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ETIOPATHOGENESIS OF ALLERGIC DISEASES

ETIOPATOGENEZA CHORÓB ALERGICZNYCH

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B. Data collection/entry
zebranie danych
C. Data analysis/statistics
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Summary

Allergic diseases are the most common chronic diseases, particularly widely spread among children, adolescents and young adults. The problem is that there is an increasing incidence of allergic diseases. The causes of such a sudden increase of incidence rate are not well known. Complex interactions of environmental factors seem to play their role in the phenomenon. These include: change in the dietary and hygienic habits, progressing industrialization and increased use of numerous chemical agents. It was shown that inhabitants of highly industrialised nations, as compared to those from the developing countries, suffer from allergic diseases more frequently (most often in USA, Australia, Great Britain, Ireland and New Zealand, least frequently in Eastern Europe, Russia, China, India and Ethiopia), inhabitants of cities rather than those of rural areas, children who have no siblings rather than those from large families [1]. Knowledge of the factors that cause or influence the course of allergy is significant as it can help prevent and properly treat this disorder. It seems especially vital as in some patients allergy can manifest itself in the form of severe anaphylactic reactions, including an anaphylactic shock burdened with high risk of death.

Keywords: environmental factors, genetic factors, allergic diseases

Streszczenie

Choroby alergiczne są jednymi z najczęściej występujących schorzeń przewlekłych, szczególnie rozpowszechnione wśród dzieci, młodzieży i młodych dorosłych. Problem stanowi fakt, że częstość występowania tych chorób stale wzrasta. Przyczyny tak gwałtownego wzrostu zachorowań nie są do końca poznane. Podkreślana jest rola złożonych interakcji czynników środowiskowych takich jak: zmiana nawyków żywieniowych i higienicznych, postępujące uprzemysłowienie i wzrost stosowania wszelakich środków chemicznych. Wykazano, że na schorzenia alergiczne częściej chorują mieszkańcy krajów wysoko uprzemysłowionych niż krajów rozwijających się (najczęściej w USA, Australii, Wielkiej Brytanii, Irlandii i Nowej Zelandii, najrzadziej w Europie Wschodniej, Rosji, Chinach i Indiach i Etiopii), mieszkańcy miast niż wsi, dzieci nieposiadające rodzeństwa niż dzieci z licznych rodzin [1]. Znajomość czynników, które wywołują lub wpływają na przebieg alergii jest bardzo ważna, aby móc zapobiegać i odpowiednio leczyć te schorzenia . Tym bardziej, że u części pacjentów alergia może objawiać się ciężkimi reakcjami anafilaktycznymi, w tym wstrząsem anafilaktycznym obarczonym wysokim ryzykiem zgonu.

Słowa kluczowe: czynniki środowiskowe, czynniki genetyczne, choroby alergiczne

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Introduction

A steady increase in the incidence of allergic diseases can be observed around the world, including Poland. This concerns both children, youth and adults. In the last three decades, the incidence has grown 2-3 fold and relates to all atopic diseases, despite the fact that during this time there has not been noticed any substantial change in human genome[1,2].

According to the White Book of Allergy in Europe, currently allergy affects every third person. It is estimated that in 2010 these disorders will take the third place after cardiovascular diseases and neoplasms [3,4].

The findings of the first stage of Epidemiology of Allergic Diseases in Poland study (ECAP), which began in 2005, were published in April 2008. They were based on personal questionnaires conducted among more than 22,5 thousand people from nine regions in Poland, out of whom one forth underwent detailed medical

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examinations. A rigorous analysis showed that 45-52% of the Polish population, more than 15 million Poles, at least once in their lifetime suffered from an allergy, whereas 28% of the surveyed people are in need of systematic treatment because of an allergic medical condition. The findings resulting from the ECAP study place Poland among the countries with the highest percentage of patients suffering from an allergy [5].

Epidemiology of allergic diseases

It is commonly known that the main factor determining the occurrence of allergy is atopy, genetic predispositions of the body to increase the production of characteristic antibodies in IgE class directed against the environmental antigen (allergens). Atopy does not necessarily indicate a disease, but an increase in susceptibility to the development of an allergy. If an allergic disease is to occur, some kind of interaction of genetic factors (atopy) and environmental ones is needed. Further, the influence of genetic predisposition on the prevalence of an atopic disease, passed onto next generations, as well as a constant increase in the number of unfavourable external factors modifying the occurrence, development and the course of an allergy cause that the problem of a constant increase in incidence of allergic diseases becomes more acute[2].

