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Improving allergy outcomes

Food Antigen Serology in Irritable Bowel Syndrome

Jay Weiss, Ph.D. and Gary Kitos, Ph.D. H.C.L.D

Introduction

Irritable Bowel Syndrome (IBS) is reported as 1 in 5 adults in the US. It is an uncomfortable disease that is characterized by symptoms such as constipation, diarrhea, and alternating constipating-diarrhea, designated C-, D-, and A-IBS respectively. These symptoms can be controlled with diet and proper medications in most people, but it can be disabling to some. Although the cause of this disease is not known, colon sensitivity to certain foods, stress and immunological response all may play a role.

Mast Cells in IBS

Investigations to help understand what the immune system does in IBS have shown that mast cells, which are primary players in allergic reactions, are more dense in lower doudenal[1], jejunal[2],illeal[3], colonic[4], and rectal biopsies from IBS patients than normal healthy controls. In addition tryptase[1], which is released upon mast cell activation, was on average found to be 5 times more concentrated in jejunal fluid. Tryptase is also implicated as one protease that may activate the PAR-2 receptor, found on cells throughout the gastrointestinal tract, and induces symptoms of D-IBS[5]. Mast cells can be triggered by neurotransmitters such as Substance P[6] and are an integral part of the brain-gut axis (BGA) that is activated by stress. Activation of mast cells via the BGA may also skew immune responses to Th_2 type that favor IgE and IgG_4 formation[7,8,9]. The same mast cells can be activated by IgE crosslinking and may be activated by IgG4 antigen complexes.

Mast Cells in Food Allergic Responses

Mast cells have long been known to have high affinity IgE receptors which when cross-linked, cause the release of an array of preformed inflammatory mediators and trigger de novo synthesis of others. The high affinity IgE receptors are unstable and persist only if IgE is bound to them[10]. Mast cells begin in the bone marrow (BMMC) as multi-potential cells and mature in the local tissues into which they migrate[11]. Mast cells mature differently in different tissues. Skin mast cells, lung mast cells, and gut mast cells are all very similar, but have differences that may be important for each different environment. It is clear that immature mast cells have IgG receptors that inhibit mast cell activation in the blood stream. It is also known that as cells mature some have stable low affinity IgG receptors that may be activated by IgG_4 immune complexes. The low affinity of these receptors prevents IgG from binding and forming immune complexes on the cells, but preformed large IgG-antigen complexes may activate the cell due to the avidity of the complex for the low affinity receptors. Although these same receptors will bind IgG_1, IgG_2, IgG_3, and IgG_4immune complexes , IgG_4 complexes do not activate complement, and would be more likely to encounter mast cells as “naked” immune complexes free of complement activation

products that would opsonize complexes with the other 3 subtypes. In addition, IgG_4 has the unique characteristic of being able to swap half-molecules with one another and forming whole antibodies with 2 different specificities[12,13]. This makes the formation of immune complexes more likely because more than one antigenic epitope can be bound in the complex.

The mucosal tissue is estimated to contain 2-3 times more plasma cells than found in the bone marrow, spleen and lymph nodes combined.[14] Ninety percent (90%) of plasma cells in the large intestine are of the IgA type, 6% IgM, and 4% IgG.[14,15] Mucosal immunoglobulins are mostly excreted, but about 10% gets into circulation. Small doses of food antigens used in sublingual immunotherapy induce significant IgE and IgG_4 increases in serum.[16] It is likely that larger doses such as those ingested at meals will induce antibodies in susceptible individuals.

IgE and IgG_4 Serology

The measurement of allergen-specific circulating IgE and IgG_4 is used to aid in the diagnosis of food allergy and both have been used to identify foods to avoid[17]. Circulating IgE has a half-life of 1-5 days, and is at least 2 weeks when attached to a mast cell. The half-life of IgG_4 is 21-24 days, but its half-life on a mast cell receptor is hours[18]. Concentration of total circulating IgG_4 is about 5,000 fold more than that of IgE. The affinity of IgE has been shown to be in the 10^{-10} to 10^{-11} M range for conformational food epitopes which is about 10,000 fold stronger than that measured for IgG[19]. Conformational epitopes have been implicated in initiation of IgE mediated food allergy and have been demonstrated to break tolerance in patients who had been tolerant[20].

