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Possible Mechanism of Symptomatic Improvement with IgG Antibody-guided Exclusion Diet in Inflammatory Bowel Disease and Irritable Bowel Syndrome

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Abstract

Recently, symptomatic improvements with food exclusion diet based on immunoglobulin G (IgG) antibodies have been reported in both inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). But the mechanisms of these results have not been explained yet. The common point of these disorders is the important role of mast cells in their pathogenesis. Mast cells are widely present in intestinal mucosa and they are responsible for both intestinal health and disorder status. IgG-antigen immune complexes can stimulate mast cells by binding to their activating Fcγ receptors. Increased IgG-food antigen complexes due to increased food specific IgG antibodies can cause more mast cell activation. Elimination of these foods may help symptomatic improvement in patients with IBD and IBS by reducing the amount of immune complexes because of lack of the food antigen part of them.

Keywords: Inflammatory bowel disease; Irritable bowel syndrome; Mast cells; Immunoglobulin G; Food exclusion

Introduction

From the beginning of this century, food specific immunoglobulin G (IgG)-guided exclusion diet has been found to be associated with symptomatic improvements in different disorders such as treatment resistant delayed food allergy [1], irritable bowel syndrome (IBS) [2-6], chronic diarrhoea [7], Crohn's disease (CD) [8-11], ulcerative colitis (UC) [12], migraine [6,13,14] and asthma [15]. The negative effects of IgG-positive foods and additives on the clinical course and laboratory findings were detected after the provocation of them in Crohn's disease patients by our clinical study, as well [16]. In three [3,9,10] of them, food exclusion diet applied according to the IgG4 antibody values. Normally, healthy individuals have IgG antibodies against food antigens [17]. In this diet, foods which have increased IgG levels above the cut-off level of healthy individuals are excluded, these foods are also called "IgG-positive".

The common feature of many of the above-mentioned diseases such as IBS [18,19] inflammatory bowel disease (IBD) [20,21], migraine [22] and asthma [23,24] is that mast cells play an important role in their pathogenesis. Although mast cells have long been recognized as only a central player in IgE-mediated allergic reactions, in last two decades it has been understood that they are multifunctional immune cells which are effective in several health and disease status [24,25]. Mast cells play a critical role in innate and adaptive immunity [23-27] and can regulate functions of immune cells such as dendritic cells, monocytes/macrophages, granulocytes, T cells, B cells, fibroblasts [26,27]. Mast cells also counteract regulatory T (Treg) cell functions [28-30]. For this reason mast cells play an important role in the pathogenesis of autoimmune disorders because Treg cells prevent autoimmune diseases by maintaining self-tolerance and suppressing effector T (Teff) cells [29,30].

Possible mechanism of IgG-food exclusion diet

Many stimuli other than IgE, such as IgG, IgA, complements, cytokines, bacterial components neuropeptides, hormones can activate mast cells [23,29,31]. Classically upon activation, mast cells release preformed mediators stored in the granules such as histamine, serotonin, tryptase and newly synthesised mediators like prostaglandins, leukotrienes, cytokines, chemokines, growth factors [23,29,31].

Mast cells can be differentially activated to release distinct patterns of mediators or cytokines [23,26] depending on the type and strength of the activating stimuli [26]. For example, mast cells can be activated with selective release of mediators without degranulation [23]. In nonallergic responses mast cells are more prevalently activated by IgEindependent factors [29]. IgG immune complexes are between these factors and activate mast cells by binding to activating Fcγ receptors (FcRs) on their surfaces [24,27,29]. Mast cells have both activating and inhibitory FcγRs, [27] because most of the activating FcγRs are in low affinity, IgG antibodies generate immune complexes before stimulating them [27]. Food and food additive antigens activate mast cells often mediated by IgG antibodies [31]. In this case, symptomatic improvements with exclusion of IgG positive foods may be due to decreased mast cell activation, related to reduce complexes because antigen parts of them do not exist.

Mast Cell-IBD and IBS Relationship

Mast cells are predominantly present at barrier sites of the body such as the skin, gastrointestinal, respiratory and urinary tracts. Mast cells are mainly located in the lamina propria of the intestine and 2-3% of all cells in this region are mast cells [25]. They are also found in the intraepithelial, smooth muscle and serosal layers [18,19]. They communicate with the adjacent epithelial, neuronal, smooth muscle and other immune cells when they are activated [18].

