Review Article

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Role of gut pathogens in development of irritable bowel syndrome

Madhusudan Grover

Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN, USA

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Acute infectious gastroenteritis is one of the most commonly identifiable risk factors for the development of irritable bowel syndrome (IBS). A number of bacterial, viral and parasitic pathogens have been found to be associated with the development of IBS and other functional gastrointestinal (GI) disorders. Epidemiological studies have identified demographic and acute enteritis-related risk factors for the development of post-infectious-IBS (PI-IBS). Immune dysregulation, alterations in barrier function, serotonergic and mast cell activation have been identified as potential pathophysiological mechanisms. Additionally, variations in host genes involved in barrier function, antigen presentation and cytokine response have been associated with PI-IBS development. However, it is unknown whether specific pathogens have unique effects on long-term alterations in gut physiology or different pathogens converge to cause common alterations resulting in similar phenotype. The role of microbial virulence and pathogenicity factors in development of PI-IBS is also largely unknown. Additionally, alterations in host gut sensation, motility, secretion, and barrier function in PI-IBS need to be elucidated. Finally, both GI infections and antibiotics used to treat these infections can cause long-term alterations in host commensal microbiota. It is plausible that alteration in the commensal microbiome persists in a subset of patients predisposing them to develop PI-IBS.

Key words *Campylobacter jejuni* - functional GI disorders - infectious gastroenteritis - irritable bowel syndrome - post-infectious irritable bowel syndrome

Introduction

Gastrointestinal (GI) infections are globally prevalent and cause significant morbidity and mortality. Chronic GI disorders including celiac disease[1], inflammatory bowel disease (IBD)[2] and irritable bowel syndrome (IBS)[3] have been causally associated with infectious gastroenteritis (IGE). Since the first description of post-infectious IBS (PI-IBS) provided by Chaudhary and Truelove in 1962 among patients with proven or presumptive episode of bacterial or amoebic dysentery[4], numerous epidemiological studies have confirmed the association between acute IGE with different pathogens and development of IBS and other functional GI disorders (FGIDs)[3]. In addition to outbreaks in community or hospitalized settings, acute IGE sustained during a travel[5] or military recruitment[6] has also been associated with development of PI-IBS. Studies in different settings and with different pathogens have yielded a wide range (4-36%) of individuals developing PI-IBS after an episode of IGE[3]. Bacterial IGE seems to be

more closely related to the development of long-term PI-IBS phenotype[7] as compared to viral IGE[8]. Long-term follow up studies suggest that bacterial pathogen related PI-IBS phenotype may persist for up to 8-10 years after the acute IGE is over[9,10]. Epidemiological studies have identified female gender, age <60 yr, smoking, enteritis severity, and pre-enteritis psychological stress as risk factors for development of PI-IBS[11]. Existing literature supports the role of enterochromaffin (EC) cell hyperplasia, altered barrier function, immune dysregulation and potentially mast cell activation in the pathophysiology of PI-IBS. However, a number of prior studies have been conducted after epidemics often involving >1 pathogen or in highly selected tertiary referral patients. Thus, there is limited insight into unique pathogen-specific mechanisms from isolated, community-based gastroenteritis cases, and into physiological and clinical sequelae based on the pathogen and host characteristics.

Epidemiology

Gastrointestinal infections with isolated (bacterial, viral), mixed (> 1 bacteria, bacteria and a virus), and unspecified (travelers' diarrhoea) pathogens have all been associated with the development of PI-IBS. Most of the larger cohorts are from outbreaks involving bacterial pathogens[12]. However, in several studies involving outbreaks, the information on the pathogen involved is often not available in all subjects and is only assumed. Although, these studies have shown a wide range (4-36%) of individuals developing PI-IBS, a meta-analysis revealed median prevalence of 10 per cent (compared to 1.2% in controls)[13]. This also showed a relative risk ranging between 2-12 and a pooled odds ratio of 7.3 for development of PI-IBS. The Table provides a comprehensive list of PI-IBS epidemiological studies according to the pathogen involved. An outbreak in Walkerton, Canada in 2000 caused by contamination of municipal water supply from livestock faecal material resulted in acute gastrointestinal illness in over half of the town's 4800 residents has provided significant epidemiological information about PI-IBS[12]. Although, pathogen information was not available in all cases, mixed bacterial infection with *Campylobacter jejuni* and *Escherichia coli* O157:H7 was found be responsible for most of the cases. Two years post-infection, a PI-IBS rate of 36 per cent among patients that had IGE during the outbreak was seen[12].

