INTERNAL MEDICINE - PEDIATRICS  

PATHOGENIC FACTORS IN POSTINFECTIOUS IRRITABLE BOWEL SYNDROME - AN UPDATE

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PATHOGENIC FACTORS IN POSTINFECTIOUS IRRITABLE BOWEL SYNDROME-AN UPDATE (Abstract): After acute infectious gastroenteritis, up to thirty percent of patients present prolonged gastrointestinal symptoms and a part of those affected patients can have the diagnostic criteria for postinfectious irritable bowel syndrome. The main diagnosis of a patient with postinfectious irritable bowel syndrome was till this summer, clinically based on Rome III criteria. The Rome IV criteria brought some changes that involve also the postinfectious irritable bowel syndrome, recognizing further the postinfectious IBS as a specific entity according to the multidimensional clinical chronic mucosal inflammation triggered by enteric infection, may underlie persistent bowel symptoms in patients who develop postinfectious irritable bowel syndrome. **Keywords:** GASTROENTERITIS, INTESTINAL INFECTION, POSTINFECTIOUS IRRITABLE BOWEL SYNDROME.

The irritable bowel syndrome (IBS) is an association of chronic and recurrent symptoms such as constipation, diarrhea, bloating and/or abdominal pain, having not any abnormalities (biochemical or structural) detectable by conventional laboratory methods. The irritable bowel syndrome affects 9-13% of the normal population at any particular period in time (1).

Irritable bowel syndrome is defined as recurrent abdominal pain on average at least 1 day a week in the last 3 months associated with two or more of the following: related to defecation, associated with a change in a frequency of stool, associated with a change in form (consistency) of stool. Symptoms must have started at least 6 months ago, according to Rome IV criteria.

The earliest description of postinfectious irritable bowel syndrome (PI-IBS) was made in 1962; Chaudhary and True-love reported that one third of their patients with a history of gastroenteritis went on to develop irritable bowel syndrome type symptoms (2). Since then, other authors have suggested that patients with an episode of infectious diarrhea have a high incidence of developing irritable bowel syndrome in the following months, with estimates ranging from 4% to 32%. How-
ever, these studies have used varying methodologies, have studied different populations, and a control group was most lacked (3,4,5,6). There are numerous reports, indicating that up to a third of people suffering from bacterial enteritis report persisting ongoing symptoms compatible with irritable bowel syndrome between six months and one year afterwards. Furthermore, though some will recover spontaneous, even at six years, nearly two thirds remain symptomatic (7).

The current conceptual framework regarding the pathogenic mechanisms for postinfectious irritable bowel syndrome suggests that postinfectious irritable bowel syndrome is associated with alteration of motility, increased intestinal permeability, an increased number of enterochromaffin cells and the intestinal inflammation persisted. This was characterized by an increased number of T-lymphocytes and also mast cells and an increased expression of proinflammatory cytokines. This suggests that an exposure to pathogenic organisms that disrupts the intestinal barrier function and alters the neuromuscular function and triggers chronic inflammation, which sustains irritable bowel syndrome symptoms (8).

The postinfectious irritable bowel syndrome is characterized by the sudden onset of symptoms mentioned in the diagnostic criteria for irritable bowel syndrome (with Rome IV criteria being the most recently defined). They appear following an episode of acute infectious gastroenteritis characterized by two or more of the following symptoms and findings: diarrhea, vomiting, fever and a positive stool culture result (9).

**Epidemiology.** Some studies (10) involving patients ill enough to be hospitalized in an infectious diseases unit, indicate that around 1/3 develop postinfectious irritable bowel syndrome, while other studies dealing with patients in the community have found a lower incidence of around 7% (5) and 9% (11). The net result is that approximately 17% of patients attending general practitioners in the UK attribute their irritable bowel syndrome symptoms to an episode of gastroenteritis (12). The incidence in the USA is much lower, around 6%, though whether this reflects differing referral practice is not certain. Infection is much commoner in the tropics where postinfectious irritable bowel syndrome might be expected to be more frequent though this has not been specifically examined. Certainly, the commonest sub-types of irritable bowel syndrome in Southern India appear to be diarrhea predominant (D-irritable bowel syndrome) (13), while in China D-irritable bowel syndrome also predominates with 65% of irritable bowel syndrome patients fitting this categorization (14). This parallels the findings in a UK study (6).

