ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 12, pp. 22177-22181, December, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

IMMUNOLGY OF INFECTIONS: CURRENT STAGE. IMMUNOLOGY OF CHILDHOOD

Zemskov A M[1]., Zemskov V M*[2]., Shishkina V V[1]., Zemskova V A[1] and Chernitsyn I M[1]

[1]Burdenko Voronezh State Medical University, Voronezh, Russia
[2]Vishnevsky Institute of Surgery, Moscow, Russia

DOI: http://dx.doi.org/10.24327/ijrsr.2017.0812.1216

ARTICLE INFO

Article History:

Received 18th September, 2017
Received in revised form 10th October, 2017
Accepted 06th November, 2017
Published online 28th December, 2017

Key Words:

Immune System, Anti-infectious Resistance, Infections.

ABSTRACT

The article analyzes the data on the immune system development and response in fetus. It describes critical periods of development and course peculiarities of infectious diseases in children, and their relations with complicated pregnancy and birth.

INTRODUCTION

Fetus immunology

Thymus

Thymus starts forming in the 2nd month of fetal life in the area of the third-fourth visceral pouches, and at first has an expressed epithelial character at the 6th week. Lymphocyte-like cells inhabit it in the 7-8th weeks. By the end of the 3rd month the organ is completely formed. Only qualitative alterations can be observed in it at a later stage (Zemskov *et al*., 2013).

Lymphatic nodes and other secondary organs of the immune system

These organs start forming in the 4th month, their final formation is completed in the post-natal period. Lymphoid follicles packed in the ileum and appendix, in the

Peyer's glands, contain precursors of plasmatic cells. They develop to mature plasmatic cells synthesizing IgA by the 14-16th weeks of fetal life (Zemskov *et al*., 2013).

Stem cells

They appear in the 3-8th weeks of embryogenesis and are at first found in the liver and the yolk sac blood islands. Bone marrow becomes their major producer at a later stage.

Lymphocytes

They are at first found in the thymus in the 9th week, then in the spleen in the 12-15th weeks. Lymphocyte-like cells are determined in blood starting with the 8-10th weeks.

T-lymphocytes

Lymphoid cells having this function are revealed in the 10-11th weeks.

B-cells

They are determined in the liver starting with the 10-12th weeks, in the spleen-starting with the 12th week.

Immunoglobulins M and G

In children IgM synthesis and secretion are registered in cells in the 11th week, IgG synthesis and secretion are registered in the 22nd week. IgM content amounts 1/10 of the maternal amount, and IgG-even less.

Immunoglobulin translocation starts in the system "mother-fetus" at the end of the 1st- beginning of the 3rd trimester of pregnancy. It should be noted that placenta behaves as an organ having an expressed selective permeability, since transplacental transfer is available only for IgG out of five classes of

*Corresponding author: **Zemskov V M**
Vishnevsky Institute of Surgery, Moscow, Russia

immunoglobulins. Maternal antibodies passing through a placenta protect a fetus, and then a baby, from infectious diseases that a mother has had. But in those cases, when a mother is immunized by fetus antibodies, pathologies occur. Anti-placental antibodies may condition increased placental permeability for organ antigens, and in certain cases result in termination of pregnancy (Zemskov *et al*., 2013).