Risk factors

***Age and gender*:** Age >60 yr was found to be protective for development of PI-IBS in a large community survey (relative risk: 0.36)[14]. Younger age was found to be an independent risk factor for PI-IBS development in the Walkerton outbreak cohort[12]. However, other studies did not confirm an effect of age on PI-IBS development[15,16]. Studies have debated the effect of gender on PI-IBS development when the effect was either not found[16] or was lost once psychological variables were controlled for[17,38]. However, in other larger studies[15] including the Walkerton outbreak cohort[12], female gender was identified as a risk factor. This goes along with the increased prevalence of IBS and other FGIDs in women.

***Smoking*:** A single study showed smoking to be associated with PI-IBS development (odds ratio: 4.8)[39]. However, smoking can be a marker for psychological distress, hence associating with PI-IBS, which makes it harder to draw any conclusions based on the limited evidence.

***Antibiotic use*:** Prevalence of PI-IBS following *Salmonella enteritidis* enteritis was not found be different among groups that did or did not use antibiotics (17.6 vs 9.3%, not significant) in one study[16]. However, another post-*Salmonella* study showed an increase in the prevalence of persistent GI symptoms in a group that received antibiotics (9.5 vs 2.9%)[40]. A travelers' diarrhoea study showed antibiotic use to be associated with development of PI-IBS (relative risk: 4.1)[18]. It is quite plausible that antibiotic induced changes in commensal microflora can persist in vulnerable subset of hosts predisposing them to long-term changes in gut physiology resulting in development of PI-IBS.

***Psychological factors*:** There was an increased prevalence of anxiety, depression, somatization, and neurotic traits at the time of IGE in the group that developed PI-IBS[19]. Patients who develop IBS report more adverse life events in preceding three months and hypochondriasis scores[38] and these features predicted PI-IBS development independent of the anxiety and neuroticism scores. A study also showed depression to be a risk factor (relative risk: 3.2)[17]. Another study showed higher levels of perceived stress, anxiety, somatization, negative illness beliefs at the time of acute enteritis to be associated with PI-IBS. Depression was not found to be a risk factor in this study[41]. The influence of psychological stress on PI-IBS is interesting and under-studied. Catecholamines

Table. Percentage of individuals developing post-infections - irritable bowel syndrome (PI-IBS) with different enteritides

Pathogen	PI-IBS % (Number infected)	Time-point for PI-IBS prevalence (months)	Setting	Reference
Bacterial				
Campylobacter jejuni	9 (188)	6	Community	21
	13 (747)	3	Community	17
Shigella sonnei	8 (295)	12-24	Community	20
	20 (101)	3	Community	23
Salmonella enteric	31 (38)	12	Elderly	24
	10 (677)	6	Community	16
Clostridium difficile	12 (41)	6	Community	25
	4 (23)	3	Community	26
Mixed (≥1) bacterial	27 (75)	6	Inpatient	19
	7 (390)	6	Community	13
	7 (192)	72	Community	27
	36 (742)	24	Community	14
	19 (742)	96	Community	9
Salmonella, *Shigella* or *Campylobacter*	32 (44)	6	Inpatient	28
Salmonella or *Campylobacter*	4 (189)	12-120		10
Unspecified	4 (318)	12	Community	29
Viral				
Norovirus	24 (89)	3	Community	8
	12 (87)[#]	6		
	22 (186)	12	Community	22
Parasitic				
Giardia lamblia	7 (1300)	12	Community	30
Trichinella britovi	14 (72)	6	Community	31
Unspecified				
	4.2 (137)	3	TD	5
	11 (97)	6	TD	32
	4 (231)	3	Community	33
	14 (118)	6	TD	18
	OR: 3.7	-	Military	34
	63*	-	TD	35
	OR=6.6[€]	0.75	Community	36
	17 (108)	6	Community	37
Mixed				
C. jejuni and EB virus	11 (748)	6	Community	15