One of the earliest reports of postinfectious irritable bowel syndrome relates to unexplained diarrhea and abdominal discomfort seen in British troops returning from the World War II North Africa campaign after amebic dysentery (15). A study from Sheffield examined 75 individuals admitted to an infectious disease unit with gastroenteritis, 25% of whom developed new irritable bowel syndrome when assessed 6 months after infection (10).

A further community survey in Nottingham, restricted to just *Campylobacter* gastroenteritis, confirmed a percentage with 9% in a new cohort of 189 infected individuals (11). More recently, there has been a case-control study from Newcastle using Rome II criteria for irritable bowel syndrome, indicating an incidence of new postinfectious irritable bowel syndrome over 6 months of 17% compared with just
1.9% of controls, odds ratio 10 (16). With the exception of the study by Parry et al (16) and Ji et al. (17), the previous studies lacked a control group to define the normal incidence of new irritable bowel syndrome in the absence of infection. This was corrected in a large study of over 550,000 patients whose records form part of a large general practice research database in the United Kingdom. This database records all interviews with the general practitioner, all prescriptions and all laboratory results. They found 318 patients with documented bacterial enteritis (54% Campylobacter, 37% Salmonella), 12 of whom had new diagnosis of irritable bowel syndrome over the next 12 months, an incidence of 40 (22-70) (mean 95% confidence intervals)/1000 patients years giving a relative risk of 11.9 when compared with uninfected controls with an incidence of just 3.5/1000 patient years. During a one year follow up, the diagnosis rate of irritable bowel syndrome was 4.4% in patients after an episode of bacterial gastroenteritis (14 subjects), compared with a rate of 0.3% in the general population cohort (2027 subjects). The weakness of this study was that stool cultures are only obtained in around 1 in 10 of all cases of gastroenteritis in the United Kingdom (6). In another cohort study of 295 patients who had recovered from bacillary dysentery (BD) and 243 control subjects (consisting of patient siblings or spouses who had not been infected with BD) is investigated the incidence of irritable bowel syndrome and FBD (functional bowel disorders) in a Chinese patient population (in Beijing). All subjects were followed up using questionnaires for 1-2 years to explore the incidence of FBD and irritable bowel syndrome, as defined by the Rome II criteria. In the BD infected cohort, the incidences of FBD and irritable bowel syndrome were 22.4% and 8.1% (in total)-10.2% (among those in no Shigella were identified) respectively, which were significantly higher (p< 0.01) than the incidences of FBD (7.4%) and irritable bowel syndrome (0.8%) in the control cohort (18). While irritable bowel syndrome is common in western societies such as the USA or UK, early studies suggest that in developing countries, the prevalence is low (1). Irritable bowel syndrome was considered by Henry Bockus to be the most valid example of a civilization disorder (19). It is speculated that low prevalence of irritable bowel syndrome in underdeveloped countries is determined by an increased exposure to infection during the child age, rather than to fiber reach meals. The colonization of the intestine by micro flora and also the development of broad immune tolerance can result from the exposure to a variety of microorganisms early in life and enables the intestinal epithelium to respond more efficiently to antigenic challenge, during an episode of gastroenteritis. This leads to symptoms that resolve more quickly. In area with better hygienic conditions, the immune system of the gut is preserved naïve to exposures. Having episodes of gastroenteritis in later life can cause inflammatory disturbances. This, but also behavioral and psychological factors, predisposes to the persistence of symptoms suggestive for irritable bowel syndrome (1).

