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# Allergic Diseases in Patients with Irritable Bowel Syndrome

**Key words:** *irritable bowel syndrome, atopy, allergic diseases.*

Allergy is the most common chronic disease in Europe. More than 150 million Europeans suffer from one or more allergic diseases (AD), and the current forecast is that by 2025 half of the EU population will be facing this problem (EAACI, 2016). The World Allergy Organization (WAO) estimates allergies prevalence rate among the world's population from 10 to 40%, depending on the country (Pawankar R. et al., 2013) [16].

Patients with allergic diseases (AD) suffer from respiratory, skin, gastroenterological symptoms and limited daily activity. Concomitant diseases that are common in patients with allergies include: esophageal reflux (GERD), rhinitis, sinusitis, anxiety and depression [3, 5, 6, 7, 8, 12]. Furthermore, studies have shown that AD is associated with intestinal functional disorder (IFD) through the immune system activation [4, 11].

At the same time, irritable bowel syndrome (IBS) is one of the most common gastroenterological diseases, which affects an average of 10–15% of the entire adult population. IBS is the most common manifestation of the functional gastrointestinal pathology, which, after its debut, in most cases, persists for a long time, quite often throughout life.

In the vast majority of cases, in the absence of «disturbing» symptoms in people under 50 years old, the primary diagnosis of IBS with a probability of 93% –97% is established on the basis of characteristic symptoms known as Roman criteria IV. According to the latter, IBS is considered as a functional intestinal disorder, in which recurrent abdominal pain is associated with altered defecation patterns that have been identified during the last 3 months at the onset of the symptoms at least 6 months before the diagnosis. In addition to such altered defecation pattern as diarrhea, constipation or a combination of them, there is often bloating and a feeling of stomach stretching, which, however, are not specific. The onset of symptoms should be no less than 6 months before the diagnosis, and the symptoms must be observed during the last 3 months [1].

Depending on the nature of the symptoms, there is IBS (IBS-D) with diarrhea, IBS with constipation (IBS-C), mixed

type of IBS (IBS-M) and undefined IBS (IBS-U) [1, 4, 6, 7, 13, 17].

IBS pathophysiology is complex, which includes disturbance of digestive organs, changes in bacterial flora, visceral hypersensitivity, dysregulation of mucous membrane immunity, and dysregulation between the central nervous system and the intestinal nervous system [10]. Immune activation is associated with both allergy and IBS.

## The role of atopy in IBS

The term «atopy» was first used by Coca and Cooke Company in 1923, and there is some evidence that this condition may be more prevalent in patients with IBS and other functional disorders of the gastrointestinal tract [3, 5, 6, 7, 14, 16, 20]. A recent study of 30,000 records of primary care in the UK for a minimum period of 5 years has confirmed the excess of atopic conditions in all functional disorders of the gastrointestinal tract, with IBS prevalence rate of 44.8% compared with the control (32.7%) [7]. Previous literature has shown that atopy is more common in patients with diarrheal IBS [4].

It was suggested that increased intestinal hyperpermeability may have a role in IBS pathogenesis. Lillestol K. [11] and his colleagues demonstrated an increase in the small intestine hyperpermeability in patients with atopic IBS compared with the control without atopic IBS. Although it turned out that there was no difference in the gastrointestinal symptoms between the two groups. In addition to changes in the duodenal patency, they showed a significant increase in the number of IgE-positive duodenal cells, as well as an increase in IgE levels in serum in patients with IBS compared to the control (Lillestol K. et al., 2010) [11]. These observations indicate that in some patients, hypersensitivity and atopy can play an important role in the common pathophysiology of allergy and IBS.

## The role of mast cells in IBS

The role of mast cells in IBS is more widely studied. Mastocytes have a recognized role in allergic diseases and are increasingly involved in IBS pathophysiology [3, 17,

20]. Surface receptors present in mast cells, allow the binding of Ig E. The antigen binding mediates mast cells degranulation, which leads to the sequential release of inflammatory mediators. These include histamine, serotonin, leukotrienes, proinflammatory cytokines. The release of these mediators causes hyperreactivity, leading to clinical manifestations associated with atopy. It is known that the mast cells release those mediators that may affect the intestinal innervation function and the smooth muscle function, causing physiological manifestations characteristic of IBS [2, 9, 16, 17, 19, 20]. There have been numerous studies indicating an increase in the number of mast cells in the gastrointestinal tract on its different anatomical areas in all IBS subtypes [5, 8, 9, 10, 12]. Mast cells have been associated with changes in the intestinal mucosal cell barrier and recently it has been demonstrated that increased mucosal permeability is associated with an increase in the number of mast cells precisely in patients with IBS-D (Lee et al., 2013) [12].