[#]Not significantly different from controls; *10/16 that reported IBS during travel had persistent IBS post-travel; [€]risk of diarrhoea (not PI-IBS). OR, Odd's ratio; TD, Travelers' diarrhea; EB, Epstein-Barr virus

and other stress mediators have been shown to play a role in modulating pathogenic infectivity and host epithelial-microbial interactions[42] which can play a role in increasing severity of enteritis and subsequent development of post-infectious phenotype.

***Enteritis severity*:** *Shigella* enteritis lasting >14 days was more significantly associated with PI-IBS development as compared to illness lasting <8 days (relative risk: 4.6)[20]. Similarly, another mixed bacterial enteritis study showed greater likelihood of PI-IBS development with illness lasting >3 weeks vs <8 days (relative risk: 11.4)[14]. Diarrhoea >7 days was associated with PI-IBS development in the Walkerton outbreak cohort[12]. Additionally, presence of bloody stools, abdominal

cramps, and > 10lb weight loss was also found to be associated with PI-IBS in this cohort. A single study examining the role of bacterial pathogenicity factors showed *Campylobacater jejuni* strain producing toxin with elongating effects on the Chinese hamster ovary cells was associated with increased risk of developing persistently deranged bowel habits[21]. Overall, this suggests that enteritis severity appears to play a role in the development of PI-IBS. However, clinical severity of enteritis might be related to microbial virulence or variations in host response. More needs to be done to elucidate role of microbial virulence factors in development of PI-IBS.

Clinical features

In the absence of a biomarker or a universally accepted definition for PI-IBS, the Rome criteria[43] for defining IBS are usually used to define PI-IBS. This requires presence of recurrent abdominal pain or discomfort at least three days/month in the last three months associated with two or more of the following: *(i)* improvement with defaecation, *(ii)* onset associated with a change in frequency of stool, and *(iii)* onset associated with a change in form (appearance) of stool. These historical characteristics must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis. To characterize as PI-IBS, the individual must not meet criterion for IBS prior to the infection and the acute IGE must be characterized either by presence of positive stool cultures or presence of ≥2 of the following: fever, vomiting, or diarrhoea. The stool cultures are often not available since a number of individuals develop acute IGE as travelers' diarrhoea. The PI-IBS phenotype is most commonly IBS-D[44] and IBS subtype phenotypic clusters have been found to remain stable over time[45]. Previous treatment for anxiety or depression was reported less frequently in PI-IBS than non-PI-IBS (26 vs 54%).

Natural history

The Walkerton outbreak cohort investigators reported the 8 year follow up data and the prevalence of IBS dropped to 15.4 per cent after 8 years, still remaining significantly increased compared with controls without history of acute IGE (OR 3.12; 95% CI 1.99 to 5.04)[9]. This suggests that PI-IBS phenotype persists for a prolonged duration. Another study showed that symptoms persist for upto 10 years following the initial infection[10]. A recent analysis of the defense database showed an increased risk of dyspepsia, constipation, and gastroesophageal reflux disease among military recruits who had suffered from IGE from norovirus[46]. In another food-borne outbreak study of norovirus, 23.6 per cent reported symptoms consistent with PI-IBS at three months vs 3.4 per cent who remained well (odds ratio: 6.9). However, at 6, 12, and 24 months, the prevalence of IBS was similar among exposed versus non-exposed individuals[8]. Vomiting during the IGE episode independently predicted risk of PI-IBS at three months[8]. From a recent viral outbreak in Italy, 13 per cent of IGE patients were found to have PI-IBS at 12 months, and most of these were mixed-IBS (IBS-M). This study also showed that the presence and severity of symptoms progressively diminished at 12 month follow up as compared to the 6 month survey[22]. Both these studies suggest that post-viral IBS may be a more transient phenomenon as compared to bacterial PI-IBS. This might be related to a lesser degree of initial epithelial damage and host inflammatory response caused by viral as compared to bacterial pathogens.

