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Atopic irritable bowel syndrome: same old hat or a new entity?

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“The lack of successful therapeutic options for irritable bowel syndrome patients is the main cause of high morbidity, poor quality of life and loss of productivity.”

Irritable bowel syndrome (IBS) remains the most common cause of gastrointestinal (GI) complaints and the most frequent reason for consultation in the gastroenterology clinic. IBS is perceived as a benign, non-progressive condition without significant tissue injury but still causing major morbidity, and is associated with considerable personal and societal burden [1]. In fact, IBS is associated with a significant decrease in quality of life, work productivity and increased utilization of more healthcare resources than those with other organic GI diseases [2]. The lack of successful therapeutic options for IBS patients is the main cause of high morbidity, poor quality of life and loss of productivity. Therefore, a better understanding of the underlying mechanism of this disorder would facilitate more effective therapy and have a major positive impact on IBS patients, their families and employers.

Initial attempts to understand the causes of IBS were hampered by the lack of standardized terminology. The Manning criteria addressed this deficiency by developing a symptom-based classification that has been refined by the Rome I, II and, most recently by the Rome III categorization [3–5]. With a standardized classification system to work with, researchers have now been able to find evidence that strongly suggests that IBS is not one disorder but a diverse group of disorders with different precipitating factors, such as bacterial overgrowth, postinfectious mucosal inflammation, food intolerance/hypersensitivity, stress and changes in diet. For example, acute intestinal infection is an initial trigger for at least a third of IBS patients and is called

‘postinfectious IBS’ [6]. Studies demonstrate the importance of environmental triggers in IBS. Although the concept that environmental factors contribute to or initiate the development of IBS is provocative, current investigations are focused on a wide range of factors and how they affect the interplay between the body and its response to the environment.

Similarly, atopic disorders reflect a broad range of illnesses arising from contact with seemingly innocuous environmental exposures. Atopy is a state of genetically determined immune hypersensitivity, which can manifest in multiple organs simultaneously or individually over a lifespan. Although the GI tract is not considered a common presenting organ in adult atopic disorders, the footprint of allergic disease can be found in this organ if looked for carefully. In an earlier report by our group, we identified a certain group of patients who had undergone intestinal biopsies for evaluation of abdominal complaints that showed increased mucosal mast cells [7]. Clinically, these same patients fulfilled criteria for IBS and appeared to have specific associated non-GI manifestations of atopic disease. We tested the idea of ‘atopic IBS’ in a recent prospective survey of consecutive unselected patients seen in the gastroenterology, allergy and immunology and internal medicine clinics [8]. Our data confirmed that seasonal allergic rhinitis, allergic eczema and atopy (allergic rhinitis, asthma and allergic eczema) were highly correlated and predictive of the presence of IBS. This was particularly seen in diarrhea-predominant IBS, regardless of the reason for appointment or the clinic visited. Food allergy alone was not predictive of IBS. In

addition, the number of IBS patients identified during the pollen season in the allergy and immunology clinic was comparable to the number seen in the gastroenterology clinic [8].

The link between IBS and atopy could be explained on the basis of a common immunological origin or the relationship of both disorders to common factors such as stress, allergen exposure or an infection. The case for an immunologic connection is feasible because the mast cell is a key element in the pathogenesis of both disorders. On the one hand, mast cells are a pivotal element in allergic disorders, while, on the other hand, mast cells have an important function in IBS as the final link in the brain–gut axis [9]. The mast cell in this role produces a variety of proinflammatory mediators that result in local end organ dysfunction as well as systemic reactions. The mast cell is activated by IgE-mediated and non-IgE-mediated stimuli that can produce gastrointestinal inflammation accompanied by respiratory and skin manifestations. The inflammation in these tissues resulting from mast cell activation reflects the Th2 cytokine profile [10]. In fact, both inhaled and ingested allergens are capable of causing simultaneous local and systemic responses, sometimes simultaneously [101]. This was illustrated in a study that demonstrated an increase in mast cells and eosinophils in the duodenal biopsies during birch pollen season in patients with seasonal allergic rhinitis [11]. The majority of these patients also complained of IBS-like symptoms and oral allergy syndrome that was associated with the severity of the pollen season. Oral allergy syndrome is a collection of symptoms such as itching of the tongue, palate and throat, sometimes accompanied by swelling of the lips and tongue [12]. The trigger for the syndrome appears to be the proteins that are shared between pollen and food such as fruits, tree nuts and vegetables. Stress also appears to be the modifying factor causing the development of the protein and exaggerates the response to these protein antigens. The pathogenic pathway of the food hypersensitivity reactions in response to these food and inhalant proteins in adults with IBS appear to be Class 2 mast cell IgE-mediated allergy [13] and IgG₄-mediated responses [14,15].