Visceral hypersensitivity has long been linked to the IBS pathophysiology, although the precise mechanisms associated with this abnormality are not fully understood. There is increasing evidence that mast cells can play an important role in visceral hypersensitivity, and in patients with IBS there is a positive correlation between the number of mast cells and the severity of pain in the abdomen (Barbara et al., 2004) [1]. This adds evidence that mast cells play an important role in IBS and have potential for pharmacological effects.

Many studies have shown that asthma and allergic disorders may be related to IBS [2, 3, 9, 14, 15, 18, 20]. However, most of these studies are based on a small sample, a questionnaire, and case-control studies. There is not enough literature to investigate the direct relationship between IgE and IBS, which is somewhat weird, given the great number of patients with IBS and allergies. There have been no studies examining IBS patients' serum for the specific IgE levels not only to food but also to household and pollen allergens. And those studies that researched food antigens, gave contradictory results. It should also be noted that these studies included a very small number of patients who were poorly selected and therefore it is difficult to draw reliable conclusions.

The aim of the work is to study prevalence and clinical features of the allergic pathology course in patients with IBS, and to establish the frequency of their sensitization to the most common allergens.

### Materials and methods of research

150 IBS patients with the average age of  $40.8 \pm 2.1$  were examined on the basis of the department of internal medicine No. 1 of Bogomolets National Medical University, gastroenterological departments of the Kyiv City Clinical Hospital No. 8 and the Kyiv City Clinical Hospital No. 18, as well as the Ukrainian-German Gastroenterology Center in 2016–2017. Among those examined, 27.4% ( $n = 40$ ) were men and 72.6%, respectively, women ( $n = 106$ ).

The control group included practically healthy people, who as to their age ( $38.2 \pm 2.1$ ) and the gender can

be compared with the main group. The control group consisted of 30 healthy volunteers ( $38.2 \pm 2.1$ ), among them there were 18 women and 12 men, which corresponded to the age and gender characteristics of the main group. All patients gave written informed consent to participate in the study.

Allergen-specific IgE by ELISA method in the serum samples of the examined individuals to food (eggs, milk, pork, hake, cod, orange, wheat flour, potatoes, apple, banana), domestic (domestic dust, cat's wool, dust mites) – *Dermatophagoides pteronissimus*, *farinae* and plant allergens (ambrosia, wormwood, birch, timothy, sunflower, rye) were determined using the Allergen test systems (Russia). According to the manufacturer's instructions, IgE antibody levels were evaluated in 4 steps – 0 (negative), 1 (low – 0.35–0.99 IU/ml), 2 (average – 1, 0–2.99 IU/ml), 3 (high – 3–6.99 IU/ml) and 4 (very high – 7.0–16.99 IU/ml). ELISA reactions were recorded on Labsystems iEMS (Finland) immunoassay analyzer.

IBS diagnosis was determined according to IV Roman criteria based on clinical signs and gastroenterological complaints, taking into account fecal masses form using the Bristol scale.

### Results and their discussion

Reaction of the intestinal mucosa to food is important in IBS pathogenesis. In this regard, when collecting anamnesis of IBS patients, food products that caused gastroenterological complaints in the examined individuals were indicated. Intolerance to food was noted in 78.1% ( $n = 114$ ) of IBS patients.

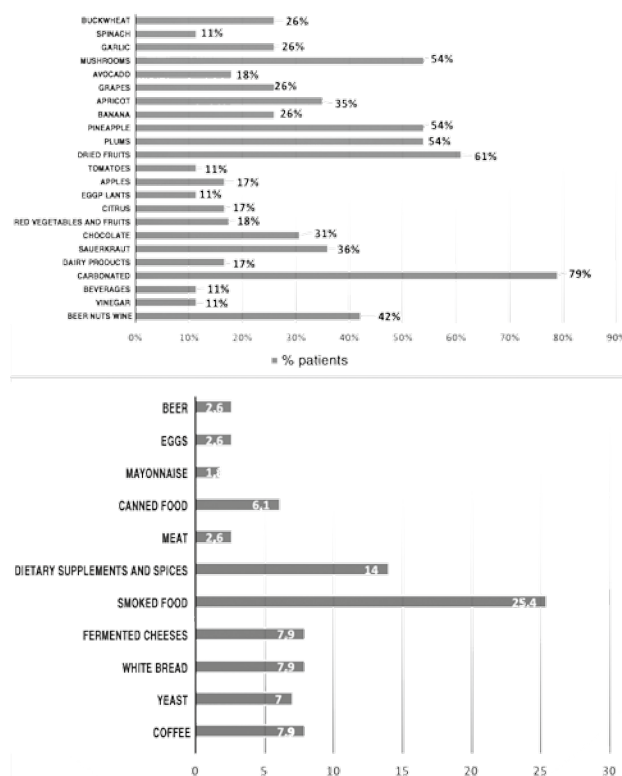


Fig. 1. Food causing gastroenterological complaints in patients with irritable bowel syndrome

According to the data presented in Figure 1, among the products complained of by IBS patients are widespread products that contain a large amount of histamine, its liberators, and food allergens: wine, vinegar, sauerkraut, spinach, avocados, bananas, chocolate, fermented cheese, smoked food, yeast, canned food, spices and various nutritional supplements.

