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*Editorial*

# Post-infectious Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is considered to be a functional disease, chracterised by the presence of symptoms of abdominal pain, bloating and abnormal defecation in the absence of organic disease (diagnosis of exclusion). Although it does not increase mortality, it strongly impairs quality of life and increases health-care costs. The prevalence of the disease varies from 3% to 22%, depending on the criteria used and the health-care system of the country, being most accurate figure the second one, since a lot of sufferers do not seek medical advice or adopt paramedical treatment.

Little is known regarding etiology. There are several theories supporting an altered intestinal motility, visceral hypersensitivity, abnormal brain interpretation of pain signals, abnormal gas propulsion, altered gut flora, and food constituent intolerance as etiopathogenetic factors, with a background of a disturbed psychological profile. The majority of patients with IBS present with increased scores of stress, anxiety, depression and hypochondriasis, symptoms that are rather part of the cause than the outcome of the disease.

A subgroup of patients who are initially diagnosed as suffering from IBS, are subsequently found to have microscopic colitis or celiac disease. The latter is present in 3% to 5% of patients with IBS symptoms. These entities, as well as lactose intolerance, low-grade Crohn's disease or the less frequent idiopathic bile-salt malabsorption, should always be included in the differential diagnosis.

As medical research goes on, the pool of IBS patients decreases. A lot of interest has centred recently on the inflammatory component of IBS. A proportion of patients with diarrhea-predominant IBS recall acute infectious enteritis as a boot for the onset of their symptoms, and 7%-33% of patients with acute bacterial enteritis will experience IBS symptoms for over 6 months. A chronic latent inflammation has been documented in mucosal biopsies of these patients. Post-infectious IBS (PI-IBS) has been linked to bacterial (campylobacter, shigella, salmonella) or parasitic (trichinella spiralis) infections.[1] The prevalence of PI-IBS is 6% to 17% among IBS patients in different series[1] and lower in older people (over 60 years old), probably due to their weaker immune system. The risk for PI-IBS correlates to the duration and severity of the initial illness. Infection in early childhood has a milder course and induces partial immunity, therefore PI-IBS is rarer in tropical areas where the prevalence of pediatric gastrointestinal infections is high. Vomiting seems to exert a protective role possibly because it reduces the ingested bacterial load. Other risk factors include female gender, hypochondriasis and adverse life events. PI-IBS is twice as frequent in monozygotic twins compared with dizygotic twins,[2] so a genetic parameter may also interfere.

Immunohistochemical staining of mucosal biopsies of patients with PI-IBS showed a sustained increase in CD3, CD4 and CD8 positive lamina propia T lymphocytes, CD8 positive intraepithelial lymphocytes (IEL) and enteroendocrine cells (EC), at 3 months and 1 year after campylobacter infection.[3] Mucosal lymphocytes secrete inflammatory cytokines, which increase gut permeability and stimulate secretion. Increases in ileal mast cells and enhanced mast cell tryptase activity have been noted in IBS patients, as well as enhanced IL-1b mRNA expression 3 months post initial infection.[4]

Genetic factors may account for persistent inflammation in a proportion of IBS patients, with low secretion of anti-inflammatory cytokines such as IL-10 and TGF-b genotypic profile similar to that seen in patients with inflammatory bowel disease.[5] Increased numbers of

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immunocompetent cells in the intestinal mucosa of IBS patients have been demonstrated by quantitative immunohistology even in specimens with normal conventional histology.[6] Fifty per cent of patients with histologically normal mucosa had positive markers of inflammation with increased numbers of IELs and CD25+ cells. CD25+ cells down-regulate inflammatory response and prevent autoimmunity; therefore their increase may be a secondary event to auto- or exogenous antigen stimulation. Campylobacter lipopolysaccharide antigen of cross-reacts with GM1 ganglioside of peripheral verves, so an autoimmune component may also participate in the process.[7] On the other hand, increased gut permeability permits exogenous bacterial or food antigens to penetrate the mucosal barrier and sustain inflammation. Persistent mucosal inflammation may proceed to the deeper layers of the bowel wall, infiltrating the myenteric plexus leading to enteric neuropathy and subsequent intestinal dysmotility.[8]

Serotonin has a pivotal role in IBS through its different 5HT receptors. As noted above, an increased number of enteroendocrine cells were found in the mucosa of PI-IBS patients, one year after the initial infection. These cells are positive for serotonin and peptide YY (PYY).[3] Serotonin increases intestinal motility and stimulates intestinal secretions while PYY has an anti-secretory effect, therefore its increase in PI-IBS mucosal biopsies is rather a secondary counter-response. Exaggerated postprandial serotonin release from the increased number of EC cells leads to frequent loose stools, which are characteristic of PI-IBS. Serotonin also has a pro-inflammatory effect, promoting tissue infiltration from lymphocytes, and may also induce hyperalgesia.[9] Alosetron, a $5HT_3$ antagonist, has been proved effective in treating diarrhea and improving quality of life in patients with diarrhea-predominant IBS.

Psychological factors may also interfere with this syndrome, since chronic stress impairs recovery from various functional gastrointestinal disorders and exacerbates inflammation. In animal models, stress reactivates quiescent colonic inflammation via T-lymphocyte pathways.[10] Anxiety and depression influences the brain-gut axis, from the spinal level (ascending painful stimuli), and central nervous system (interpretation of the stimuli), to the descending pathways (antinociceptive response), leading to the full clinical expression of the syndrome.

If infection and chronic inflammation were the causes of PI-IBS then anti-microbial or anti-inflammatory treatment would be a novel therapeutic approach. Indeed, antibiotic treatment improves symptoms in up 50% of the patients, mainly by reducing bacterial overgrowth and altering the gut flora.[11] On the other hand, a three week-treatment with prednisolone improved the histological but not the clinical outcome, due possibly to the very long life of the EC cells (160 days).[12]

In conclusion, PI-IBS seems to be a distinct subgroup of IBS with different pathogenesis and a slightly better prognosis than the other types of IBS – about half of the patients will recover at 6 years. A combination of a triggering environmental factor (infection), a genetic predisposition (abnormal immune response) with psychologic distress, may account for this entity and may lead to a different therapeutic approach in the future.

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