Allermetrix Liquid Allergen Advantage

The Allermetrix specific- IgE, IgG, and IgG_4 assays incorporate liquid-phase allergens which have been shown to be less denatured than the more commonly used solid-phase allergen technology[21] and preserves conformational determinants[22]. Solid phase allergens are mostly denatured with many linear epitopes exposed that are not normally seen by the immune system during normal exposure. Therefore many of the detected antibody responses to solid-phase allergens may be diagnostically irrelevant. Solid-phase allergen tests used for testing IgG antibodies to foods often have positive reactions for many different foods, and if used for guiding avoidance may unnecessarily restrict a patients's diet. Allermetrix liquid-phase allergen system usually detects fewer reactions to foods because the test detects more conformational determinants and not reactions with denatured allergens, which makes an avoidance diet easier to follow.

IBS and Allergy

There have been a number of investigations to look at the association of IBS and allergy. When evaluating allergy both positive skin prick tests (SPT) and specific IgE (sIgE) have been used to classify patients as allergic. In some studies specific IgG (sIgG) and specific IgG_4 ($sIgG_4$) have been used for additional analyses. Both IgE and IgG_4 responses are Th_2,type 2 T-helper cell,

mediated, and IgG, which is predominantly IgG_1, is Th_1 mediated. It has been demonstrated in a number of studies that IBS patients are significantly more likely to have positive SPT results than healthy controls.[23,24,25] In one study inhalant SPT were not significantly different than healthy controls, but food SPT results were significantly more positive in IBS patients.[25] In other studies, there was no significant difference between IBS and controls when evaluated by SPT or sIgE.[26,27] In the same studies sIgG and $sIgG_4$ were significantly higher in IBS patients to certain foods. It is conventional wisdom to avoid foods to which sIgE can be demonstrated when history and symptoms suggest the patient is allergic to the reactive food. However, it has not been conventional to avoid foods to which IgG can be demonstrated. In fact IgG_1 responses are commonly seen to food when patients have mouth ulcers or compromised gut permeability[28]. IgG_4 responses have not been as well studied, but in general, IgG_4 responses result from long term exposure and are associated with a Th_2 response[29].

Use of Serology in IBS Patients

Both sIgG and $sIgG_4$ have been used to develop avoidance diets for IBS patients.[30,31,32] In these three studies, the elimination of foods to which IBS patients had elevated either sIgG or $sIgG_4$ responses resulted in clinical improvement as measured by questionnaire. In one study, which used $sIgG_4$, [31] rectal compliance was measured and found to be significantly better in patients who had excluded foods.

The connection between IBS and food allergy is emerging in at least a subset of IBS patients, and it seems that allergic reactions in the gut can account for some IBS symptoms. The fact that neural activation can enhance allergic responses also adds to the potential for allergic exacerbation of the disease. Identification of specific IgE responses to food is clearly important in these patients and may indicate the presence of underlying allergic disease.

Food allergy is a difficult diagnosis in the practice of allergy and certainly no easier in IBS patients. However, sIgG which measures all subclasses of IgG, IgG_1, IgG_2, IgG_3, and IgG_4, is not useful for diagnosis because all 4 subclasses have different effects. Only IgG_4 has been implicated in mast cell activation, and does not bind complement. In serological studies using both IgE and IgG_4, diagnostic sensitivity of the two tests together is 91%, higher than any other combinations of SPT or serological test in the same group of patients. The use of specific IgG_4 in conjunction with specific IgE for foods will identify foods to which IBS patients may have allergic responses. Elimination of these foods can reduce symptoms and improve patient well being.

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