In addition to gastroenterological complaints, some of the examined patients showed allergic complaints (Table 1) and allergic diseases (Table 2).

Allergic manifestations were reported by 62.0% of patients (n = 93), allergic diseases were detected in 56% of patients (n = 85).

**Table 1. Clinical allergic symptomatology in patients with irritable bowel syndrome**

Clinical signs	Number of patients	Percentage
Increased tear secretion Swelling of the lips	22	24.7
Itchy eyes	35	39.3
Itchy nose wings	22	24.7
Nasal stuffiness	45	50.6
Nasal discharge	35	39.3
Sneeze	41	46.1
Cough	25	28.1
Short of breath	7	7.9
Itching rashes	45	50.6
Mouth and throat burning	16	17.9
Lips swelling	16	17.9

**Table 2. Allergic diseases in patients with irritable bowel syndrome**

Confirmed allergic pathology	IBS patients with allergy, n = 84	All IBS patients, n = 150
Allergic rhinitis (AR), n = 43	51.2%	28.7%
Food allergy (FA), n = 16	19%	10.7%
Urticaria fever (UF), n = 38	45.2%	25.3%
Angioneurotic edema, n = 6	7.1%	4%
Bronchial asthma, n = 6	7.1%	4%
Insectic allergy, n = 9	10.7%	6%
Pollen disease, n = 34	40.5%	22.7%
Atopic dermatitis (AD), n = 13	15.5%	8.7%

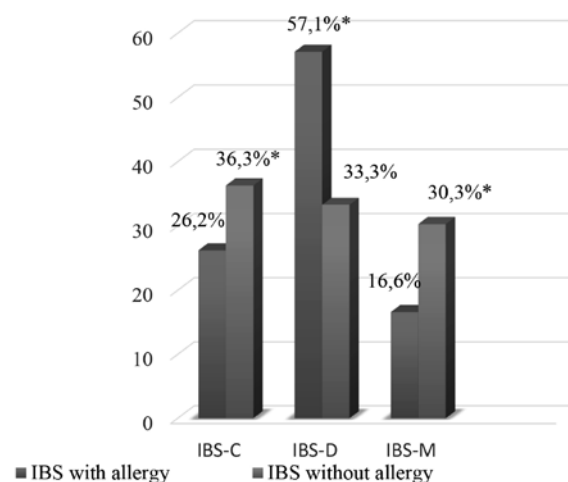
48 patients (32.9%) complained about an allergic reaction to drugs, almost half of them (48%) – to antibiotics. Among other drugs reported by the examined patients there were vitamins of B group,  $\beta$ -blockers, lidocaine and nimesil.

As it can be seen from the above data, allergic rhinitis (51.2%) and pollen disease (40.5%), drug allergy (42.9%), food allergy and urticaria fever, atopic dermatitis (15.5% of patients) were most commonly found in IBS patients with allergic diseases.

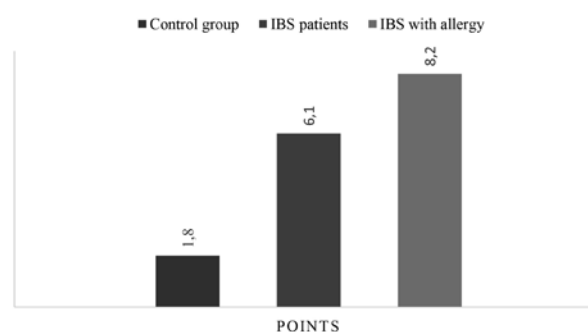
As it can be seen from the data on Figure 2, in classical IBS, there was no probable difference in the frequency of the disease main subtypes detection. In contrast, in patients with IBS with concomitant allergy they were more likely to be present, in IBS-D (57.1% of all cases) and much less in IBS-M (16.6% of all cases). The frequency of these subtypes detection in IBS patients with concomitant allergies was significantly different from those with classical IBS.

The abdominal pain syndrome assessed using the visual analog scale in IBS patients and concomitant allergies is significantly more distinct than in the general group of IBS,  $6.1 \pm 0.21\%$  vs  $8.2 \pm 4.2\%$  (Figure 3).

In patients with IBS in general in the group there is a moderate increase in the indexes when determining the total IgE ( $143.1 \pm 24.9$  U/ml, donors –  $44.6 \pm 7.2$  U/ml).



**Fig. 2. Frequency of major subtypes detection in IBS patients**



**Fig. 3. Significance of abdominal pain syndrome (according to 10-point scale)**

IgE concentration had a wide spread of data in patients with IBS (3.9–905.0 U/ml) and was high (more than 100 U/ml) in 47.3% (71 persons) of patients.