Immunology of a baby

A healthy mature baby born by a healthy mother with physiological course of pregnancy has a certain immune status and an adequate level of factors of non-specific anti-infectious resistance. Neonatal period, especially early period of adaptation, is considered to be determining in terms of survival and quality of the succeeding life. Adaptation of a newborn's body to extrauterine life results from radical functional reconstruction of all organs and systems. The immune system together with the nervous and endocrine systems appears to be integrating, responsible for preservation of the internal environment stability of a fetus and a newborn body under stress and high antigen load at birth and in the post-natal period. It is the state of the immune system, that finally determines baby's survival and quality of life, level of disablement or rehabilitation. However, the state of the immune system of a newborn cannot be defined as immunodeficient. Together with the decrease of some parameters (e.g. level of γ-interferon production, level of molecule class II expression of the main complex of histocompatibility on monocyte-macrophage cells) a wide range of the most important immunity values in mature newborns (monocytes and macrophages ability to produce interleukin-1, tumor necrosis factor-α, level of interleukin-2 produced by lymphocytes and others) is compared with that in adults. Certain immunity characteristic of a newborn is significantly higher than similar findings in adults (level of lymphocyte spontaneous proliferation in the reaction of blast-transformation, cytotoxic activity of lymphokine-activated killers and so on). A mature newborn has a specific, different from adults, biologically viable state of the immune system that prevents development of excessive reactions of the systemic inflammation, autoimmune processes, proper organs and tissues destruction, shock. The neonatal immune system helps a baby to survive in the conditions of intensive skin and mucosa colonization by microflora, and in case of inaccessible auto-antigens entry into the systemic blood flow on the background of perinatal hypoxia and damage of biological barriers penetration. It is built to gradually obtain the information about the environment in the early childhood and gradual formation of the normergic immune response. One of the leading mechanisms in the post-natal adaptation of the immune system of newborns is activation of the system of cytokines which play an important role in defense against microorganisms colonizing baby's skin and mucosa, activating phagocytosis and triggering immune processes in T-lymphocytes. In the early period of adaptation laboratory signs of the systemic inflammatory reaction are reported in healthy newborns on the background of high antigen load (increased serous level of interleukine-1, tumor necrosis factor-α, acute phase proteins). In physiological conditions it is not accompanied by the development of clinical signs of the systemic inflammation, infectious toxicosis and polyorgan insufficiency. The following factors encourage development of infectious-inflammatory disorders of bacterial, viral and fungal etiology in newborns, especially in preterm newborns: little transplacental transfer of maternal antibodies class IgG until 35-36 weeks of gestation; insufficiency (CD19+) B- lymphocytes of a fetus and newborn to switch synthesis of IgM immunoglobulins to IgG immunoglobulins; increased consumption of immunoglobulins in the early period of adaptation on the background of skin and mucosa colonization by the environmental microflora; apoptosis of immature B-lymphocytes of a newborn under massive microbial invasion (Volodin *et al*., 2002, Khaitov *et al*., 2009). We can observe ***physiological leukocytosis*** that reaches 12-15·10^9cells/l in newborns at the moment of birth. T-cells constitute more than 35% of all cells. Their number is moderately decreased in relative values, but this number is permanent in absolute values considering leukocytosis. 60% of all T-lymphocytes are cells with helper functions, 15% - T-suppressors/ cytotoxic. Content of antibody-dependent killers is also considerably decreased comparing to the level of adults.

Characteristics of lymphocytes

T-cells constitute approximately half of the total number of lymphocytes. The total number of the peripheral blood lymphocytes at birth in the first day constitutes 24-30%, and the absolute number-3-9 bln/l. After that their relative number increases and by the 4-5th day it reaches 40-50%, the absolute number-2.5-10 bln/l. Lymphocytes of newborns are different and characterized by high metabolic activity, their DNA and RNA synthesis is increased. Blast transformation reaction is well expressed on the background of cultivation with PHA in both-mature and preterm newborns. High level of spontaneous transformation is registered in 6-10% average, where, as in adults, this value is about 0.2%. In general babies have the following peculiarities of the immune status chains.

T-component of the immunity

The number of T-lymphocytes is prevailing at birth but they appear to be underactive. In newborns 50-65% of T-cells belong to T-helpers; 25-30% - to T-suppressors/cytotoxic. In preterm babies T-lymphocytes express thymic antigens in the neonatal period.

B-component of the immunity

Unlike the cell immunity, the humoral immunity system starts to actively function only after birth under the influence of antigenic excitation. The number of B-cells, mostly immature, is stimulated at birth. IgG content in blood is usually higher than in a mother's body, since transplacental transfer of this immunoglobulin is an active process. IgM in the serum is usually absent or determined in minimal amounts. IgA, as a rule, are absent or appear in trace concentrations. By the end of the first week the amount of IgA and IgM is slightly increased. The amount of IgG is significantly decreased by the 2nd-3rd weeks and reaches minimal concentrations at the 1-4thmonths. In general, isotypic class switching of immune globulins is delayed.

