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# The hyper IgE syndrome in medical practice of allergists and immunologists

**keywords:** *total serum IgE, allergic pathology, infectious diseases, virus Epstein-Barr.*

During the life process, despite the wide range of negative environmental factors, the human body tries to preserve their genetic «purity», his identity. The antigenic support of homeostasis is primarily duty of the immune system, which has a complex set of interacting innate and adaptive mechanisms. One of them is the mechanism of degranulation of mast cells, mediated by immunoglobulin E (IgE). Therefore, this mechanism is a physiological and extremely beneficial for the body [9].

Production of the immunoglobulin begins after 11 weeks of embryonic development and gradually increased from birth to adolescence. Adults concentration of IgE can reach to 100 IU / ml and decreases in the elderly [14]. The synthesis of IgE is a T-dependent process. The main interleukin (IL), which is involved in switching plasma cells from synthesis of IgG on IgE, IL-4 is mediated by T helper type 2 (Th2). Moreover, Th2 produce series of cytokines: IL-3, IL-5, IL-10, IL-13. Because of IL-4, IL-13, they act on B cells that produce IgE; by IL-4, IL-10 – on mast cells and basophils, providing degranulation process a number of bioactive substances; by IL-5 – on eosinophils that migrate from the peripheral blood to the allergic inflammation. Activation of these cells provides the implementation of pathochemical and pathophysiological stages of atopic reactions. Herewith, g-IFN, which produced in Th1, inhibits the synthesis of IgE and promotes the synthesis of IgG (namely g-IFN and IL-4 works as an antagonists) [17, 27]. Thus, the development of allergic reactions occurs due to changes in imbalance of Th1 and Th2 towards to Th2 against the background of high concentrations of IL-4, IL-5, IL-10, IL-9, IL-13. Actually, these data are often used for diagnosis of atopic reactions. However, in the current literature, reports that an important marker in the diagnosis of atopy for newborn baby is a level of g-IFN in cord blood, namely its low concentration [19].

The inclusion of IgE in the protective reaction occurs at overcoming antigen / allergen of primary barriers, who formed by sIgA and humoral factors of natural and adaptive immunity. This situation may arise, on condition of immunodeficiency disorders and conditions – deficit of sIgA, the reducing of phagocytic activity of antigenpresenting cells, and an extremely large dose of antigen / allergen [1, 4]. The detection of high concentrations of total IgE in serum is an important additional tool that lets you to differentiate the allergies among many pathologies.

For the last years, the global medical statistics noted the high growth of allergic diseases including atopic. Atopic diseases are a group of multifactorial diseases, the development of which is determined by the influence of both genetic factors and environmental factors. It is crucial to say that is inherited not a specific allergic disease, but only a predisposition to it [7, 10]. At the stage of sensitization due recognition of allergen is synthesized the specific IgE, which are fixed on the membranes of mast cells and basophilic granulocytes. Recently, they also found the cells Langerhans and eosinophils. Among frequent diseases which accompanied by increased levels of IgE in serum, and also presence of specific IgE noted: allergic rhinitis, atopic asthma, atopic dermatitis, urticaria, angioedema, allergic gastroenteropathy, allergic bronchopulmonary aspergillosis, etc. However, it should be remembered that according to different authors, 15-30 % of patients with atopic diseases have the levels of IgE within the age norm. Also in clinical practice often found the elevated levels of IgE, which is associated with the operation of a number of drugs [7].

In contradistinction of these atopic diseases, the congenital immunodeficiency syndrome (Job syndrome Di George) is a relatively rare in clinical practice. The Job's syndrome, described by Davis and others (1966) – autosomal dominant form of genetic disease

caused by a deficiency of STAT3. It is characterized not only classic triad syndrome – hyper IgE, dermatitis, recurrent infections of the skin and lungs, but also diseases of connective and skeletal tissue. Today described (Brenner et al., 2004) and another autosomal recessive form, the genetic cause of which needs the further research. Clinically it is differ from the dominant by the absence of pathological lesions of connective tissue, however, the bigger frequency of virus (human herpes virus 1, 2 and 3 type) and fungal skin lesions, the presence of neurological syndromes [28]. To the diseases, which also accompanied by increased levels of IgE belongs the selective IgA-deficiency syndrome, syndrome of Wiskott-Aldrich, alcoholic cirrhosis, infectious mononucleosis, celiac disease, idiopathic hemosiderosis of pulmonary, drug-induced interstitial nephritis, syndrome Churg-Strauss, nodular polyarteritis, IgE-myeloma and so on.