Genetic factors

Because there is an incontestable contribution of genetic factors to the rise of the factors determining atopy, there are currently ongoing studies aiming to determine them precisely. These studies are hindered by the fact that even in the same family allergy can manifest itself in different clinical form, such as rhinitis, asthma or atopic dermatitis. Individual family members may also be allergic to totally different allergens. Another disturbing fact is that children descendent from families burdened with atopy show an increased risk of morbidity for such diseases. The risk of an atopic disease in children of healthy parents is around 10-15%. When one parent is affected, the risk increases to 30-40%, whereas when both of the parents suffer from an atopic allergy, the risk is over 60% [2].

Atopy is caused by multigenic inheritance. Until now, we have identified tens of gens determining the occurrence or modifying the course of an allergy, localized in different regions on particular chromosomes. Among others, a correlation was shown between a gene localized on chromosome 4 with bronchial hyperactivity; on chromosome 6 with total concentration of IgE in serum and eosinophilia; on chromosome 7 with total concentration of IgE in serum and bronchial hyperactivity; on chromosome 11 with total concentration IgE in serum, positive skin test results with allergens and asthma; on chromosome 13 with atopy characteristics; and on chromosome 16 with total concentration of IgE in serum, bronchial hyperactivity and asthma [6,7]. Detailed characteristics of particular genes are shown in table 1.

Table 1. Characteristics of genes linked with different phenotypic traits of atopic allergy [2]

Chromosome region	Trait linked to a gene	Correlation coded by the gene
5q	high level of total IgE bronchial hyperactivity asthma severity of asthma bronchial hyperactivity high level of total IgE atopy	IL-3, IL-4, IL-5 receptor $_{\beta}2$
6p	specific IgE, total IgE asthma	HLA-DR TNFα
7q	specific IgE, total IgE	TCRB, TCRG
11q	atopy, asthma	receptor for IgE FcεRI CC16
12q	asthma	IFNγ
14q	specific IgE, total IgE	TCRA
16p	atopy, atopic dermatitis	IL-4R
17q	asthma	chemokine

Environmental factors

Environmental factors play a big role in the etiopathogenesis of allergic diseases. Allergens are definitely the most important of them. Not only is their presence significant, but also their concentration and exposition time. An example could be the fact that in children descended from families with atopy, asthma develops all the more frequently and earlier, if higher concentration of household dust allergens (mites) are present in the direct surroundings [2,8].

The significance of a constant rise in the air pollution is also being emphasized [9]. Germany, which was divided into two countries after 1945, is a good example. Both of the territories were characterized by radically different environmental factors. In the former East Germany, where the industrial activity developed, an increase in carbon dioxide in the atmospheric air was observed. In the former West Germany, however, the atmosphere contained significant amounts of nitrogen dioxide because of the intensive vehicle traffic. The studies conducted by Heinricha et al. showed that the incidence of allergic diseases in West Germany increased significantly in people born after the year 1960. Such an increase was not noted in East Germany though. After the unification of both countries, atmospheric pollutants became more uniform and the inhabitants' way of life became similar on the whole German territory. Then, it was noticed that the differences in frequency of atopic allergic diseases both in the eastern and western territories were slowly diminishing [2,10]. It should also be mentioned that the presence of motor vehicles fuel particles in the atmosphere was significant as it contributed to the changes.

Formation of toxic substances such as sulphur dioxide, nitrogen oxides, carbon monoxide, ozone, benzene, formaldehyde, hydrocarbons and diesel exhaust particles (DEPs) results from incomplete fuel and diesel oil combustion [11]. The emissions from diesel engines produce more than 90% of such particles. Their size is usually smaller than 1 millimicron and therefore they can easily get into the respiratory tract. Further, these particles absorb plant pollens on their surface, which aid the penetration of nasal mucous membranes as well as the penetration into the lower respiratory tract. The exposure to diesel emission particles, after the prior provocation by an allergen, causes an increased expression of IL-4, IL-5, IL-10 and IL-15, enhances adhesion of eosinophils to the epithelial cells and leads to their degradation, as well as activates production of IgE in nasal mucosa [12].