Phagocytic component

The number of neutrophils in blood is relatively high at birth: 50-70% and 4.5-20 bln/l. It starts decreasing to 30-40% - 2.5-6 bln/l on the 4th day. Monocytes constitute 4-9% - 0.6-2 bln/l

during the whole newborn period. Neutrophils absorbing capacity is not decreased, however, their digestive activity is weakened, this results in incomplete phagocytosis. The number of NBT-positive neutrophils in the spontaneous reaction (reflects oxygen cell metabolism at the level of superoxide anion generation) constitutes 14-20% in babies of the first two weeks of life, whereas in the alternative age-2-10%. The rise of these cells' number in the induced test is not very high, i.e.phagocytic reserve at this age is not considerable. Monocytes of newborns are characterized by low bactericidal activity and insufficient migration capacity.

Critical periods in the life of a child

Currently they distinguish six critical periods in the life of a child, which are characterized by the most body vulnerability (Zemskov *et al*., 2016).

The first critical period

The critical period of the fetal life is considered to be the period of 8-12 weeks, when differentiation of the organs and cells of the immune system occurs.

The second critical period

The second critical period is the period of neonatality, when a body is exposed to the impact of a great number of antigens. The immune system is susceptible to severe suppressive influences at this time, and the passive humoral immunity is conditioned by maternal antibodies. There has been registered functional disbalance of T-lymphocytes, and not only CD8-cells, but also immature thymocytes and other cells realize their suppressive function.

The third critical period (3-6 months)

The third critical period is characterized by the weakened passive humoral immunity in relation with catabolism of maternal antibodies. In such a case, the suppressive directionality of the immune reactions is preserved on the background of expressed lymphocytosis. The primary immune response with dominating IgM synthesis without the immune memory formation develops to the most antigens. This type of the immune response occurs in vaccination against tetanus, diphtheria, pertussis, poliomyelitis, measles, and the secondary immune response with IgG-antibodies formation and stable immune memory develops only after the 2^{nd}-3^{rd} vaccination.

The fourth critical period

The fourth critical period is the second year of life of a child. The primary character of the immune response to many antibodies is preserved at this period, but, switching to IgG-antibodies formation is possible. However, synthesis of IgG2 and IgG4 subclasses is delayed. Suppressive directionality of the immune mechanisms starts to change into helper directionality. The system of local immunity is not developed; children are susceptible respiratory viral infections.

The fifth critical period

The fifth critical period is the 4^{th}-6^{th} years of life. At this age average IgG and IgM concentration in blood corresponds to the level of adults, IgA concentration in plasma does not reach its final values, however, IgE content in blood amounts to maximal values. This period is characterized by the high frequency of atopic, parasite, immune-complex diseases.

The sixth critical period

The sixth critical period is, as a matter of fact, the pubertal period (in girls from 12-13 years, in boys from 14-15 years). A pubertal growth spurt is combined with decreased mass of the lymphoid organs. Increased secretion of the reproductive hormones (firstly, androgens) leads to suppression of the cellular component of the immunity and stimulation of its humoral mechanism.

Clinical groups of high risk ARVI development in children

Group I-newborns and babies of the early age (several months-2 years)-physiological immunodeficiency.
Group II-children with the late start of the immune biological reactivity.
Group III-children with low body mass, imbalanced feeding, hypotrophy.
Group IV-children born in ill pregnant women (viral infections, pyelonephritis, urethritis, pyodermia and others).
Group V-children of older age with chronic heart, lung, kidney and others diseases).