The helminthiasis, as WHO experts say, today, unfortunately, became as the «neglected diseases». The leading pathogenetic factor in the acute phase of helminthiasis is an allergic. The role of allergens play a functional somatic antigens and worms, which are largely produced antibody class IgE. For example, when the patients have ascariasis, the level of IgE increases to 15-20 times [5, 6].

Thus, the high prevalence of pathological disorders, which involving with the increases the levels of IgE, a variety of clinical forms, including rare, insignificant competence and awareness of physicians about clinical laboratory and immunological criteria for the diagnosis of allergic diseases point to the urgency of identifying and setting the etiological factor of hyper-IgE syndrome.

The relevant researches was conducted during 10 years (2005-2015.) in the Lviv Regional Medical Center of Clinical Immunology and Allergology. Based on these studies was revealed the hyper-IgE-syndrome 3567 patients, that accounting for more than half of the patients (53.9 %). It was found the tendency to increase the prevalence of the syndrome, especially in the last five years (2010-15 years). Established that the hyper-IgE-syndrome often appears in females (61.2 %) and patients young and middle age. In particular, for persons of 20-35 years old the prevalence of hyper-IgE-syndrome was observed in 30.7 % of cases; 36-50 years – 29.1 % in those over 65 years – by 3.9 %.

Analysis of clinical cases of detection of hyper-IgE showed that most increase of this immunoglobulin was in association with allergic diseases such as allergic rhinosinusitis (85.6 %), hay fever (98.1 %), asthma (68.3 %), alergic dermatitis (47.3 %), drug allergies (32.1 %), chronic urticaria (28.8 %) and other (36.2 %). To a lesser extent the hyper-IgE-syndrome was found in patients with infectious diseases (658), autoimmune disorders (246), parasitic diseases (124), primary immune deficiencies (36), immunoproliferative diseases (9) and other diseases – 17 cases. All patients were treated and are on the dispensary at the Lviv Regional Medical Center of Clinical Immunology and Allergology. The results, which indicated the high prevalence and tendency to increase of hyper-IgE syndrome.

Although the patients with infectious diseases the hyper-IgE-syndrome occurs less frequently compared, both allergic pathology, but we focused on the association this syndrome with herpes infections in the stage of replication activity. According to the literature the activation of a number of intracellular virus may be the trigger of allergic disorders, including the human herpes virus types 1 and 2 often accompany atopic dermatitis and angioedema; human herpes virus type 3 - contact dermatitis; CMV – dermatitis, allergic sinusitis and asthma and so on. However, according to our observations, the largest association of hyper-IgE-syndrome called Epstein-Barr virus.

According to scientific literature, the rate of virus infection of the child population is 50-80 %, and adults – 90-100 %. In the majority of infected organisms the virus is in the latency period, when the number of viral copies are negligible and the cells are not destroyed. Reducing of general and local immunity for any reason is a potential activator of EVV in the body. The main mechanisms that inhibit the viral replication process, are the factors of cellular and humoral immunity. With poor quality or reduced response primarily of cellular immunity, the chronic infection of EBV becomes the trigger of pathological disorders [1, 3].

The scientific literature reports that infection with this virus in early childhood is the trigger of asthma and atopic dermatitis [5]. In the study of serum total IgE was determined that the level of immunoglobulin was lower in EBV seropositive persons aged from 6 to 29 months compared to older persons in which results were opposite. It is explained by the fact that in the first years of life the level of total IgE is low due to the age characteristics of the immune system [6]. According to others data, in experiments in vitro elevated levels of interleukin 4 (IL-4) promotes polyclonal activation of EBV infected B lymphocytes with switching of synthesis by these cells immunoglobulins of IgM, IgG, IgA to IgE [8, 9]. There is evidence that the key role of pathogenesis of the chronic infection of EBV plays the clonal expansion of EBV T-lymphocytes and natural killer cells (NK) [7]. By the results of several studies in patients with primary defeat of virus of these cells are identified significantly higher levels of the total serum of IgE against the background of relatively low titers of IgM, IgG. Also in these individuals was observed the hyperergic reaction to the mosquito bites [4]. According to our research in patients with chronic EBV-infection in the stage of reactivation were found the combined immunodeficiency by the phagocytic lymphocyte-type violations complicated by 18.0 % in hyper-IgE-dependent syndrome without obvious clinical manifestations of allergic reactions in history. In some of these individuals, with the mainly affecting the nervous system the level of serum IgE was more than 3000 IU / mL [2]. Instead, in 75.0 % of patients with allergic syndrome on the background of EBV infection in the stage of replicative activity was detected the increase of total serum IgE. In addition, we found that when mixed infection of EBV with cytomegalovirus (CMV) and human

herpes virus type 6 (HHV 6) the hyper-IgE syndrome was detected in 21.7 % of subjects and in most of them accompanied by severe allergic disorders.

