The newborn's immune system

O sistema imunológico do recém-nascido

Lílian Martins Oliveira Diniz[1] Bruna de Campos Guimarães e Figueiredo[2]

ABSTRACT

Newborns and young infants present an immature immune system, which makes them more susceptible to infectious agents present during this period. It is known that newborns are more vulnerable to infections than children and adults. Observed differences in the innate and adaptive immunity are responsible for decreased neonate's defenses. The defects in the adaptive immunity require previous contact with antigens, while the innate system requires no prior immune experience. The innate immunity is the first line of defense against pathogens and is composed by the responses from granulocytes, monocytes, macrophages, and dendritic and natural killer cells. Some pathogens, responsible for intra-uterus, intra-partum, and postpartum infections stimulate fetal and neonatal immune responses. These agents include the group B streptococcus, Escherichia coli, Listeria monocytogenes, herpes simplex virus, Cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, respiratory syncytial virus, Toxoplasma gondii, and Candida albicans. A better understanding of the functioning of the immune system in the neonatal period allows the doctor to perform preventive and therapeutic measures that improve the care of infections during this period. This review aims to discuss recent advances and current understanding on the newborn's immunity focusing on immunological aspects related to their enhanced susceptibility to infections, which are responsible for significant morbidity and mortality in the neonatal period.

Key words: Immune System; Infant, Newborn; Infant; Infection; Immunity, Innate; Noxae.

[1] Ph.D. in Health Sciences: Children and Adolescent Medicine. Adjunct Professor at the Department of Pediatrics at the Medical School from the Federal University of Minas Gerais (UFMG). Member of the Pediatric Infectious Diseases Group from the Medical School from UFMG. Belo Horizonte, MG – Brazil.
[2] Pediatrician and Immunologist. Mater Dei Hospital. Belo Horizonte, MG – Brazil.

RESUMO

Os recém-nascidos e lactentes jovens apresentam seu sistema imunológico imaturo, o que os torna mais suscetíveis aos agentes infecciosos presentes nesse período. Sabe-se que os neonatos são mais vulneráveis às infecções que as crianças e os adultos. Diferenças observadas na imunidade inata e adaptativa são responsáveis pelo prejuízo das defesas do neonato. Os defeitos da imunidade adaptativa requerem o contato prévio com antígenos, enquanto o sistema inato não necessita de experiência imunológica prévia. A imunidade inata é a primeira linha de defesa contra os patógenos e é composta pela resposta de granulócitos, monócitos, macrófagos, células dendríticas e natural killer. Alguns patógenos responsáveis pelas infecções intraútero, intraparto e pós-parto estimulam a resposta imune fetal e neonatal. Esse agentes incluem o estreptococo do grupo B, a Escherichia coli, a Listeria monocytogenes, o herpes simples, o citomegalovírus, o vírus Epstein-Barr, o vírus varicella-zoster, o vírus respiratório sincicial, o Toxoplasma gondii e a Candida albicans. O melhor entendimento do funcionamento do sistema imunológico no período neonatal é capaz de tornar o médico apto a desempenhar medidas preventivas e terapêuticas que melhorem os cuidados das infecções durante esse período. Essa revisão tem como objetivo discutir avanços recentes e o entendimento atual da imunidade do recém-nascido, dando ênfase aos aspectos imunológicos relacionados à acentuada suscetibilidade às infecções, as quais são responsáveis por significante morbimortalidade no período neonatal.

Palavras-chave: Sistema Imunológico; Recém-Nascido; Lactente; Infecção; Imunidade Inata; Substâncias Nocivas.

Corresponding Author:
Lílian Martins Oliveira Diniz
E-mail: lilianmodiniz@gmail.com

INTRODUCTION

The newborn's immune system has limited ability to mount an effective response from the quantitative and qualitative point of view against invasive pathogens implying more susceptibility to infections. It is known that the earlier the gestational period, less developed is the immune system at birth, so that extreme premature neonates (< 28 weeks) can show 5-10 times higher rates of infection than term newborns.[1]

The neonate is highly dependent on the maternal passive transfer of antibodies during fetal and neonatal early life. The immune development will only be complete in late childhood.[1] Breast milk is an important example of the transfer of passive immunity in the post-natal period. It has antimicrobial, anti-inflammatory, and immuno-regulatory functions. It contains secretory IgA, which colonizes the gastrointestinal and respiratory tracts in the neonate, active cells (phagocytes, natural killer cells, and lymphocytes), cytokines (IL-4, IL-6, IL-8, IL-10) and lysozyme, lactoferrin, and peroxidase, and antimicrobial lipids.[2]