Peculiarities of infections in children

At the end of the XX^{th} century it was widely stated by the leading global scientists that appearance of new anti-bacterial and anti-viral preparations, vaccines, use of modern methods of prevention allow completely eliminating infections, at least in the developed countries. This concept appeared to be completely false (Pokrovsky *et al*., 2013). Analysis of the inpatient structure for the recent decade demonstrated decreased incidence of such infections as measles, mumps. This was obtained due to improved methods of prevention and, primarily, mass vaccination. WHO programs on elimination of infections in children (programs on measles elimination and decreased morbidity of German measles and mumps) played a great role in this. A significant decrease of the incidence of German measles was registered with the introduction of mass vaccination against this disease, but the level of isolated cases has not been obtained yet; the incidence level is 6.79 per 100 000 people. Mump incidence in children has reduced to 3.33, but this finding is higher than the target determined by WHO-no more than 1 ill child per 100 000 children (Zemskov *et al*., 2015).

Mass vaccination against pertussis started in 60-70s hasled to significant decrease of the disease morbidity (from 400-500 per 100 000 people to 30-50 per 100 000 people) and mortality. However, dynamics of the decreased incidence of pertussis has been decelerated recently. Thus, in children it constitutes 15.8 per 100 000 people, and no vaccination is done in adults. The alarming fact nowadays is the incidence of pertussis in vaccinated children. Poliomyelitis elimination has resulted in not only the absence of clinical cases of the disease, but also disappearance of wild strains of the virus from the environment.

The incidence of viral hepatitis A, B, C is also reducing. The fact of 23.2% decrease of hepatitis B incidence is especially pleasant. The alarming fact was the fact of growth of

uncontrolled infections for the past year: acute enteric infections, especially caused by the specified causative agents,- by 11.4%, anthrax-in 8 times, hemorrhagic fevers-in 1.8 times, brucellosis-by 41.2%, rabies-in 2.1 times, trichinosis - in 2 times, a disease caused by human immunodeficiency virus-by 18.9%. The highest incidence is the incidence of respiratory infections and influenza. According to the official data the incidence of influenza is annually decreasing nowadays. They distinguish the following peculiarities of the current epidemiological situation in influenza: 1) several influenza viruses are circulating simultaneously: A (H3N2, H1N1, H5N1, H7N7, H9N7) and B; 2) there are cases in people caused by the bird flu virus; 3) the world is waiting for the possible appearance of a new influenza virus extremely dangerous for a human; 4) the number of mixed infections of virus-viral and virus-bacterial etiology is increasing. Influenza virus was revealed most frequently; in this context influenza A virus was registered more often. The second more often was parainfluenza; in this context, parainfluenza virus was mostly often reported in children under 3, their proportion constituted 42.1% of all parainfluenza cases. Parainfluenza type III prevailed in preschool children. Adenovirus infection was mostly often registered in children under 6. Respiratory syncytial virus was not found in the examined children.

Microflora of the oral cavity is the important factor of the infection development in children. Staphylococcus aureus and β-hemolytic streptococcus group A were reported to be the prevailing pathogenic flora in the oral pharynx. Opportunistic microorganisms with the heavy growth excluding fungi and associations with pathogens were revealed in 24.7% of people. They included Streptococcus viridans-52.2%; Staphylococcus epidermidis - 30,4%; Staphylococcus war.-13,0%; Bronch. Catarralis- 4,3%. On this background, Candida fungi with the high level of bacterization were found in 9.7% of all examined pre-school children.

Purulent otitis media

The following signs and symptoms were observed in this disease in children: inhibition of T-component of the immunity, decrease of the number of natural killers, decrease of neutrophil metabolic activity, decrease of IL-4 concentration responsible for CD4+ T-lymphocytes activation on the background of IgM, IgG hyper immune-globulinemia,CIC and pro-inflammatory cytokine IL-8 accumulation. The presence of expressed inflammatory process was evident in patients. Components of the formula of immune system disorders (FISD) including three parameters to the most extent altered from the standard level of healthy people were determined with the help of the coefficient of diagnostic consideration calculated on the basis of the analysis of mean values dynamics and their dispersion. They appear to be $CIC_3^+IgM_2^+NK_2^-$ - excess of circulating immune complexes of the limited evidence, accumulation of heavy IgM and deficiency of natural killers, II degree. The indicated state of the immune reactivity proves decrease of defense reaction expressiveness; this can lead to the pathologic process chronization, its recurrences, development of concomitant complications.