The emissions of diesel fuel not only exacerbate the symptoms of the already existent allergic disease, but also aid in the development of new ones. This would explain the increased incidence of pollinosis in city inhabitants as compared to the people who inhabit rural areas and the exacerbation of symptoms in patients with the already existent pollinosis. That is why, so many studies on the role of rural environment highlight its role as a factor decreasing the risk of allergy development [10,13].

It is not only environmental pollution that plays a significant role in etiopathogenesis of allergic diseases. As a consequence of change in lifestyle, living space hygiene has also become more important, because modern people spend on average 30-80% of their time indoors. This causes that not only an increased level of nitrogen dioxide is dangerous, its sources being gas stoves, coal heaters, fireplaces as well as cigarette smoke, but also the presence of numerous volatile substances derived from materials used for building, decoration and conservation of houses, such as for example formaldehyde [14]. Lack of natural air ventilation, particularly in air-conditioned spaces, favours an increase of the above mentioned substances. It also causes a higher concentration of allergens, disease causing microorganisms, including bacteria, moulds, house dust mites as well as cockroach allergens. Furthermore, a long-lasting stay in indoor spaces, as well as the common use of UV skin filters is connected with a decreased exposure of the skin to sun, which results in a decreased synthesis of vitamin D[15].

Another notable development is greenhouse effect caused by an increase of CO_2 in the atmosphere due to human industrial activity, which results in global warming. Higher air temperature stimulates earlier and longer blooming, which increases the risk of exposure to airborne allergens. Besides, an additional exposure to pollutants that acts synergistically intensifies the overall allergic response [13,16].

How the above mentioned factors affect people was shown on the two populations: Finish and Russian, who inhabit the same geographic area of Karellia. The comparison was conducted at two distinct points in time, i.e. in 1997/98 and 2007. It was determined that morbidity for allergic diseases in subsequent Finnish generations was increasing both in children and in adults, while in the Russian population such an increase in morbidity for allergic diseases was not observed. This could be explained by the differences between the areas. The area inhibited by Russians is characterised by a smaller degree of industrial development, and greater exposure to a more varied bacterial environment, including bacterial endotoxins derived from the farm animals environment, which are typical surroundings of the Russian population [17].

It is bacteria of Acinetobacter (gammaproteobacteria) species that showed a particularly protective action, which has anti-inflammatory genetic modification properties, and which showed a decrease in the risk of allergy as well as pneumonia development in the conducted in-vitro studies. In one of the studies on skin microbiota in healthy people without atopy, a higher concentration of Acinetobacter and anti-inflammatory molecule expression was found, as compared to the skin of those with atopy. Bacteria of the Acinetobacter group promote anti-inflammatory Th1 cell type response [18].

In the Sandin et al. study of children population with positive skin test results, it was observed, that in those in whom higher concentration of IgA in saliva was found, allergic diseases developed less frequently, as compared with children who had a low concentration of this immunoglobulin. High concentration of IgA occurred more often in children who had older siblings as well as in those who had at least several infections in the period of

their early childhood [19]. In the study conducted by Kusunoki et al., on the group of eleven thousand children, a decreased risk of food allergy development was observed along with the corresponding increasing number of older siblings, which most probably is related with more frequent infections among large family [20].

The European project GABRIEL carried out on the population of Polish children aged 7-12 years, in the region of Lower Silesia, showed a more frequent occurrence of atopy in children living in the city environment as compared to those inhibiting the rural areas, but no changes were observed in this study with regard to the frequency of bronchial asthma occurrence [21].

Other factors affecting the intestinal microflora, which accompany humans from the beginning of their existence, are parasites. It was observed that parasitic infections have a protective action in regard to the development of allergic diseases, and the treatment of the parasitic infestation favours the development of allergies and autoimmunological diseases. This finding was confirmed by many studies in different world populations. In the developed countries, where parasites are relatively rare in comparison to the developing countries, allergic and autoimmunological diseases constitute a common health problem [22].

The advancement of medicine is also causing a wide use of medications, whose long term effect is being studied only now. It is believed that many substances which exist today may be the cause for allergy development in the future.

