

IgG-dependent allergy and selected gastrointestinal diseases

Alergia IgG-zależna a wybrane choroby przewodu pokarmowego

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Prz Gastroenterol 2013; 8 (4): 225–229

DOI: 10.5114/pg.2013.37443

Key words: IgG-dependent allergy, diet, inflammatory bowel disease, irritable bowel syndrome.

Słowa kluczowe: alergia IgG-zależna, dieta, nieswoiste zapalenie jelit, zespół jelita drażliwego.

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Abstract

IgG-dependent allergy may be one of the causative or perpetuating factors for gastrointestinal diseases, such as irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Reactions in which IgG antibodies are involved result in more delayed responses compared to IgE-dependent allergy. Abnormal IgG-dependent reactions to food lead to the formation of immune complexes and, as a result, to the development of chronic inflammation. In spite of that, IgG-dependent allergy is considered controversial, as some scientists consider these reactions physiological. An elimination diet based on the results of IgG testing against specific food antigens is beneficial in the treatment of IBS and IBD.

Streszczenie

Alergia IgG-zależna może być jedną z przyczyn rozwoju lub podtrzymania chorób przewodu pokarmowego, takich jak zespół jelita nadwrażliwego (*irritable bowel syndrome* – IBS) czy nieswoiste zapalenie jelit (*inflammatory bowel disease* – IBD). Reakcje, w których biorą udział przeciwciała IgG, powodują bardziej opóźnioną odpowiedź w porównaniu z alergią IgE-zależną. Nieprawidłowe reakcje IgG-zależne na pokarm skutkują powstaniem kompleksów immunologicznych i w konsekwencji przewlekłym stanem zapalnym. Mimo to alergia IgG-zależna jest kontrowersyjna, gdyż niektórzy naukowcy uważają opisane reakcje za fizjologiczne. Dieta eliminacyjna oparta na wynikach badania dotyczącego IgG względem swoistych antygenów pokarmowych przynosi korzyści w terapii IBS i IBD.

Introduction

The fundamentals of contemporary immunology were laid down more than a 100 years ago by Clemens von Pirquet, who conducted studies at the scarlet fever ward of a paediatric clinic in Vienna. Based on his own results he coined the term ‘allergy’ (derived from the ancient Greek words *allos*, meaning ‘various’, and *ergos*, meaning ‘work, function’) to refer to an altered abnormal reactivity of the immune system that becomes manifest during a second exposure to a specific antigen. Von Pirquet attempted to find a link between two, what seemed to be, opposite phenomena that were observed in patients following exposure to vaccinia and equine

antisera. He noticed that some of the patients who had been given the antiserum developed generalised and local symptoms, such as fever, skin rash, arthropathy and lymph node oedema – collectively referred to as ‘serum sickness’. Similar symptoms were also reported following the use of diphtheria and tetanus antisera. Therefore, injection of the antisera not only led to the development of immunity but also to a hypersensitivity reaction. Von Pirquet suggested that the term ‘allergy’ should be used to describe a factor which induces hyperreactivity of the immune system following one or several exposures [1]. This definition of allergy did not, however, specify the direction of the changes. Mean-

while a reaction of the immune system to an already known antigen may be harmful for the body (allergic reactions) and protective (elimination of the infectious agent). Therefore the definition of the allergen needed to be made more specific, particularly in light of the discovery that also non-immune mechanisms are involved in the body's response during exposure to an allergen [2].

Classification of hypersensitivity

Over the years, the definition of allergy was often used incorrectly. In the 1990s the European Academy of Allergy and Clinical Immunology (EAACI) systematised the terminology of allergy. The EAACI report was updated

in 2001 and its aim was to introduce an amended nomenclature applicable to allergic and related diseases that could be used irrespective of the patient's age and the affected organ. The new terminology took into consideration the latest developments in the understanding of the mechanisms initiating and mediating allergic reactions. According to the EAACI definition, hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects. Classical responses to infection, toxic reactions and autoimmune phenomena are outside the scope of this definition. Hypersensitivity should not be considered equivalent to hyperreactivity, which refers to an excessive but normal reaction to a defined stimulus. Non-allergic hypersensitivity refers to hypersensitivity in which immunological mechanisms cannot be proved. The classification of hypersensitivity is depicted in Figure 1 [3]. Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms, such as asthma, rhinoconjunctivitis or eczema/ dermatitis. The term 'atopy' should only be used to describe the clinical features and predispositions and not to describe disease entities. Allergy is a hypersensitivity reaction initiated by immunological mechanisms. Allergy can be antibody- or cell-mediated. Allergens are antigens which cause hypersensitivity in which immunological mechanisms are involved.

