microbial environment could prove to have a major influence on the expression of IBS across the globe.\textsuperscript{69} It is speculated that a high childhood exposure to infection, rather than high residue diet, is responsible for the low prevalence of IBS in underdeveloped countries. Exposure to a variety of microorganisms early in life could result in the colonization of the intestine by microflora, as well as the development of broad immune tolerance, that enable the intestinal epithelium to respond more efficiently to antigenic challenge, as during an episode of gastroenteritis. As a result, symptoms resolve more quickly. On the other hand, the intestinal immune system remains relatively naïve in the more hygienic environment associated with improved socioeconomic conditions. In this situation, exposure to gastroenteritis in later life would result in a greater inflammatory disturbance. This, together with psychological and behavioural factors, predisposes to the persistence of symptoms manifesting as IBS.

**CONCLUSION**

Thirty years after Henry Bockus pronounced IBS a disorder of civilization, Read predicted a worldwide epidemic of IBS in 1994.\textsuperscript{70} The recent experience of formerly developing countries, particularly in Asia, would appear to bear this out.

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