The frequent use of paracetamol and/or antibiotics during pregnancy and in first years of life may increase the risk of development of allergic diseases in children, including bronchial asthma, atopic dermatitis and allergic rhinitis, which was observed in a few cohort studies in different populations [23,24,25]. However, not all of those studies confirm such correlations [26].

The use of medications increasing the pH of the stomach in pregnant women is related to an increased risk of development of asthma in children. It is also believed that a long term use of medications neutralizing the acidity of the gastric juice increases the frequency of food allergy occurrence, which was also confirmed on a mouse model [27].

The use of substances containing plant protein on a damaged skin may induce an allergy toward the same protein that is caused when it is contained in some foods. Therefore, the selection of substances for skin care in children with atopic dermatitis is so crucial [28, 29].

Allergic contact dermatitis is another allergic disease caused by environmental factors. Many metals, especially nickel, chromium, copper and cobalt, are used in jewellery, coins, parts of clothing (e.g. belts, trousers), mobile phones, dental materials, leather dyes, etc. Nickel contact allergy dermatitis is one the most frequent allergic skin problems due to the high use of this metal in daily life and its presence in drinking water in different quantities [30].

Unfavourable life style changes also impacted nutrition adjustments, including in particular an introduction of new products into diet, industrially processed foods, food additives (such as for example: dyes and preservatives), which all affected changes in the intestinal flora [31,32]

Besides, the importance of travel abroad, during which exposition to new allergens might take place, is being emphasized in discussing the ethiopathogenesis of allergic diseases. It is believed that the following factors also play their own role: the exposition to disease causing microorganisms; interference within human immunological system, which includes among others anti-infectious immunizations; the use of immunomodulating drugs, as well as an increased exposition to stress. However, these data need further research in order to fully confirm their role in the development and course modification of allergic diseases [2, 10, 33].

On the other hand, environmental factors may have an influence on an increased frequency of allergies occurrence, which is shown in table 2.

Table 2. Environmental factors which may influence an increase in frequency of allergies [2, 7]

Pollution of external environment
• Atmospheric pollution • Vehicle traffic (emissions) • Ozone • Chemical and biological pollution • Cigarette smoke • Building construction (new materials, thermal insulation, diminished ventilation, increased room humidity)
Lifestyle changes
• Longer stay indoors • More frequent travel – exposition to different allergens

Change in the way of nutrition
• New products • Manufactured processed foods • Food additives (among others pigments, preservatives, additives) • Change in the bacterial flora
Exposition to allergens
Size and socio-economic status of the family
Role of infections
Iatrogenic factors
• Preventive vaccinations • Antibiotics • Discrimination of aspirin
Exposure to stress and ways of fighting it

As for food allergy, it has been found so far that the risk factors include: male gender among children, female among adults, black and Asian races, vitamin D insufficiency, low consumption of omega-3 fatty acids and antioxidants as well as obesity, high level of hygiene and the time when new products are introduced into child's diet [2].

Food served either too early or too late may be the reason for the development of an allergic reaction. It is currently believed that the so called „window of immunological tolerance induction" is between the 4th and 6th month of life and during this period the largest variety of different foods should be introduced into the child's diet so that the immunological system may get acquainted with them without developing an allergic reaction [34].

Conclusions

It seems obvious that the allergy development occurs only in people with genetic predisposition, the so called atopy. According to this premise, the allergy is currently defined as a TH2 type hypersensitivity for non-harmful antigens (allergens) of complex genetic background. The basis for the development of the so-called hygienic atopy theory is explained by the mutual interdependence of genetic and environmental factors. Individuals with a Th1 response defect (independent of a tendency for atopy) are also susceptible to many infections (bacterial and viral) because of the deficit of INF-γ, IL-12 and IL-2, which are essential for the activation of cytotoxic cells. It may therefore be speculated that those people who lived before antibiotics were introduced died in the early period of life as a result of infections and, in consequence, could not pass on the above mentioned immunological anomaly to their offspring. This in turn resulted in a natural selection in the population with effective Th1 response in the the first half of the 20th century, while most of the carriers of the Th2 type response were unable to survive. According to one theory, the moment antibiotics were introduced for therapeutic purposes on a wide scale, the above mentioned natural selection succumbed to modification, which finally led to an increase in carriers with genetically predominant type Th2 response, vulnerable to the development of atopic disease. In some individuals of the present day population, the lack of Th1 incentives resultant from „sterile" conditions in which children grow up may have contributed to the intensification of allergy. Although presently the hygiene theory seems to be the most convincing interpretation of the atopy genesis in the light of current knowledge of its mechanism, many aspects of the condition still remain to be discovered in this area [35].

