

strategy that invariably provoked fury, a provocation of the irritable bowel, and a demand for a further opinion. Step by step we gradually progress.

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CURRENT KEY DEVELOPMENTS

Irritable bowel syndrome – the new inflammatory bowel disease?

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Irritable bowel syndrome (IBS) is currently diagnosed from symptoms which include chronic abdominal pain/discomfort associated with disturbed or altered bowel habit in the absence of structural or metabolic changes.¹ This would seem to exclude significant gut inflammation but recent studies suggest the need to rethink.² Progress in defining the mechanisms underlying IBS research has been limited by an inability to subdivide a very heterogeneous population. Recent research has attempted to overcome this limitation by focusing on a small subgroup of patients whose IBS developed after a bout of infectious gastroenteritis.²

Post-infective IBS as a model to study functional gastrointestinal diseases

Post-infective IBS (PI-IBS) is by definition the development of IBS in individuals with previously normal bowel function. Unlike other irritable bowel syndromes it has a defined start date and a known precipitant. It represents nature's experiment, infection being a random event not obviously dependent on personal choice. This provides a rare opportunity to study the mechanisms underlying the development of IBS. Numerous studies have confirmed earlier reports demonstrating an increased incidence of functional gastrointestinal (GI) diseases following GI infections (Table 1).^{3,4,5} Adverse risk factors include an initial illness lasting >3 weeks, toxigenic bacteria, female gender, and age <60.^{4,5,6}

Clinical features

These are similar to unselected IBS with diarrhoea (IBS-D) namely frequent urgent loose stools, bloating, mucus per rectum and a sense of incomplete evacuation.^{5,7} There is an important interaction between adverse psychological factors and mucosal inflammation, which both independently increase the risk of developing PI-IBS.^{7,8}

Pathophysiology

Campylobacter jejuni enteritis is associated with a high incidence of PI-IBS,⁵ one of the highest incidence ever reported being noted in an infection which combined both *Escherichia coli* O157:H7 and *C. jejuni*.⁹ Several detailed studies of rectal biopsies following *C. jejuni* enteritis have been undertaken which showed an acute inflammatory response with incomplete resolution in those with persistent symptoms.¹⁰ T lymphocyte, macrophage and enteroendocrine cell numbers all increased in parallel.^{7,10} These histological changes were associated with visceral sensitivity to rectal balloon distension and accelerated colonic transit, features also seen in other IBS-D patients.⁸

Abnormalities of serotonin metabolism in IBS

5HT is likely to be important mechanistically in PI-IBS as it causes secretion and propulsive motility and 5HT3 antagonists improve symptoms in IBS-D.¹¹ Postprandial release of 5HT is increased in the PI-IBS, with a decreased release in constipated IBS.¹² Mucosal 5HT is taken up via an active transporter SERT and metabolised to 5-hydroxyindole acetic acid (5HIAA). Mucosal 5HIAA/5HT ratio is depressed in PI-IBS spite of increased 5HT release, suggesting a defect of uptake of 5HT by enterocytes. While this idea is supported by animal studies showing inflammation decreases SERT expression data on mRNA for SERT in IBS colonic mucosa is conflicting.¹³⁻¹⁶ SERT function can also be assessed in circulating platelets using the H³-impramine binding assay. This is

markedly reduced in IBS-D, a low level predicting a good response to a 5HT₃ antagonist suggesting this is associated with excess 5HT effects.¹⁷

Drivers of chronic inflammation in IBS

Mast cells and gut permeability

While the acute inflammation occurs in those infected, it is unclear why in some patients this continues at a low level for many years.¹⁸ One possibility is continued abnormalities of gut permeability which have been noted in PI-IBS^{10,19} By increasing access of gut bacterial antigens this could account for low-grade chronic inflammation. Psychological stressors by activating immune cells, particularly mast cells, might cause this persistent increased permeability. Mast cells have been shown to be increased in both the ascending colon and duodenum of IBS patients and can be activated by stress.²⁰⁻²² Furthermore animal models strongly suggest that acute stress can increase gut permeability via activation of mast cells, though whether chronic low-level stress does the same is uncertain.²³

Psychosocial stress and cytokines

Acute stress exerts proinflammatory effects in experimental animals as well as humans with inflammatory bowel disease (IBD).²⁴⁻²⁵ Psychological stresses have even more obvious effects in IBS,²⁶ increasing the risk of PI-IBS two-threefold^{7,8} while chronic ongoing life stresses such as divorce, imprisonment and loss of employment effectively prevent resolution of IBS symptoms.²⁷ Psychological distress has been associated with increased plasma cytokines and social stresses are known to activate the immunocytes directly.²⁸⁻³⁰ Several recent studies have shown increases in circulating cytokines in IBS though their significance is unknown. Cytokines orchestrate the ‘illness behaviour’ which is seen after infection so it is feasible that some of the non-GI symptoms so common in IBS, including backache,

Table 1. Incidence of post-infective irritable bowel syndrome (PI-IBS).

Study	PI-IBS (%)	FU		Organism	Country
		months	n		
McKendrick 1994 ³	31	12	38	Salmonella	Sheffield, UK
Gwee, 1996 ⁴	39	3	75	Mixed	Sheffield, UK
Neal, 1997 ⁵	7	6	390	Bacterial	Nottingham, UK
Thornley, 2001 ⁶	9	6	180	<i>C. jejuni</i>	Nottingham, UK
Dunlop, 2003 ⁷	13	6	747	<i>C. jejuni</i>	Nottingham, UK
Wang, 2004 ³²	8	12-24	295	Shigella	Peking, China
Ji, 2005 ³³	7	6	101	Shigella	Seoul, Korea
Mearin, 2005 ³⁴	12	12	677	Salmonella	Catalonia, Spain
Marshall, 2006 ³⁵	27.5	24	2,069	<i>E. Coli</i> O157:H7 <i>C. jejuni</i>	Walkerton, Canada

n = number.

headache, insomnia and lethargy could be due to increased cytokines. Sorting out whether this is cause or effect will require intervention studies either with anti-inflammatory or psychological therapies. The results of such studies may well have relevance for the subgroup of IBD patients who suffer from IBS-like symptoms even when overt inflammation has subsided.³¹

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