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IRRITABLE BOWEL SYNDROME AND FOOD ALLERGY IN CHILDREN

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The article reviews the relationship between the food allergy and irritable bowel syndrome (IBS) in children and shows the increase in the incidence of the IBS in children with food allergy. The increased level of serum IgE is observed in patients with food allergies and IBS as well as increased density of IgE-producing cells in the intestinal mucosa biopsy. Thus,шлл the common features of IgE-mediated response in the IBS and food allergies pathogenesis are traced. Presumably IgE-mediated reactions are localized only in the intestinal mucosa with positive results of the COLAP test in children with IBS, and the skin prick-test and determination of the level of specific IgE in serum being less informative. Nevertheless, there is little evidence of the role of IgE-mediated allergic response in IBS in atopic children. The role of the mast cells was recently shown in the pathogenesis of IBS with the increase of the number of the mast cells in the gastrointestinal tract in all subtypes of IBS. When binding to an antigen, surface receptors presented on mast cells are bound to IgE leading to degranulation, thus involving progressive release of the inflammatory mediators. Mediators of inflammation affect the nerve receptors, the function of the smooth muscles, increasing the permeability of the intestinal wall. On the contrary many studies present non IgE reactions in IBS. It is believed that serum levels of IgG and IgG4 are higher in patients with both IBS and food allergy and may be related to the selective permeability of the intestine for food allergens. The question is whether this is a specific reaction or a nonspecific response to an increase in the permeability of the intestinal mucosa. The relationship between food allergy and irritable bowel syndrome requires further study.

Keywords: irritable bowel syndrome; food allergy; children.

СИНДРОМ РАЗДРАЖЕННОЙ КИШКИ И ПИЩЕВАЯ АЛЛЕРГИЯ У ДЕТЕЙ

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Рассмотрена проблема взаимосвязи пищевой аллергии (ПА) и синдрома раздраженной кишки (СРК) у детей. Отмечено увеличение частоты СРК у детей с ПА. У больных с ПА и СРК выявлено увеличение уровня IgE в сыворотке крови, а также повышение плотности IgE-продуцирующих клеток в биоптатах слизистой оболочки кишечника. Предполагается наличие IgE-опосредованной реакции в патогенезе СРК при ПА и наличие локализованных только в слизистой оболочке кишечника IgE-опосредованных реакций. Об этом свидетельствуют положительные результаты теста COLAP у детей с СРК, а идентификация кожным прик-тестом и определение уровня специфических IgE в сыворотке крови менее информативны. Однако сегодня нет убедительных доказательств роли IgE-опосредованного аллергического ответа при СРК у детей с атопией. Установлена роль тучных клеток в пато-

физиологии СРК. Продемонстрировано увеличение числа тучных клеток в желудочно-кишечном тракте при всех подтипах СРК. Поверхностные рецепторы, присутствующие на тучных клетках, связываются IgE. При связывании с антигеном происходит дегрануляция тучных клеток, которая способствует последовательному высвобождению медиаторов воспаления. Медиаторы воспаления оказывают влияние на нервные рецепторы, функцию гладких мышц, повышение проницаемости кишечной стенки. Целый ряд исследований посвящен аллергическим реакциям, не связанным с IgE и СРК. Существует мнение, что уровни сывороточных IgG и IgG4 выше у пациентов с СРК и пищевой аллергией и могут коррелировать с избирательной проницаемостью кишечника к пищевым аллергенам. Обсуждается патогенез увеличения уровня специфических IgG и IgG4 при СРК и аллергии: это специфическая реакция или неспецифический ответ на повышение проницаемости слизистой кишечника. Взаимосвязь пищевой аллергии и синдрома раздраженной кишки требует дальнейшего изучения.

Ключевые слова: синдром раздраженной кишки; пищевая аллергия; дети.

The relationship between systemic allergic disorders and irritable bowel syndrome (IBS) is an area of intense interest [3]. Several studies demonstrated that the incidence of IBS was higher in patients with bronchial asthma and those with bronchial obstructive syndrome among those without asthma [53], and a significant number of studies describe an increase in the frequency of IBS in patients with bronchial asthma and other atopic diseases [6, 18, 24, 41–43, 51]. Tobin et al. (2008) [51] described a distinct subgroup of patients with atopic IBS, who presented with typical IBS symptoms in combination with atopic symptoms. In a cohort study of 4,089 children, Olén et al. (2014) studied the relationship between atopic diseases and/or food sensitization and abdominal pain in 12-year-old adolescents [40] and found that 9% of the subjects experienced abdominal pain. The authors demonstrated that in children with bronchial asthma, allergic rhinitis, eczema and food sensitization, the risk of abdominal pain was higher, which increased in parallel with the increase in the number of allergic diseases in these subjects. Asthma in the first two years of life and food sensitization at the age of eight years were the most significant risk factors for abdominal pain at the age of 12 years [40]. A questionnaire survey of the parents of 2463 children conducted in St. Petersburg [5] also reported a similar frequency of abdominal pain in school-aged children (9.87%); interestingly, 28.8% (720) of the respondents reported various manifestations of food intolerance.