Mechanisms

***Mucosal cellular changes*:** Post-*Campylobacter* IBS is characterized by an increase in rectal mucosal enterochromaffin (EC) cells, lamina propria T-lymphocytes[17,47], CD8 intraepithelial lymphocytes and calprotectin-immunoreactive (ir) cells[47]. Post-*Shigella* IBS is characterized by increase in ileal mast cells and nerve fibers immunoreactive for neuron-specific enolase, substance P, and 5-hydroxytryptamine (5-HT, serotonin) seen adjacent to the mast cells[20]. Another study showed an increase in 5-HT-ir EC cells, peptide YY (PYY)-ir EC cells, intraepithelial lymphocytes, CD3, CD8 lymphocytes, mast cells and CD68 cells[48]. Colonic mucosal supernatants from PI-IBS patients resulting from unspecified IGE caused stimulation of peritoneal mast cell protease-activated receptor (PAR_2) mRNA expression[49]. Another study looking at mucosal tissue, however, showed decrease in mast cell PAR_4 expression but unchanged PAR_2 expression[50]. Mast cell numbers were unchanged but activated mast cells and tryptase concentration were increased in supernatants from PI-IBS patients (unspecified IGE). Similar to post-*Campylobacter* IBS, increased mean chronic inflammatory cells[38], EC cells, lamina propria T lymphocytes without any changes in mast cell numbers were seen[44]. Overall, EC cell hyperplasia and activation seem to play a significant role in pathophysiology of PI-IBS, however, the role of mast cells is unclear at this time.

***Alterations in gut permeability*:** An increase in 0-6 h lactulose/mannitol (L/M) ratio initially and at 12 wk

has been observed after acute IGE with *C. jejuni*; however, it is unclear if these patients met criteria for IBS[47]. Another study showed increase in 3-6 h Cr^{51} EDTA excretion initially after *Campylobacter* gastroenteritis and at 6 months, however, this cohort is also not confirmed to have IBS phenotype[51]. Increased L/M excretion after overnight collection has also been reported in PI-IBS patients from the Walkerton outbreak cohort[52]. Using ^{51}Cr-EDTA excretion, proximal small bowel permeability was found to be altered in PI-IBS (unspecified pathogen); however, in this study non-PI-IBS patients had greater alterations in small bowel permeability as compared to PI-IBS patients[53]. *In vivo* permeability alterations or *ex vivo* changes in mucosal barrier function are unknown in PI-IBS resulting from other bacterial or viral pathogens.

***Cytokine expression*:** No differences were seen in mucosal interleukin (IL)-10, tumour necrosis factor (TNF)α and IL-1β expression in post-*Campylobacter* IBS[51]. Peripheral blood mononuclear cell TNFα cytokine expression has been found to be increased in post-*Campylobacter* IBS, however, no differences were seen in IL-10, or IL-1β expression. This study also showed increased TNFα rs1800629[51]. Another post-*Campylobacter* study did not show any differences in IL-18 and interferon (INF)γ polymorphisms[54]. Increased terminal ileal and rectosigmoid IL-1β expression in post-*Shigella* IBS[25] and rectal IL-1β expression in post-mixed infection IBS[55] have been seen. Patients with PI-IBS following mixed infection showed an increase in peripheral blood mononuclear cell TNF-α, IL-1β, IL-6, and lipopolysaccharide-stimulated IL-6 levels[56].