### Conclusions

During 10 years(2005-2015.) in the Lviv Regional Medical Center of Clinical Immunology and Allergology was found 3567 patients with hyper-IgE syndrome with a tendency to increased prevalence in recent years.

Hyper-IgE Syndrome is often among the females (61.2 %) and patients young and middle age.

The identify of hyper-IgE syndrome most of all is associated with allergic pathology, in particular with hay fever (98.1 %), allergic rhinosinuitis (85.6 %) and others.

### Список літератури

1. Балаболкин, И. И. Проблемы профилактики аллергических заболеваний у детей [Текст] / И. И. Балаболкин // Педиатрия. – 2003. – № 6. – С. 4–7.
2. Банадига, Н. В. Грудне вигодовування та становлення імунітету у дитини [Текст] / Н. В. Банадига // Клінічна імунологія. Алергологія. Інфектологія. – 2006. – № 3. – С. 5–8.
3. Беш, Л. В. Алергичний марш: перспективи профілактики і прогнозу [Текст] / Л. В. Беш. – Львів: Каменяр, 2010. – 68 с.
4. Беш, Л. В. Проблема дисбактеріозу кишечника у практиці дитячого алерголога: дискусійні питання і можливості їх вирішення [Текст] / Л. В. Беш // Педиатрія. Акушерство. Гінекологія. – 2010. – № 3. – С. 12–13.
5. Бодня, Е. И. Клинико-иммунологические аспекты паразитарных болезней [Текст] / Е. И. Бодня, И. П. Бодня // Здоров'я України. – 2008. – № 2. – С. 18–19.
6. Вінницька, О. В. Гельмінтози: діагностичний пошук та лікування [Текст] / О. В. Вінницька // Здоров'я України. – 2009. – № 4. – С. 11–13.
7. Гнатейко, О. З. Региональные особенности аллергических заболеваний у детей Львовской области и основные факторы, ответственные за их развитие [Текст] / О. З. Гнатейко, О. М. Садова // Современная педиатрия. – 2004. – № 3. – С. 59–61.
8. Зербіно, Д. Д. Екологія людини. Екологічна патологія. Екологічні хвороби [Текст] / Д. Д. Зербіно // Мистецтво лікування. – 2010. – № 1. – С. 86–90.
9. Казмирчук, В. Е. Аллергия и псевдоаллергия: пора не путать эти понятия [Текст] / В. Е. Казмирчук // Клінічна імунологія. Алергологія. Інфектологія. – 2008. – № 3. – С. 11–15.
10. Нагорна, Н. В. Екологія та алергічна патологія у дітей: медико-соціальні аспекти [Текст] / Н. В. Нагорна, Г. В. Дубова // Алергія у дитини. – 2009. – № 1. – С. 30–32.
11. Полозенко, О. В. Негативний вплив стресів на здоров'я людини [Текст] / О. В. Полозенко // Здоровий спосіб життя. – 2006. – № 14. – С. 44–46.
12. Ранні клініко-лабораторні діагностичні критерії імунodefіцитів [Текст]: інформаційний лист / Н. Г. Горовенко [та ін.] // НМАПО імені П.Л. Шупика. – Київ: НІФП, 2004. – 5 с.
13. Ревякина, В. А. Аллергические заболевания у детей и окружающая среда [Текст] / В. А. Ревякина, О. К. Нетребенко. – К.: Реклама-Принт, 2005. – 239 с.
14. Тотолян, А. А. Иммуноглобулин Е: структура, продукция, биологические эффекты и диагностическое использование [Текст] / А. А. Тотолян // Алергологія. – 1998. – № 2. – С. 4–7.
15. Atopy, asthma and antibodies to Ascaris among rural and urban children in Kenya [Text] / M. S. Perzanowski [et al.] // J. Pediatr. – 2002. – V. 140. – P. 582–588.
16. Bonneau, R. Stress-induced modulation of the immune response [Text] / R. Bonneau, J. Kiecolt-Gloser. – Columbus (Ohio), 2011. – 270 p.
17. Bowis, J. Allergic diseases. Minor irritation or major aggravation [Text] / J. Bowis. – USB Pharma SA, 2009. – 23 p.