Meningitis in children

Serous meningitis

The following signs and symptoms are evident in patients in the acute period: disbalance of the immune system, T-cytotoxic/ suppressive cells deficiency, CIC excess, decrease of the complement content. Increased leukocyte level, IgA decrease, activated NBT expressiveness are significantly determined. B- and T-components of the immunity appear to be markers of the immune disorders: $B_1^-(Tc_2^-IgA_2^-)T_1^-$. Formula analysis reveals immune-suppressive directionality of alterations.

Purulent meningitis

Expressiveness of the immune disorders was more severe than in serous meningitis. There were revealed the excess number of leukocytes, IgA, IgM and insufficient amount of B-cells and T-helpers, IgG, activity of spontaneous and induced NBT and a complement. The following findings were taken as leading findings with the help of the diagnostic consideration coefficient: $Tx_1^-IgA_2^+T_1^-$ (Zemskov *et al*., 2007).

Children's morbidity in complicated pregnancy and birth

Direct correlation between the phagocytic number in umbilical cord blood and latency period with the correlation coefficient (r=0, 46) was found when performing a correlation analysis in children. Reverse correlation was revealed between gestosis and CD95+ lymphocyte level (r=-0, 48), activated NBT (r=-0,42) in umbilical cord blood. Positive correlation was reported between the presence of gestosis and CD8+ lymphocyte content in umbilical cord blood (r=0,43). Multi directional correlations were determined between IgG concentration on the 5th day and breathing disorders ((r=-0.44), duration of artificial lung ventilation (r=-0.43), gestosis (r=-0.43), acute renal failure in newborns (r=-0.43), jaundice duration (r=-0,47). In addition to this, unidirectional correlation between CD95+ lymphocyte level on the 4-5th day and hydramnios (r=0.43), between the CD56+ lymphocyte number on the 4-5th day and perinatal affection of the CNS (r=0.47) was also marked. The performed correlation analysis revealed negative dependence between NBT active in umbilical cord blood and hypamnions (r=-0.43), between the level of CD4+ lymphocytes on the 4-5th day and hydramnios (r=-0.45), vaginal candidosis in mother during pregnancy (r=0.53), endometritis (r=-0.57). There was also found negative correlation between IgG level in umbilical cord blood and herpes viral infection in mother during pregnancy (r=-0.45). Based on this analysis and considering all the above mentioned correlations we can assume that somatic and gynecologic maternal pathologies, as well as complicated pregnancy course, have an impact on the immune status formation of a newborn (Bugrym, 2011).

The performed study has demonstrated that children having suffered from severe asphyxia have alterations of the immune findings typical for infectious diseases. Considering this fact, children having suffered from severe asphyxia need administration of an individual immunocorrecting therapy aimed to stimulate various components of the immune system.
Impact of the immune status on the resistance level has been specified in children having suffered severe asphyxia. Thus, statistically significant negative correlation of the CD3+ lymphocytes level and the resistance level (R^2= -0.12, p=0.02)

has been specified in children at birth; this means that the increase of CD3+ lymphocytes number results in the low index value of acute diseases. Investigating dynamics of CD3+ lymphocyte values from birth to the 4-5th day of life in the examined group of patients, the authors revealed that the index value of acute diseases and the body resistance level significantly depend on the dynamics of CD3+ lymphocyte values level (R^2=0.10, p=0.04), i.e. the increased difference of values from the first to the fifth day of life resulted in the increased index values of acute diseases. When investigating CD4+ lymphocyte values at birth, authors received data about the dependence of the resistance index on CD4+ cells level (R^2=-0.11, p=0.03); thus, the less the number of CD4+ cells, the higher the index of acute diseases. Correlation between the CD8+ cytotoxic T-lymphocyte level at birth and the resistance index was also revealed (R^2= -0.16, p=0.01), i.e. the decreased number of CD8+ cells resulted in the increased index value of acute diseases.