This paper discusses adverse reactions of a delayed nature developing after ingestion of foods. According to the EAACI nomenclature, these reactions are referred to as 'food hypersensitivity' or 'food allergy', as IgE-independent immunological mechanisms are involved here, namely IgG antibodies (Figure 2) [3].

Food allergy is currently one of the most common disease entities. The scale of the problem is particularly extensive in highly developed countries, which is related to the so-called hygienisation of life. The factors involved in the development of allergic reactions include both genetic and environmental factors. The prevalence of diagnosed IgE-dependent food hypersensitivity is estimated at 5.4–9.3% in infants and 1.4–2.4% in adults [4]. Meanwhile the prevalence of IgG-dependent allergy in Europe and the United States may be up to 45% [5]. An increased risk of this type of allergic reaction is seen with selected functional disorders of the gastrointestinal tract, such as irritable bowel syndrome (IBS). Detailed studies are required to investigate the actual role of IgG-dependent allergy in the pathogenesis of IBS and other functional disorders of the gastrointestinal tract.

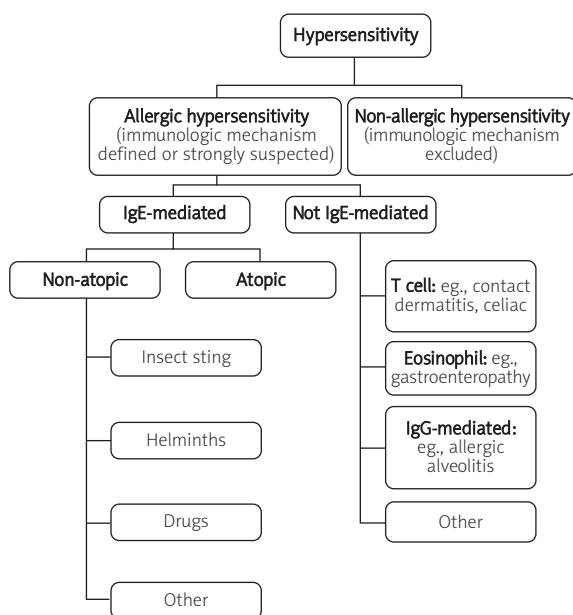


Fig. 1. Division of hypersensitivity reactions (from: Johansson SGO, et al. Allergy 2001; 56: 813–24)

Ryc. 1. Podział reakcji nadwrażliwości (za: Johansson SGO, et al. Allergy 2001; 56: 813–24)

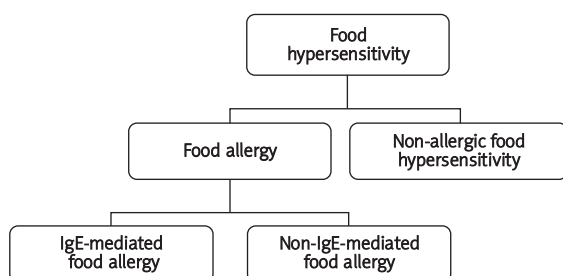


Fig. 2. Types of food hypersensitivity (from: Johansson SGO, et al. Allergy 2001; 56: 813–24)

Ryc. 2. Typy nadwrażliwości pokarmowych (za: Johansson SGO, et al. Allergy 2001; 56: 813–24)

There is still a widespread erroneous belief that food allergy is exclusively associated with IgE antibodies. However, according to recent data, IgG-dependent hypersensitivity, characterised by a delayed immune response, also plays a very significant role in the pathogenesis of food allergy. In addition, determination of serum IgG opens new diagnostic pathways for patients who are hypersensitive to food components [6].