Mast cells involve in physiological processes of the intestine such as regulating blood flow, permeability, secretion, peristalsis, and also host defence against pathogens [25].These physiological responses are related to regulating effects of mast cell mediators, released by IgE or non-IgE-dependent stimulations [18]. Small amount of immune complexes which generate from low-level IgG antibodies and their food antigens may be one of these stimulators for physiological functions in healthy individuals.

Recently, increased intestinal mast cell activation has been considered to play an important role in the pathogenesis of both IBD [20,21] and IBS [18,19]. The relationship between increased mast cell mediators and pathophysiologic factors was mostly investigated in IBS and found to be related increased excitability of senso-secreto-motor neurons and visceral hypersensitivity, disturbed motility, and altered secretion [18,19]. These factors are responsible for abdominal pain, bloating, and diarrhoea in patients with IBS and most likely IBD to a certain degree. When IgG antibodies, especially against to very frequently consumed foods are increased, immune complexes generated them may cause more mast cell activation and hence more symptoms. In addition, reduced junctional adhesion molecule-A expression due to mast cell tryptase was shown in IBS patients [32]. As a result, increased mast cell activation may cause increased bacterial, food and additive antigen absorption due to increased possible mechanism of IgG-food exclusion diet intestinal permeability which is also one of important pathophysiologic factors for both IBS and IBD.

Is there a difference between IBD and IBS in terms of IgG positive foods?

Since 2005, I have observed symptomatic improvements in many patients with functional and autoimmune gastrointestinal disorders such as overlap between irritable bowel syndrome and functional dyspepsia (IBS-FD), CD and UC.

According to my personal data; while some frequently utilized foods or thickening food additives have high positivity rates, near or more than 40% and reach to 65% as in wheat, hen's egg, guar gum (E412) and agar (E406), some others have less than 5% as in potato, olive, black tea in all three diseases. These high rates in all diseases have been also seen in rarely utilized food like vanilla and some types of mushrooms.

Some foods have higher positivity rates in both CD an IBS-FD than UC like yeast (baker's), sunflower seed, cow's milk and products, tomato, coffee, garlic and pistachio. However, some others have higher positivity rates in CD than both IBS-FD and UC as in maize, peach and honey mixture.

In general, the number of IgG positive foods is highest in CD, followed by FDIBS and at least in UC. IgG positivity does not seem to be related the eating frequency and amount of foods and also presence either autoimmune or functional gastrointestinal disease.

Objections to food specific IgG antibody tests

Although IgE and IgG antibodies and their receptors on mast cells were detected in nearly same years e.g., in late 1960, early 1970's, [27] IgG-mediated mast cell reactions have not fully been understood [24]. Nevertheless recently IgG dependent mast cell activation has begun to be considered as allergies [27,31]. On the other hand, the importance of food specific IgG antibodies has not accepted by some physicians because of this antibodies present in healthy individuals in small amounts. Additionally, some IgG positive foods may not cause symptoms because their complexes engage inhibiting FcγRs and thus cause confusion.

Reported good results of studies depending on IgG4 antibodies is another cause of confusion and also objection. This subclass of IgG antibodies are accepted as "blocking antibodies" especially in the context of allergies because they can prevent excessive immune responses against sterile antigens [33]. The explanation of their good results may be presence both IgG and IgG4 positivity for some of the same food antigens especially the ones consumed frequently such as gluten, yeast, milk and products, and egg.

Conclusion

The possible underlying mechanism of symptomatic alleviations of both IBD and IBS with exclusion of IgG positive foods is due to decreased mast cell activation and reduction of the immune complexes as a result of the lack of food antigen fragment of them. Food-specific IgG antibody guided exclusion diets may give a chance either as a main therapy in IBS or as an adjuvant therapy in IBD. This type of diet may even be useful in mast cells activation syndromes. Future studies seem to be necessary to definitely confirm this situation. Finally, IgG-IgG4 complexity needs further investigation with exclusion diet studies comparing IgG and IgG4 antibodies.

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