Presence of allergen-specific IgE was detected in serum of 137 patients (91.2% of the subjects).

The conducted studies to determine the allergen specific IgE showed that the allergic reaction in this or that extent was to all the allergens studied. The main factors that give an allergic reaction (more than 20% of patients) are egg protein, milk, orange, potatoes, wormwood, timothy grass and sunflower (Table 3, 4, 5).

However, significantly more IBS patients have a high level of sensitization to domestic dust mites (DDM).

Consequently, allergic diseases are widespread among IBS. Allergic manifestations of different character had 62.0% of patients, and after an examination allergic diseases were defined in 56% of patients. Among IBS patients allergic rhinitis (51.2%), pollen disease (40.5%) and urticaria fever (19%) are most commonly found.

In IBS patients with concomitant allergy, IBS-D type was significantly more common (57.1% of all cases), and there was also a much greater pain abdominal syndrome than in patients with classic IBS.

91.2% of the patients examined had allergen-specific IgE to the studied allergens.

However, IBS patients have a significantly higher sensitivity to home dust mites (HDM) than the control group.

HDM is the ubiquitous environmental factor, the complete elimination of which is virtually impossible. At the same time, they are one of the most common household allergens that cause allergic rhinitis, pollen disease, bronchial asthma, and cross-allergic food reactions in sensitized individuals.

Earlier these allergens were considered exclusively respiratory. In the publication by Gut Tulic and co-authors, HDM-allergens Der p1 are found in significant quantities and can be detected in the intestines of a person, thereby also participating in intestinal inflammation.

Presence of HDM allergens in the intestines of a person gives us an idea of another possible trigger and provokes and complicates the course of IBS factor in a number of individuals.

## Conclusions

The data obtained indicate that sensitivity to HDM in patients suffering from IBS is significantly higher than among healthy people, as well as they prove the presence of another ecological trigger that has not previously been detected, which can contribute to intestinal disease in susceptible individuals.

The defined patient category needs further follow-up, as well as the determination of the treatment effectiveness by limiting contact with the potential allergen, exclusion of products that have cross-reactivity with home dust mites, use of antihistamines and hyposensitization with allergen-specific immunotherapy.

The concept of «combined respiratory channels» in which the bronchial mucosa inflammation in asthma can affect inflammation of the nasal mucosa with rhinitis,

**Table 3. Number of patients with irritable bowel syndrome that have allergic sensitization to food allergens (determination of allergen-specific IgE)**

No.	Allergen	Donors n=30		IBS patients n=150	
		number	percentage	number of patients	percentage
1	Egg white	2	6.7	38	19.3*
2	Milk	2	6.7	27	18*
3	Pork	3	10.0	25	16.6
4	Hake	1	3.3	7	4.6
5	Cod	1	3.3	6	4.0
6	Orange	5	16.7	32	21.3
7	Yolk	2		13	8.6
8	Wheat flour	2	6.7	9	6.0
9	Potato	5	16.7	44	29.3
10	Apple	3	10.0	16	10.6
11	Banana	1	3.3	8	5.3

Note: \* – the difference is probable ( $p < 0.05$ ) between the control and IBS patients

**Table 4. Number of patients with irritable bowel syndrome that have allergic sensitization to household allergens (determination of allergen-specific IgE)**

No.	Allergen	Control group n=30		IBS patients n=150	
		number	percentage	number	percentage
1	Domestic dust	1	3.3	9	6.0
2	Cat's fur	2	6.7	22	14.6
3	<i>Dermatophagoides pteronissimus</i>	7	23.3	96	64.0*
4	<i>Dermatophagoides farinae</i>	7	23.3	64	42.6*

Note: \* – the difference is probable ( $p < 0.05$ ) between the control and IBS patients

**Table 5. Number of patients with irritable bowel syndrome that have allergic sensitization to pollen allergens (determination of allergen-specific IgE)**

No.	Allergen	Control group n=30		IBS patients n=150	
		number	percentage	number	percentage
1	Ragweed	1	3.3	16	10.9
2	Wormwood	2	6.7	35	23.9*
3	Birch	1	3.3	7	4.8
4	Timothy	4	13.3	32	21.9
5	Sunflower	4	13.3	31	21.2*
6	Rye	4	13.3	25	17.1

Note: \* – the difference is probable ( $p < 0.05$ ) between the control and IBS patients

as well as an increase in the intestinal mucosa inflammation and changes in permeability in patients with allergic diseases suggests that the term «combined respiratory channels» can extend to «single mucous membrane» and

that some symptoms of the gastrointestinal tract typical for patients with allergic diseases are the result of allergic inflammatory changes occurring in the gastrointestinal tract mucosa.

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