To a lesser extent the hyper-IgE syndrome detected in patients with infectious diseases (658 cases) and autoimmune disorders (246 cases).

18.0 % of patients with chronic EBV-infection in stage reactivation diagnosed the immunodeficiency abuse by the phagocytic lymphocytic-type, complicated by the hyper-IgE syndrome without obvious clinical manifestations of allergic disorders in anamnesis.

In 75 % of patients with allergic syndrome on the background of EBV-infection in the stage of replicative activity detected elevated levels of serum IgE.

In 21.7 % of people against the backdrop of acute mixed infection (EBV + CMV + HHV6) found the hyper-IgE syndrome, accompanied by severe allergic disorders.

### References

1. Balabolkin II. Problemy profilaktiki allergicheskikh zabo-levaniy u detey (The problems of prevention of allergic diseases in children). *Pediatrics*. 2003;6:4–7.
2. Banadiga NV. Grudne vigodovuvannya ta stanovlennya imunitetu u ditini (Breastfeeding and formation of immunity in child). *Klin Immunol Alergol Infektol*. 2006;3:5–8.
3. Besh LV. Alergichnyy marsh: perspektivi profilaktiki i prognozu (Allergic march: prospects for prevention and prediction.) *L'viv: Kamenyar*; 2010. 68 p.
4. Besh LV. Problema disbakteriozu kishchnika u praktitsi dityachogo alergologa: diskusiyni pitannya i mozhlyvosti ikh virishennya. (The problem of intestinal dysbiosis in children's allergist practice: discussion questions and their possible solution). *Pediatrics Akusherstvo Ginekologiya*. 2010;3:12–13.
5. Bodnya EI, Bodnya IP. Klinikoimmunologicheskie aspekty parazitarnykh bolezney (Clinical and immunological aspects of parasitic diseases). *Zdorov'ya Ukraini*. 2008;2:18–19.
6. Vinnits'ka OV. Gel'mintozi: diagnostichnyy poshuk ta likuvannya (Helminthes, diagnostic search and treatment). *Zdorov'ya Ukraini*. 2009;4:11–13.
7. Gnateyko OZ, Sadova OM. Regional'nye osobennosti al-lergicheskikh zabo-levaniy u detey L'vovskoy oblasti i osnovnye faktory, otvetstvennye za ikh razvitie (Regional features of allergic diseases in children in Lviv region and the main factors responsible for their development). *Sovremennaya pediatria*. 2004;3:59–61.
8. Zerbino DD. Ekologiya lyudini. Ekologichna patologiya. Ekologichni khvorobi (Human Ecology. Environmental pathology. Environmental illness). *Mistetstvo likuvannya*. 2010;1:86–90.
9. Kazmirchuk V E. Allergiya i psevdooallergiya: pora ne putat' eti ponyatiya (Allergies and pseudoallergy: It is time not to confuse these concepts). *Klin imunol Alergol Infektol*. 2008;3:11–15.
10. Nagorna NV, Dubova GV. Ekologiya ta alergichna patologiya u ditey: medikosotsial'ni aspekti (Ecology and allergic disease in children: medical and social aspects). *Alergiya u ditini*. 2009;1:30–32.
11. Polozenko OV. Negativnyy vpliv stresiv na zdorov'ya lyudini (The negative impact of stress on human health). *Zdoroviy sposib zhittya*. 2006;14:44–46.
12. Gorovenko NG, et al. Ranni klinikolaboratorni diagnostichni kriterii imunodefitsitiv (Early clinical and laboratory diagnostic criteria of immunodeficiencies). *Informatsiyiny list NMAPO imeni P.L. Shupika*. Kyiv: NIFP; 2004. 5 p.
13. Revyakina VA, Netrebekno OK. Allergicheskie zabo-levaniya u detey i okruzhayushchaya sreda (Allergic diseases in children and the environment). *Kyiv: ReklamaPrint*; 2005. 239 p.
14. Totolyan AA. Immunoglobulin E: struktura, produktsiya, biologicheskie efekty i diagnosticheskoe ispol'zovanie (Immunoglobulin E: structure, production, biological effects and diagnostic use). *Allergologiya*. 1998;2:4–7.
15. Perzanowski MS, et al. Atopy, asthma and antibodies to Ascaris among rural and urban children in Kenya. *J Pediatr*. 2002;140:582–588.