References:

1. Haahtela T, von Hertzen L. Asthma and atopy - the price of affluence? Allergy. 2004; 59: 124-137. https://doi.org/10.1046/j.1398-9995.2003.00433.x
2. Rutkowski K, Sowa P, Rutkowska-Talipska J, Sulkowski S, Rutkowski R. Allergic diseases: the price of civilisational progress. Postepy Dermatol Alergol, 2014; 31(2): 77–83. https://doi.org/10.5114/pdia.2014.40936
3. European Allergy White Paper Summary. [Internet]. The UCB Institute of Allergy 2004 [cited 2017 Jan 20] Available from: http://www.ucb.com/_up/tuioa_com/images/europeanallergywp-summary_tcm114-11424.
4. Jahnz-Różyk K. Choroby alergiczne na początku XXI w. Przew Lek. 2007; 2:155-159 (in Polish).

5. Samoliński B. Epidemiologia alergii i astmy w Polsce - doniesienie wstępne badania ECAP. Terapia 2008; 04: 127-131 (in Polish).
6. Bousquet J, Khaltaev N, Cruz AA Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008; 63 (86): 8-160. https://doi.org/10.1111/j.1398-9995.2007.01620.x
7. Barnes KC. Genetic studies of the etiology of asthma. Proc Am Thorac Soc. 2011; 8(2): 143–148. https://doi.org/10.1513/pats.201103-030MS
8. Yan D-C, Chung F-F, Lin S-J, Wan G-H. The relationships among Dermatophagoides pteronyssinus exposure, exhaled nitric oxide, and exhaled breath condensate pH levels in atopic asthmatic children. Wang. Y, ed. Medicine. 2016; 95(39): e4825. https://doi.org/10.1097/MD.0000000000004825
9. Takizawa H. Impact of air pollution on allergic diseases. Korean J Intern Med. 2011; 26: 262-273. https://doi.org/10.3904/kjim.2011.26.3.262
10. Romański B, Bartuzi Z. Alergia i nietolerancja pokarmów u osób dorosłych: Alergia skrzyżowana. In: Alergia i nietolerancja pokarmów. Problem społeczny i lekarski współczesnej cywilizacji. Romański B, Bartuzi Z., editors. Katowice: Śląsk sp. z.o.o. 2004. p. 311-330 (in Polish).
11. Ghio AJ, Smith CB, Madden MC. Diesel exhaust particles and Airways inflammation. Curr Opin Pulm Med. 2012; 18:144–50. https://doi.org/10.1097/MCP.0b013e32834f0e2a
12. Searing DA, Rabinovitch N. Environmental pollution and lung effects in children. Curr Opin Pediatr. 2011; 23(3): 314-8. https://doi.org/10.1097/MOP.0b013e3283461926
13. D'Amato G, Pawankar R, Vitale C, Lanza M, Molino A, Stanziola A, et al. Climate Change and Air Pollution: Effects on Respiratory Allergy. Allergy Asthma Immunol Res. 2016; 8(5): 391-395. https://doi.org/10.4168/aair.2016.8.5.391
14. Tagiyeva N, Sheikh A. Domestic exposure to volatile organic compounds in relation to asthma and allergy in children and adults. Expert Rev Clin Immunol. 2014; 10: 1611–39. https://doi.org/10.1586/1744666X.2014.972943
15. Reinholz M, Ruzicka T, Schauber J. Vitamin D and its role in allergic disease. Clin Exp Allergy. 2012; 42(6):817-26. https://doi.org/10.1111/j.1365-2222.2011.03923.x
16. Takaro TK, Knowlton K, Balmes JR. Climate change and respiratory health: current evidence and knowledge gaps. Expert Rev Respir Med. 2013;7: 349–361. https://doi.org/10.1586/17476348.2013.814367
17. Laatkainen T, von Hertzen L, Koskinen JP, Mäkelä MJ, Jousilahti P, Kosunen TU, et al. Allergy gap between Finnish and Russian Karelia on increase. Allergy, 2011; 66: 886-892. https://doi.org/10.1111/j.1398-9995.2010.02533.x
18. Fyhrquist N, Ruokolainen L, Suomalainen A, Lehtimäki S, Veckman V, Vendelin J, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. J Allergy Clin Immunol. 2014; 134(6): 1301-1309. https://doi.org/10.1016/j.jaci.2014.07.059
19. Sandin A, Björkstén B, Böttcher MF, Englund E, Jenmalm MC, Bråbäck L. High salivary secretory IgA antibody levels are associated with less late-onset wheezing in IgE –sensitized infants. Pediatr Allergy Immunol. 2011; 22: 477-81. https://doi.org/10.1111/j.1399-3038.2010.01106.x
20. Kusunoki T, Mukaida K, Morimoto T, Sakuma M, Yasumi T, Nishikomori R, et al. Birth order effect on childhood food allergy. Pediatr Allergy Immunol. 2012; 23: 250-4. https://doi.org/10.1111/j.1399-3038.2011.01246.x
21. Sozańska B. Środowisko wiejskie – antidotum na alergie? Alergia. 2014; 2: 41-43 (in Polish).
22. Maizels RM. Parasitic helminth infections and the control of human allergic and autoimmune disorders. Clin Microbiol Infect. 2016; 22: 481-486. https://doi.org/10.1016/j.cmi.2016.04.024
23. Wang JY, Liu LF, Chen CY, Huang YW, Hsiung CA, Tsai HJ. Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases. Int J Epidemiol. 2013; 42: 1087-1099. https://doi.org/10.1093/ije/dyt121
24. Amberbir A, Medhin G, Hanlon C, Britton J, Venn A, Davey G. Frequent use of paracetamol and risk of allergic disease among women in an Ethiopian population. PLoS ONE, 2011; 6(7): e22551. https://doi.org/10.1371/journal.pone.0022551
25. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjuntivitis and eczema in children aged 6-7 years: analysy from Phase Three of the ISAAC programme. The Lancet. 2008; 372: p1039-1048. https://doi.org/10.1016/S0140-6736(08)61445-2
26. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, et al. Paracetamol use in early life and asthma: prospective birth cohort study. BMJ. 2010; Sep 15;341:c4616. https://doi.org/10.1136/bmj.c4616