The index of acute diseases was found to be dependent on the CD19+ at birth (R^2= -0.12, p=0.02), i.e. the less the number of CD19+ cells, the higher the index of acute diseases. Correlation between the index of acute diseases and dynamics of CD95+ lymphocyte values from birth to the 4-5th day of life (R^2=-0.10, p=0.04) was determined. Decreased difference of values from the first to the fifth day resulted in the low level of resistance, with the increased index values of acute diseases. IgA level in umbilical cord blood correlated with atopic dermatitis (p=0.01, R^2= 0.25) and anemia (p=0.03, R^2= 0.27). Significant correlation of the CD56+ lymphocyte level in umbilical cord blood and intestinal disbiosis (p=0.04, R^2= 0.17), urinary tract infections (p=0.04, R^2= 0.05), vulvovaginitis (p=0.009, R^2= 0.31) were revealed. It should be noted that no significant correlations between the resistance level and the CD56+ lymphocyte level (R^2= -0.03, p=0,7); CD95+ (R^2= -0.001, p=0.33); NBT spontaneous(R^2= -0.007, p=0.27); NBT active (R^2= -0.035, p=0.15); the neutrophil activation index (R^2= -0.03, p=0.9); phagocytic value (R^2= -0.06, p=0.09); phagocytic number (R^2= -0.019, p=0.5); IgA (R^2= -0.033, p=0.16); IgG (R^2= -0.03, p=0.8); IgM (R^2= 0.02, p=0.5) were revealed; no correlation between the index of acute diseases and immune values on the 4-5th day was also found.

CONCLUSION

Thus, this work analyzes the immune system reaction in fetus, describes in details immunology of a baby with various conditions of the immune system compartments. It determines critical periods of the development and course peculiarities of infectious diseases in children, their relations with the complicated pregnancy and births. The authors also specify clinical groups of high risk infections development in children.

References

1. Bugrym N.V. Peculiarities of cell and humoral immunity in newborns, Cand. *Dissert. Voronezh*. 2011.174 p. Russia.
2. Volodin N.N., Degtyareva M.V., Dmitrieva S.V. *et al*. Reference book in immunotherapy. Moscow. Publishing House:"Dialog". 2002. 479 p. Russia.
3. Zemskov A.M. Zemskov V.M., KorotkikhI.N. *et al*. Immune disorders and their correction in purulent-inflammatory processes. Moscow. Publishing House: "Triada-X". 2007. 159 p. Russia.
4. Zemskov A.M., Zemskov V.M., Zemskova V.A., Zoloedov V.I. Reference book of a clinical immunologist "Theoretical, practical and applied aspects of the clinical immunology at the current stage". Moscow. Publishing House: "Triada-X". 2015. 704 p. Russia.
5. ZemskovA.M., EsaulenkoI.E., ChereshnevV.A., ZemskovV.M., SuchkovS.V., KozlovV.A., KaraulovA.V., KonoplyaA.I., Bolotskih V.I., PopovV.I., LutskyM.A., Evsegneeva I. V., ZemskovM.A., Zemskova V. A., ZoloedovV.I. Immunology. Electronic textbook with applications. Approved by FIRO. Moscow. Publishing House:"GEOTAR-Media". 2016. 127 authorlists. Russia. http://www. studentlibrary.ru/ru/book/01-GEO-201601.html.
6. Pokrovskiy V.I., Pak S.G., Briko N.I. Infectious diseases and epidemiology. A guidebook. Moscow. 2013.1008 p. Russia.
7. ZemskovA.M., ZemskovV.M., Chereshnev V.A. (Ed.) Immunology. Encyclopediain 5 volumes. Publishing House: "Triada-X". Moscow. 2013. 1962 p.
8. Khaitov R.M., Pinegin B.V., Yarilin A.A.. A guidebook in clinical immunology. Diagnostics of the immune system disorders. Moscow. Publishing House: "GEOTAR-Media". 2009. 345 p. Russia.

How to cite this article:

Zemskov A M *et al*.2017, Immunolgy of Infections: current stage. Immunology of childhood. *Int J Recent Sci Res.* 8(12), pp. 22177-22181. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0812.1216

****