Studies also demonstrated the high incidence of IBS (93%) and the high prevalence of atopic diseases (approximately 60%) in adult patients with food allergies [36]. In 2010, Lillestol et al. assessed symptoms and response to the skin prick test and measured serum allergy marker levels (general and specific immunoglobulin [Ig]E, tryptase and eosinophilic cationic protein), intestinal permeability, IgE- and tryptase-positive cells and eosinophils in duodenal biopsy samples in patients with food allergies. They found that in patients with atopic diseases, compared to nonatopic patients, the intestinal permeability and the number of IgE-producing cells were increased; however, gastrointestinal symptoms did not differ between the two groups. Another study reported an increase in serum IgE levels of patients with IBS compared with the control subjects [36]. Overall, these observations suggest that some patients with food intolerance and atopy might have an IgE-mediated and mast cell-associated IBS component.

The role of mast cells in the IBS pathophysiology has been recently recognized [18, 51]. Surface receptors on mast cells enable binding of antigens with IgE, which promotes degranulation of the mast cells and the consistent release of inflammatory mediators including histamine, serotonin, and proinflammatory cytokines. The release of these mediators underlies the hyperresponsiveness that causes the clinical manifestations of atopy; these mediators also affect the nerve receptors and smooth muscle functions and lead to an increase in the permeability of the intestinal wall, which is closely related to the IBS pathogenesis [1, 2, 4, 17, 33, 51]. Numerous studies demonstrated an increase in the number of mast cells throughout the gastrointestinal tract in all IBS subtypes [22, 32, 33, 37], and visceral hypersensitivity was shown to positively correlate with the number of mast cells [13]. In addition, activation status of the mast cells and their interaction with nerve receptors was shown to be altered in IBS [14]. Administration of the mast cell stabilizer ketotifen was shown to reduce the visceral sensation of pain in patients with IBS compared with the placebo treatment [30]. All together, these findings provide abundant evidence for the role of mast cells in the IBS pathogenesis and emphasize the potential for investigation of new therapies.

One study revealed that basophils, in addition to mast cells, contributed to the pathogenesis of atopic diseases and IBS [47].

IgE plays a central role in the pathophysiology of type I hypersensitivity. After initial contact with

an allergen, dendritic cells represent the allergen to antigen-specific T cells. In some individuals, T cells respond to this interaction by releasing a variety of cytokines, thus stimulating the development of B cells that can produce antigen-specific IgE. Circulating IgE binds to receptors on the surface of both mast cells and basophils, and subsequent exposure to the allergen results in cross-linking of IgE molecules on mast cells and their degranulation [25]. To date, there is no conclusive evidence of the role of IgE-mediated allergic response in IBS, especially in patients with concomitant atopy. The studies on this topic are few, unrelated and contradictory; the methods used by these studies are also widely variable [8, 38, 44]. For example, in one study, 24 IBS patients, including 12 patients with atopy and 12 patients without atopy, underwent a blind food challenge after a three-week hypoallergenic diet. In 14 patients, one or more food products or food additives caused typical IBS symptoms, nine of whom (all from the atopy group) had elevated total serum IgE levels [44]. In a study on intestinal permeability that included 17 children with IBS state, starvation period followed by a specific food challenge led to postprandial changes in nine children; all nine children had a burdened history of allergies and/or a high total serum IgE and responded to the exclusion of food [44]. Elevated IgE fragment crystallizable (Fc) levels in fecal extracts were detected in 73% of patients with food allergy that was confirmed by prick tests and radioallergosorbent tests (RASTs). In contrast, none of the healthy subjects had detectable fecal IgE Fc. In subgroup analysis of the IBS patients, IgE Fc was found in the feces of 22 of the 32 patients (68.8%). Simultaneous measurement of alpha-I antitrypsin in blood serum and feces eliminated the possibility of extravasation of plasma proteins (including IgE) as the cause of these results [8]. In another study, the incidence of total IgE increase in IBS was found to be 34.5% [38].