The complexity of the pathogenic pathways that underlie the mechanism of food reactions in IBS patients may explain the difficulty in diagnosing atopic IBS and why IgE-based standard food skin and radioallergosorbent tests are not reliable. A more productive approach may be to identify the cross-reacting foods associated with pollen allergy and then use fresh extracts of the food proteins for standard skin and patch tests. Further studies are needed to validate this approach in identifying those atopic IBS patients with food allergy. Another approach is use to IgG₄ antibody titers against food antigens advocated by several researchers [16,17]. However,

these antibodies are seen in many subjects without symptoms and unless a predictive threshold is identified, could simply represent normal IgG response to food antigens without clinically relevant allergic reactions. Further studies are required to establish the specificity of IgG serology before its use can be recommended in clinical practice.

Additionally, mast cells are a key components of the innate immune system [18]. Mast cells play a role in both IBS and atopy by contributing to the visceral hypersensitivity, intestinal dysmotility and the stress response. Mast cells are important in mucosal barrier function and may have a role in the alteration of gut microbiota demonstrated in both IBS and atopic dermatitis and asthma [19,20]. Thus, it is reasonable to consider therapeutic interventions to control mast cell activation in patients with atopic IBS. Indeed, blocking mast cell mediators, such as histamine, has produced significant symptom reduction in IBS patients [7]. However, a randomized, double-blind placebo-controlled study is required to determine whether mast cell-directed therapy is effective in the treatment of IBS patients with history of atopic disorders (atopic IBS). Examples of these therapies are mast cell stabilizers, inhibitors of mast cell activation and inhibitors of mast cell products such as H1/H2 blockers.

To summarize, recognition of atopic triggers, such as seasonal allergic rhinitis and atopic eczema, in adults with accompanying IBS will offer an opportunity to investigate immune hypersensitivity mediated by mast cells and determine the characteristics of cell–cytokine interactions and profiles. Clinically, it will allow

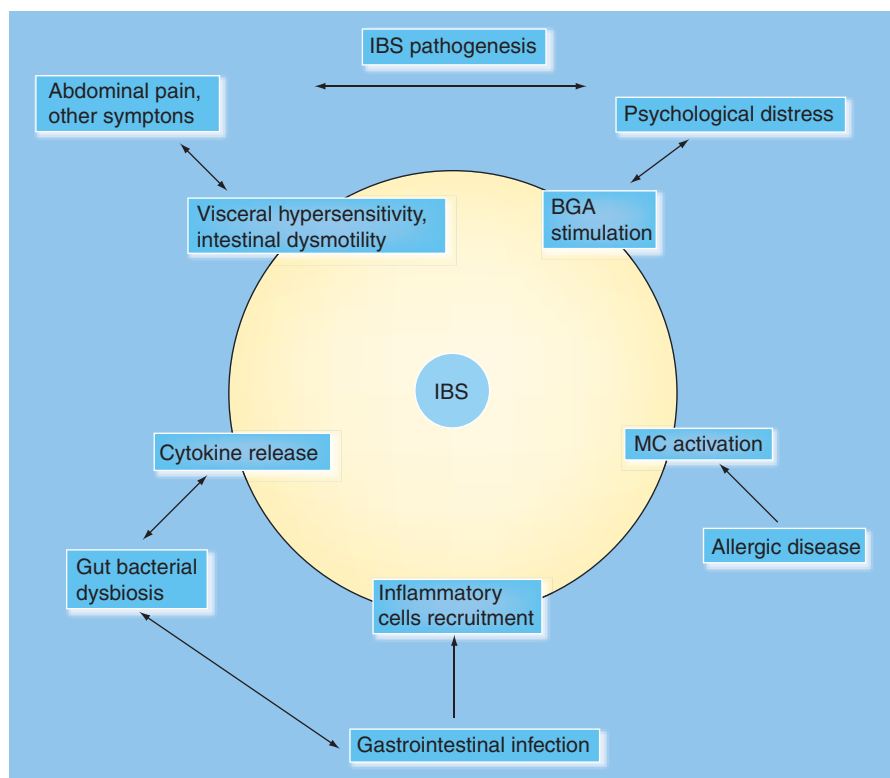


Figure 1. Mechanisms of IBS pathogenesis.

BGA: Brain–gut axis; IBS: Irritable bowel syndrome; MC: Mast cell.

us to determine the importance of Class 2 IgE-mediated food allergy [8,21] and the interplay between inhaled and ingested antigen in producing symptoms. This approach will lead to appropriate food elimination. It will also allow the assessment of treatment with histamine blockers, cromolyn and leukotrienes antagonists which could provide symptom control in at least a subgroup of patients with IBS that we have called atopic IBS.

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