IgG-dependent allergy is directly caused by increased permeability of the intestinal barrier. When homeostasis is preserved, this layer is tight and highly selective, so that only the desired nutrients enter the bloodstream from the intestinal lumen, while access of potentially noxious substances and pathogens is impeded. This barrier also plays a role in immune processes and in the prevention of infection (by binding pathogens by sIgA, for instance). The main structural elements of the intestinal barrier responsible for its correct functioning include autochthonic microorganisms, sIgA, enterocytes along with their so-called tight junctions, Peyer's patches, M cells, antigen-presenting cells (APCs) and lymphocytes. The analyses showed that damaged tight junctions between the enterocytes are the underlying abnormality of IgG-dependent food allergy. The correctly functioning tight junctions between the intestinal cells ensure that the barrier shows the required selectivity. Loosening of the tight junctions makes it possible for larger particles – not only nutrients but also toxins and microorganisms – to penetrate the barrier. The increased permeability of the intestinal barrier is referred to as leaky gut syndrome. When elements that originate from the intestinal lumen enter the bloodstream an immune response is triggered. While this response is necessary to eliminate noxious substances and microorganisms, it is at the same time undesirable with respect to the neutral food particles. Ingestion of food therefore leads to chronic activation of the immune system in which IgG antibodies are involved. This results in the development of chronic inflammation. The delayed nature of the reaction is a considerable diagnostic obstacle that makes it impossible for the patient to identify the factor causing the allergy. This results from the characteristics of IgG-dependent responses. While IgE antibodies are responsible for acute, immediately developing allergic reactions, IgG-dependent reactions take much longer to develop. These antibodies play a significant role in the shaping of the body's normal immune response. The binding of IgG with a bacterial or viral antigen results in antigen coating and formation of an immune complex. The formation of the immune complex triggers further immune responses: activation of the complement and stimulation of the release of proinflammatory cytokines (IL-1, IL-6, TNF- α), proteolytic en-

zymes and free radical pathway enzymes. The developing inflammation is accompanied by mechanical damage to the surrounding tissues. As a consequence of the above processes, coated antigens are phagocytosed. The activity of IgG is identical as far as food antigens are concerned. As the food components in patients with leaky gut syndrome enter the bloodstream from the intestinal lumen on a continuous basis, the immune mechanisms undergo constant activation, which results in chronic inflammation.

Clinical manifestations

The clinical manifestations of chronic IgG-dependent reactions depend on the target tissue or organ to which the immune complexes composed of IgG and the food antigens are transported with the bloodstream. High levels of the complexes accompany such dissimilar disease entities as migraine, irritable bowel syndrome, atopic dermatitis, chronic fatigue syndrome, Crohn's disease, etc. The protective property of IgG antibodies becomes a property that severely burdens and disturbs the body's homeostasis. This type of hypersensitivity is the so-called delayed allergy. The signs and symptoms develop within 8–72 h after ingestion of the offending food. As mentioned above, patients do not associate a given symptom with the food they ate, especially because of the lack of the characteristic "allergic" symptoms. This is the fundamental argument that highlights the controversial nature of type III food allergy. Mild severity of the clinical manifestations or their complete lack is generally associated with a considerable delay of the reaction in time or with low titres of IgG in the blood (low permeability of the intestinal barrier). IgG-dependent food hypersensitivity may affect various organs and systems, such as the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain, lip oedema), skin (urticaria, erythema, rash, pruritus, angio-oedema), respiratory tract (rhinitis, sneezing, itchy throat, laryngeal oedema, hoarseness, cough, stridor, dyspnoea, asthma), cardiovascular system (tachycardia, hypotension, arrhythmia) and nervous system (dizziness, asthenia, fainting) [7].

Effects of elimination diet

According to Isolauri *et al.*, an elimination diet based on the results of the measurement of IgG levels may be equally beneficial in terms of symptom relief as is the case with IgE-dependent allergy [2]. A study conducted in 2001 by York Nutritional Laboratory investigated the usefulness of an elimination diet used after determination of serum levels of the "controversial" IgG antibodies. A total of 4200 patients with symptoms were enrolled in the study but only 1761 were included in the final statis-

tical analysis. As many as 50% of the subjects observed a considerable improvement of health after introduction of the elimination diet and 70% reported health benefits [5]. This study is suggestive enough to justify the need for investigating the potential contribution of IgG-dependent allergy to many disease entities. In this paper, we characterise the mechanism underlying the effects of type III allergy on functional disorders and disease entities associated with the gastrointestinal tract.