The role of allergy in the IBS pathogenesis was also studied using anamnesis; prick test; determination of total IgE level and specific IgEs against food allergens, and eosinophilia; and intestinal challenge with food allergens by colonoscopy. In a study, the frequency of food allergy based on immunological tests was 14.4%, and the diagnosis was confirmed in 3.2% of the cases utilizing endoscopic challenge [16]. Interestingly, in another study including 20 IBS patients who developed gastrointestinal symptoms after wheat intake, the elimination diet led to the resolution of symptoms, which returned after the challenge. Although only 50% of the patients were seropositive for wheat-specific IgE, immunoblot analysis revealed that IgE was bound to both the soluble and insoluble wheat proteins all patients [48]. The authors concluded that the traditional methods used to diagnose IgE-mediated hypersensitivity were inadequate for allergological screening of the subgroup of patients with IBS. To explain their results, the authors proposed two hypotheses: 1) low serum IgE levels; 2) the inadequacy of the currently used methods for the diagnosis of food allergies to wheat. These possibilities explain why enteropathy caused by wheat-specific IgE is rarely diagnosed.

Many studies reported the discrepancy between the anamnestic data on reactions to food products and the results of immunological tests [28, 49, 52]. For example, a study found that there was no correlation between the patients' allergies and test results: While the patients reported intolerance to dairy products, raw foods, spicy foods, coffee, and alcohol, the tests indicated intolerance to fish, rice, wheat, sweet potato, celery, and onions [28]. The IgE-mediated allergic reactions were proposed to be localized in the intestinal mucosa. In one study using colonoscopic allergen provocation (COLAP) in 70 patients with IBS and clinical findings of food allergy as well as 5 healthy volunteers, the patients were evaluated 20 minutes after the injection of three allergens (milk, wheat, and hazelnut) into the mucosal membrane of the blind intestine. These allergens were selected individually, taking into account each patient's anamnesis and the presence of specific IgEs in the serum. The evaluation was performed by a semi-quantitative method that evaluated the presence of hyperemia and bullas using a scale ranging from 0 to 4. A reaction with a score of 2 or more was considered positive. In 74% of the IBS patients, the COLAP test was positive in response to at least one food allergen, whereas none of the healthy volunteers had a reaction [16]. Biopsy specimens from the sites with a positive response showed an increase in the number of mast cells and eosinophilic infiltration. A subsequent three-month elimination diet in the COLAP-positive patients was effective in 89% of the cases. The strong correlation of the clinical data with COLAP, which was poorly correlated with the skin prick test and the level of specific serum IgE, suggest that COLAP might aid in the identification of local IgE-mediated mechanisms [16, 31]. In another study, COLAP using cow milk protein as an allergen confirmed the association of IBS with allergy to cow milk protein, which was not associated with serum specific IgE or IgG/IgA [34].

The response to the cavitary administration of antigens was previously demonstrated by visual-

ization with endosonography, transabdominal ultrasonography, magnetic resonance imaging, and confocal laser endomicroscopy [7, 10, 11, 21]. The thickening of the intestinal walls, increased peristalsis, and influx of large amounts of fluid into the lumen were noted, which are typical for IgE-mediated food allergy reactions due to the degranulation and release of mediators from the mucosal mast cells [36, 46].

Successful treatment of IBS patients with administration of monoclonal antibodies against IgE provides further support for the IgE's role in the pathogenesis of IBS, at least in some patients [36, 46].

A number of studies investigating non-IgE-allergic reactions in IBS revealed that the IgG4 subclass, which is produced in response to T2 cytokines, can lead to the release of histamine as well as IgE antibodies [15, 29]. Serum IgG and IgG4 levels are higher in patients with IBS and food allergy, which might be due to the selective permeability of the intestine to food allergens. Previous studies investigated the pathogenesis of the increase in the level of specific IgG and IgG4 antibodies in IBS and allergies and whether this was a specific or nonspecific response to an increase in the permeability of the intestinal mucosa [9, 12, 19, 23, 39, 45, 54]. Although some studies found that the elevation in IgG levels and production of IgG4 might be part of a normal immune response to food antigens [20, 27, 50], most studies suggest that assessment of both specific IgG4 and IgE antibodies to food allergens might be useful for evaluating food allergy in IBS patients [45]. Thus, elimination diets based on specific IgG4 antibodies were demonstrated to achieve a significant clinical effect in several studies [9, 12, 19, 23, 39, 54]. A systematic review of seven clinical trials revealed that the efficacy of this type of diet selection ranged from 15% to 71% and that the most frequently excluded foods were milk, wheat, eggs, potatoes, and celery [39]. Nevertheless, the methodologies in these studies were not always adequate, which limited the validity of the results, especially since some of the studies failed to find a correlation between the level of IgG4 antibodies and the presence of symptoms [35, 55].

Thus, to date, albeit the obvious relationship between food allergy and IBS, the underlying mechanisms should be further elucidated in future studies. Whether IBS or food allergy is the cause and whether intestinal symptoms in patients with allergic diseases is a manifestation of a systemic allergic condition or IBS remain unclear. Answers to these questions will open up new prospects for using an elimination diet to treat IBS patients.

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