Gastroenteritis due to viral etiology is mostly associated with acute episodes of diarrhea and little residual injury. This might be associated with a lower incidence of postinfectious irritable bowel syndrome, in comparison with infection due to bacterial pathogens. In an outbreak of presumed viral gastroenteritis, one quarter of the patients developing gastroenteritis reported symptoms of postinfectious irritable bowel syn-
drome at 3 months after the outbreak (8). Consistent among these studies is the suggestion that postinfectious irritable bowel syndrome is different for any ethnic group or environment and became a global phenomenon. The prevalence or incidence of postinfectious irritable bowel syndrome varies in part because of differences in study methodology, including the criteria used to define irritable bowel syndrome. In general, Rome II criteria generate lower estimates than Rome I or III. Postinfectious irritable bowel syndrome has a defined moment of onset in comparison with sporadic irritable bowel syndrome. Features of the inciting infectious illness such as diarrhea, abdominal cramps, increased stool frequency, bloody or mucous stools, and positive stool culture and weight loss are potent predictors of long term outcome. The risk of postinfectious irritable bowel syndrome appears to correlate with the severity of the acute enteric infection, increasing at least two-fold if diarrhea lasts more than 1 week and over threefold if diarrhea lasts more than 3 weeks. Bloody stools, abdominal cramps and weight loss are also associated with high risk, with abdominal cramps increasing the risk fourfold (8).

Pathogenic mechanisms. Prospective studies provide strong evidence that the development of postinfectious irritable bowel syndrome involves an interactive multifactorial etiopathogenic process. Psychological factors: like hypochondriasis, an important life event stress preceding the infectious episode were strong predictors for the developing of irritable bowel syndrome. Increased expression of interleukin 1 β mRNA present in rectal biopsies and increased numbers of intraepithelial lymphocytes and T-lymphocytes in recto-sigmoid biopsies suggest that the pathogenesis of postinfectious irritable bowel syndrome is also sustained by an inflammatory process. Possible other mediators include TNF-α and interferon-γ. Inflammation is usually associated with activation of cyclo-oxygenase 2 (COX-2) enzymes and an associated rise in prostaglandins, which sensitive visceral afferents and stimulate secretion and intestinal propulsion (20). The other striking abnormality was an increase in entero-endocrine cells which may explain an increased serotonin release by test meal which others have reported (21).

In animal models inflammation can induce entero-endocrine cell hyperplasia and increase serotonin release but the effects on bowel motility are unpredictable since in this model there was receptor desensitization and impaired peristalsis (22).

A study from China regarding postinfectious irritable bowel syndrome observed a similar increase in the inflammatory markers above mentioned. They also discovered the numbers of mast cells in terminal ileum biopsies of both postinfectious irritable bowel syndrome as well as non-postinfectious irritable bowel syndrome patients were increased compared with controls. Another study from New Zealand discovered high levels of mast cells in colonic biopsies taken from patients with irritable bowel syndrome with non-specific microscopic inflammation on conventional histology. The particularity in this study was the finding of immune activation in a group of irritable bowel syndrome patients whose presentation was atypical for postinfectious irritable bowel syndrome. These patients had more chronic irritable bowel syndrome symptoms, with an insidious onset and their colonic biopsies were judged to be normal on conventional histology.

Role of inflammation in irritable bowel syndrome. Epidemiological studies sug-
suggest an association between inflammation following prior infection and the persistence of irritable bowel syndrome symptoms. The interdependence of prior infection and psychological status has also been consistently documented (22), and this may question the role of persistent inflammation as an independent risk factor. The data are interpreted as evidence of the importance of psychoneuroimmune interactions; it is unclear whether the inflammation is a key common final pathway to non-specific psychological influence on intestinal function, and the prior infection potentially unrelated other than as an initiator of the cascade of events. A summary of the epidemiology data also shows that the prevalence of PI-irritable bowel syndrome is no more prevalent than irritable bowel syndrome in the general population. A second approach is to review the quantitative differences in the inflammation and their association with symptoms. Many studies have documented increased numbers of CD3, CD25 or mast cells in ileal, colonic or rectal biopsies, but the differences for lymphocyte counts between controls and irritable bowel syndrome are small, with predominant overlaps in the counts between the two conditions (24). The third line of evidence to be examined is the response to anti-inflammatory treatment of irritable bowel syndrome. A controlled trial has shown that, among carefully selected patients with postinfectious irritable bowel syndrome, prednisone 30 mg b.i.d. was not significantly better than placebo and while placebo resulted in the customary, no change in score was noted in the prednisone treatment group, significant 30% change in median symptom score relative to baseline (25).