The potential role of type III allergy in the pathogenesis of irritable bowel syndrome (IBS) is being extensively investigated. The IBS is a chronic functional disorder of the intestines manifested by frequent abdominal pain, bloating and constipation and/or diarrhoea, which may occur alternately. The prevalence of IBS in the population is high and is estimated at 12–22% [8]. Given the heterogeneity of the abnormalities and the multifactorial aetiology of IBS, the involvement of IgG-dependent hypersensitivity in the initiation of the pathological changes seems likely. Interestingly, most patients suffering from functional disorders of the gastrointestinal tract report that certain foods exacerbate their symptoms [9]. The management of IBS focuses mainly on administration of antispasmodic drugs, drugs that modify intestinal function, antibiotics, antidepressants and analgesics. Atkinson *et al.* [10] showed that an elimination diet can be effective in relieving the symptoms of IBS. After 12 weeks of the diet a 10% improvement in well-being and resolution of the symptoms were observed ($p = 0.024$). The quality of life also improved. Notably, in patients who decreased the restrictiveness of the diet a 24% worsening of the symptoms was observed compared to patients strictly adhering to the dietary guidelines. Drisco *et al.* [8] conducted a study in 20 patients meeting the Rome II criteria for IBS. The patients followed a diet for 6 months that was based on the results of the tests for IgG-dependent allergy. The patients were also instructed to use a probiotic. The study showed abnormal titres of IgG antibodies specific for selected food components in all the patients. Using a diet based on the results of IgG-dependent allergy testing led to a statistically significant improvement in symptoms (improved stool frequency, pain relief) ($p = 0.05$) and the quality of life ($p = 0.0001$). The further step of the analysis involved an open extension. The patients adhering to the diet reported considerable improvement that was greater than the improvement observed with the intake of a probiotic. Also other researchers see the point in introducing a diet based on measurements of the levels of IgG antibodies to food antigens in patients with IBS [9, 11]. However, a necessity is emphasised to carefully select research tools, i.e. tests that are based on reliable methods and that assess the correct param-

eter [9]. The best tools for the assessment of type III allergy are assays that assess all the IgG subclasses (IgG1–IgG4) quantitatively (ELISA). Tests for IgG-dependent allergy should be regularly validated for the assessment of actual diagnostic parameters. Many types of tests for food hypersensitivity that do not meet these criteria are currently available. Some of them are qualitative tests and are intended for home use by the patient, which eliminates the possibility of conducting a reliable diagnostic evaluation. The results of other tests are strongly affected by interfering factors, such as infection or treatment with non-steroid anti-inflammatory drugs. For this reason the selection of an appropriate test to assess the levels of IgG antibodies to food components should be a priority.

The justifiability of using a diet based on the results of the tests assessing type III allergy has also been shown in patients with Crohn's disease [12]. The authors of the analysis, given the multifactorial aetiology of the disease, suggested a potential contribution of the immune response to food antigens to the maintenance of inflammation. For this reason a pilot study was conducted in 79 adult patients with Crohn's disease. The control group consisted of 20 healthy volunteers. The study showed markedly higher serum levels of IgG in patients with organic bowel disease compared to the control group. IgG antibodies to cheese and to baker's yeast were demonstrated in 84% and 83% of the patients, respectively. Following a diet based on the results of the measurement of specific IgG for food antigens considerably improved stool frequency, pain and patients' well-being. Decreased secretion of interferon γ (IFN- γ) by T cells was also observed. The levels of the EDN protein in the stool did not, however, change. The findings of the study demonstrate that implementation of a diet based on testing for IgG-dependent allergy in patients with Crohn's disease is justified. However, this is the first analysis of this type and therefore drawing any binding conclusions requires further dietary studies in a group of patients with inflammatory bowel disease.

Summary

The efficacy of a diet based on the measurement of IgG antibodies specific for food components has also been demonstrated in other disease entities. Excellent results have been obtained in patients with migraine, type 2 diabetes mellitus, obesity and atopic dermatitis. The results obtained so far suggest the necessity of further analyses assessing the actual significance of IgG-dependent allergy in the aetiology of numerous chronic diseases. A diet based on testing results may become an alternative and safe treatment for patients with chronic conditions.

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