***Gene expression*:** The Walkerton outbreak cohort showed variations in three genes to be independently associated with PI-IBS. These are cytokine gene *IL6* [rs206986; OR 1.509 (1.031-2.209)], tight junction E-cadherin gene *CDH1* [rs16260; OR 1.398 (1.069-1.829) and *TLR9* [rs 5743836; OR 1.536 (1.080-2.182)] encoding for pattern recognition receptor for bacteria that detects unmethylated CpG dinucleotide[57]. Together, this reflects a role of host immune activation and barrier function genetics in the development of IBS in that cohort. In another study[51], mucosal expression of CCL11 [chemokine (C-C) motif ligand l], CCL13, Calpain 8 and TNFSF15 (TNF superfamily member 15) increased while NR1D1, G-protein coupled receptor 161 (GPR161) and gamma-aminobutyric acid receptor subunit epsilon (GABRE) decreased post-*C. jejuni* group (not PI-IBS). *TNFα* rs1800629 minor allele frequency was increased in post-*C. jejuni* group compared to healthy controls[51]. Polymorphisms in *IL-18* and *INF γ* were studied in a *C. jejuni/coli* gastroenteritis cohort but none were found to be linked with the development of PI-IBS at 6-month follow up[54].

Treatment

The first step in the management should be to illicit the history of IGE preceding the onset of symptoms. This finding can often be a subtle on history and patients may just endorse acute onset of symptoms during or after a travel without recall of classical symptoms of acute IGE. A stool culture is unlikely to be available in most cases. Although PI-IBS is characterized by acute onset of symptoms after a GI infection, many patients provide a history of respiratory illness preceding the onset of IBS. Although, this cannot be typically characterized as PI-IBS, it can be considered to be in the same spectrum of FGIDs. Once PI-IBS is clinically suspected, it is often helpful to educate the patient about the role of gut infections in development of IBS symptoms and a suspected causal link can be helpful in "legitimizing" the disorder. It is also helpful to reassure since the PI-IBS is likely to improve over time than deteriorate, especially if a viral pathogen is suspected to be involved.

Subsequently, the overall clinical management is driven by nature and severity of the symptoms and is not different from management of IBS, details of which can be found elsewhere[58]. A few clinical trials specific to PI-IBS have been performed. In a randomized, double-blind, placebo controlled trial of prednisolone at a dose of 30 mg/day for three weeks, lamina propria T-lymphocytes decreased but no differences were seen in EC cell counts or clinical endpoints of abdominal pain or diarrhoea[59]. An open-labelled trial of 18 patients using mesalamine 800 mg three times a day for 30 days showed improvement in scores for abdominal pain, distension, stool frequency and consistency[60]. This study also showed similar improvements in 43 non-PI-IBS patients treated with same dose and duration of mesalamine. Another double-blind, placebo controlled study using mesalamine (Asacol®) 1.6 g twice a day in 20 patients with PI-IBS showed improvement in global symptoms, abdominal pain, bloating, stool urgency, frequency, or consistency and quality of life[61].

Conclusions

Gastrointestinal infections with pathogenic microbes constitute an important risk factor for development of IBS and other FGIDs. In spite of a

significant knowledge of epidemiological risk factors, little is known about pathophysiological mechanisms of PI-IBS. Existing literature supports the role of immune dysregulation, altered barrier function, EC cell activation and host genetics. Much needs to be done to identify novel mechanisms such as the role of microbial pathogenicity factors, alterations in host commensal microbiota, and post-infectious plasticity in the neuromuscular apparatus of the gut. From the stand-point of the host, alterations in gut physiology using deep phenotyping measures in studies of GI transit, sensation and permeability and central nervous system changes using functional brain imaging will be necessary to find subsets of PI-IBS patients with unique physiological alterations. Overall, this subset of IBS provides an opportunity to prospectively recruit patients and study mechanism for PI-IBS and IBS in general. Additionally, studies involving isolated, identifiable pathogens will likely provide more relevant mechanistic information.

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Reprint requests: Dr Madhusudan Grover, Assistant Professor, Division of Gastroenterology & Hepatology
Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: grover.madhusudan@mayo.edu