Prognosis. Like other types of irritable bowel syndrome, symptoms in postinfectious irritable bowel syndrome fluctuate but are generally chronic. Spiller found only 43% had recovered at six years which was not significantly different from the 31% of those with pre-existing irritable bowel syndrome (26).

Hypothesis on the cause of increasing irritable bowel syndrome prevalence in developing countries. It is speculated that low prevalence of irritable bowel syndrome in underdeveloped countries is determined by a high childhood exposure to infection, rather than high residue diet. The microflora colonization of the intestine and the development of broad immune tolerance can result from the exposure to a variety of microorganisms early in life and enables the intestinal epithelium to respond more efficiently to antigenic stimulation leading to symptoms that resolve more quickly, during an episode of gastroenteritis. On the other hand, the intestinal immune system remains relatively naive in the more hygienic environment associated with improved socioeconomic conditions. Acquiring acute gastroenteritis later in the life results in inflammatory changes. This factor together other factors, i.e. with psychological and behavioral factors, predisposes to the persistence of symptoms manifesting as irritable bowel syndrome (1).

Postinfectious IBS in Rome IV era. The Rome IV criteria bring (27) some new approaches in the field of functional gastrointestinal disorders and specifically in IBS (28). The pain remains the main feature of IBS diagnosis and frequency of pathological stools have major importance in subtyping IBS following the presentation of the stools according to the Bristol scale. The postinfectious entity is further acknowledged. Its definition changed together with the definition of the IBS as a category, not specifically because of the infectious trigger. However the infectious trigger has to
be mentioned according to the multidimensional clinical (29).

CONCLUSIONS
Our conclusion is that Rome IV recognize further the postinfectious IBS as a specific entity, according to the multidimensional clinical chronic mucosal inflammation triggered by enteric infection may underlie persistent bowel symptoms in patients who develop postinfectious irritable bowel syndrome.

REFERENCES
Pathogenic factors in postinfectious irritable bowel syndrome - an update


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**HYDROGEN PEROXIDE VASORELAXATION INVOLVES S-GLUTATHIONYLATION OF VOLTAGE-DEPENDENT K CHANNELS**

H$_2$O$_2$ is an endothelium-derived hyperpolarizing factor (EDHF), but H$_2$O$_2$ effects vary with the vascular bed and experimental conditions. If H$_2$O$_2$ relaxes rat mesenteric artery, what is the mechanism? Methods: myography of isolated resistance arteries, patch clamp of mesenteric arterial smooth muscle cells (MASMCs), streptavidin pull-down assays with biotinylated glutathione ethyl ester. Relaxation of precontracted arteries by H$_2$O$_2$ was reversed by dithiothreitol, reduced by 4-aminopyridine (4-AP), blocker of voltage-dependent K channels (K$_v$) channels, but not by blockers of big-conductance Ca$^{2+}$-activated K$^+$ channels or of inward rectifier K$^+$ channels. H$_2$O$_2$ increased K$_v$ currents; this was prevented by glutathione reductase; K$_v$ incorporates glutathione (GSH) in the presence of H$_2$O$_2$. Thus, H$_2$O$_2$ activates Kv channels (maybe via S-glutathionylation) with artery relaxation, while the basal redox status of MASMCs determines K$_v$ response to H$_2$O$_2$. (Park SW, Noh HJ, Sung DJ et al. Hydrogen peroxide induces vasorelaxation by enhancing 4-aminopyridine-sensitive Kv currents through S-glutathionylation. *Pflugers Arch* 2015; 467(2), 285-297).

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