18. Childhood exposure to infection and risk of adult onset wheeze and atopy [Text] / C. Border [et al.] // *Thorax*. – 2007. – V. 55. – P. 383–387.
19. Breastfeeding and allergy counselling: theory and practice [Text] / T. Arvola [et al.] // *Acta Paediatr.* – 2000. – V. 89. – P. 365–374.
20. Comparison of cigarette smoke-induced acute inflammation in multiple strains of mice and the effect of a matrix metalloproteinase inhibitor on these responses [Text] / A. Morris [et al.] // *J. Pharmacol. Exper. Therap.* – 2008. – V. 327, № 3. – P. 851–852.
21. Concentration of total serum IgE in parasitized children and the effects of the antiparasitic therapy on IgE levels [Text] / B. Durmaz [et al.] // *J. Trop. Paediatr.* – 1998. – V. 44, №2. – P. 121.
22. Detection of specific IgE to human milk proteins in sera of atopic infants [Text] / A. Cantisani [et al.] // *FEBS Lett.* – 1997. – V. 412. – P. 515–517.
23. Eliminating a region of respiratory syncytial virus attachment protein allows induction of protective immunity without vaccine-enhanced eosinophilia [Text] / T. E. Sparer [et al.] // *J. Exp. Med.* – 1998. – V. 49. – P. 1921–1926.
24. Hall, C. B. Respiratory syncytial virus and parainfluenza virus [Text] / C. B. Hall // *N. Eng. J. Med.* – 2001. – V. 344. – P. 1917–1924.
25. Mangan, N. E. Helminthmodified pulmonary immune response protects mice from allergeninduced airway hyperresponsiveness [Text] / N. E. Mangan, A. N. McKenzie, P. G. Fallon // *J. Immunol.* – 2006. – V. 176, № 1. – P. 138–147.
26. Padgett, D. How stress influences the immune response [Text] / D. Padgett, R. Glaser // *Trends in immunology.* – 2003. – V. 24, № 8. – P. 444–457.
27. Serum IgE levels in white and Metis communities in Saskatchewan [Text] / J. W. Gerrard [et al.] // *Ann. of Allergy.* – 1976. – V. 37. – P. 91–100.
28. The hyper IgE syndromes [Text] / A. F. Freeman [et al.] // *Immunol Allergy Clin North Am.* – 2008. – V. 28 (2). – P. 1–14.
16. Bonneau R, Kiecolt-Gloser J. Stress-induced modulation of the immune response. Columbus (Ohio); 2011. 270 p.
17. Bowis, J. Allergic diseases. Minor irritation or major aggravation. USB Pharma SA; 2009. 23 p.
18. Border CC et al. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax*. 2007;55.:383–387.
19. Arvola T, et al. Breastfeeding and allergy counselling: theory and practice. *Acta Paediatr.* 2000;89:365–374.
20. Morris A, et al. Comparison of cigarette smoke-induced acute inflammation in multiple strains of mice and the effect of a matrix metalloproteinase inhibitor on these responses. *J Pharmacol Exper Therap.* 2008;327(3):851–852.
21. Durmaz B, et al. Concentration of total serum IgE in parasitized children and the effects of the antiparasitic therapy on IgE levels. *J Trop Paediatr.* 1998;44(2): 121 p.
22. Cantisani A. et al. Detection of specific IgE to human milk proteins in sera of atopic infants. *FEBS Lett.* 1997;412:515–517.
23. Sparer TE, et al. Eliminating a region of respiratory syncytial virus attachment protein allows induction of protective immunity without vaccine-enhanced eosinophilia. *J Exp Med.* 1998;49:1921–1926.
24. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Eng J Med.* 2001;344:1917–1924.
25. Mangan NE, McKenzie AN, Fallon PG. Helminthmodified pulmonary immune response protects mice from allergeninduced airway hyperresponsiveness. *J Immunol.* 2006;176(1):138–147.
26. Padgett D, Glaser R. How stress influences the immune response. *Trends in immunology.* 2003;24(8):444–457.
27. Gerrard JW, et al. Serum IgE levels in white and Metis communities in Saskatchewan. *Ann of Allergy.* 1976;37:91–100.
28. Freeman AF, et al. The hyper IgE syndromes. *Immunol Allergy Clin North Am.* 2008;28(2):1–14.