27. Oyoshi, MK, Oettgen, HC, Chatila TC, Geha RS, Bryce PJ. Food allergy: Insights into etiology, prevention and treatment provided by murine models. J Allergy Clin Immunol. 2014; 133(2): 309–317. https://doi.org/10.1016/j.jaci.2013.12.104
28. Radhakrishna N, Prickett S, Phan T, Rolland JM, Puy R, O'Hehir RE. Anaphylaxis to oats after cutaneous sensitization by oatmeal in skin products used for the treatment of atopic dermatitis: J Allergy Clin Immunol Pract. 2016; 4: 152–153. https://doi.org/10.1016/j.jaip.2015.07.005
29. Wassmann A, Werfel T. Atopic eczema and food allergy. Chem Immunol Allergy. 2015; 101: 181-90. https://doi.org/10.1159/000371701
30. Saito M, Arakaki R, Yamada A, Tsunematsu T, Kudo Y, Ishimaru N. Molecular Mechanisms of Nickel Allergy. Int J Mol Sci. 2016; Feb; 17(2): 202. https://doi.org/10.3390/ijms17020202
31. Vojdani A, Vojdani C. Immune reactivity to food coloring. Altern Ther Health Med. 2015; 21 Suppl 1:52-62.
32. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, et al. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A. 2014; 111(36): 13145–13150. https://doi.org/10.1073/pnas.1412008111
33. Rutkowski R, Kosztyła-Hojna B, Rutkowska J. Alergiczny nieżyt nosa – problem epidemiologiczny, ekonomiczny i społeczny XXI wieku. Pneumonol Alergol Pol. 2008; 76: 348–352 (in Polish).
34. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis and traetment. J Allergy Clin Immunol. 2014;133: 291-307. https://doi.org/10.1016/j.jaci.2013.11.020
35. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol. 2010; 160(1): 1–9. https://doi.org/10.1111/j.1365-2249.2010.04139.x