Lymphoid and myeloid progenitors that are in the yolk sac since the fourth week of gestation migrate to the liver, the primary hematopoietic organ during this period, where they proliferate suffering only a slight differentiation. Subsequently, they are found in the spleen, thymus, and bone marrow.[1] Immunity can be classified into innate (nonspecific) or acquired (specific), which, in turn, is divided into humoral and cellular immunity. Vaccines work by stimulating specific immunity, which is exercised by means of antibodies (humoral immunity) and lymphocytes with effector function (cellular immunity). Antibodies can be serum antibodies acting in the bloodstream or secretory antibodies blocking and preventing the penetration of microorganisms through mucous membranes. Defense against microbial invasions includes the rapid and independent antigen development from innate immunity and the slow and specific development of adaptive immunity.[1, 3, 4]

METHODOLOGY

This study constitutes a revision of the specialized literature in which scientific articles were consulted and selected from searches in the MEDLINE and LILACS databases. Articles of relevance and representative of the theme were selected, as well as text books on the subject.

REVIEW OF THE LITERATURE

The immunology in the fetus and newborn

Innate immunity

Innate immunity is the first line of defense upon exposure to an infectious agent and is activated regardless of previous contact with antigens. It is made up of epithelial barriers (skin and mucous membranes), cytokines, and proteins from the complement system and circulating cells (phagocytes and natural killer cells).[5]

The newborn's skin is immature and more permeable, possibly due to inadequate production of free fatty acids and alkaline pH. The breach of integrity in the skin that occurs during this period in hospitalized patients can act as a facilitator for the entrance of pathogens. The production of secretory IgA is absent in the first days of life, leading to a greater vulnerability of the mucous membranes to invasions by pathogenic microorganisms in the respiratory and gastrointestinal tracts.[3,4]

Cytokines are low molecular weight proteins, secreted in response to an antigen, which modulate the intensity and duration of the immune and inflammatory response. They are produced by phagocytes (macrophages and neutrophils), natural killer cells (NK), and T helper lymphocytes. The main cytokines in innate immunity are interferon α, β, and γ, tumor necrosis factor (TNF), and interleukins (1, 6, 10, 12, 15, 18).[4]

Proteins of the complement system are activated in a cascade and have as their function the opsonization of antigens and cell lysis from the formation of the membrane attack complex. They are reduced in newborns. During pregnancy, there is little maternal transfer of complement proteins. At birth, they reach levels approaching 60-90% of adult values in term newborns and 47-70% in preterm infants.[4] Levels similar to those of adults are only achieved after one year of age.[6]

The NK cell is a type of lymphocyte that destroys virus-infected cells, intracellular microorganisms, and neoplastic cells based on the production of γ interferon (INF γ). NK cells in newborns present reduced function with less cytotoxic action against viruses, although they are equivalent in numbers to those in adults.[4]

Mononuclear inflammatory cells, especially mastocytes and macrophages, are the sentinels of the de-

fense system against pathogens that win the epithelial barrier. They produce the tumor necrosis factor α (TNF α) that recruits innate system cells (neutrophils, monocytes, and dendritic cells) and modulates antigen presentation to T lymphocytes.[3,5] The newborn has monocytes and macrophages with reduced function that harm phagocytosis.[5]

Neutrophils are the latest cells to appear in the fetus and are only produced in large numbers after birth. They are reduced in number and effectiveness in the newborn. Its concentration increases dramatically between 12 and 24 hours after birth.[1] Impairment in chemotaxis, rolling, adhesion, and migration up to the site of infection, and reduced oxidative activity, which is its mechanism of cytotoxicity, are observed in newborns.[7] The newborn is less able to elevate the number of circulating neutrophils in response to a stimulus. Thus, it is believed that the inability to mobilize the medullary pool during stress is associated with septic conditions in this age.[1,3]

Other inflammatory mediators such as fibronectin, coagulation factors, and kinin system are also reduced at birth. All these deficits are partly responsible for the reduced ability to opsonization, reduced ability to lyse gram-negative bacteria and some viruses, low generation of inflammatory processes, and reduced chemotaxis of polymorphonuclear cells and monocytes.[4,6]

Adaptive immunity

The deficit in innate immunity entails reduced activation of the adaptive system because these two components are interlinked. The adaptive immune response is divided into cell-mediated response and antibody-mediated response. Lymphocytes are their effector cells.

Cellular immunity

Precursors of T cells are identified in the fetal liver in the seventh week of pregnancy; however, they still do not express CD3 on their surface. They migrate to the thymus where their proliferation is completed. Between 18 and 24 weeks, T lymphocytes are already in a similar number to that of an adult. It is in the thymus that the T cell receptor formation occurs giving the specificity and recognition capability of self to these cells (self).[1]

Although newborns present greater number of T cells in circulation at birth than adults, most are immature cells and a few are memory cells, a fact explained by the small intrauterine exposure to antigens.[1,4]

The cellular immunity is exerted by T lymphocytes with its subtypes T helper (CD3+ and CD4+) and T cytotoxic (CD3+ and CD8+). The T-helper lymphocytes have two subtypes, depending on its pattern of production of cytokines: Th1 that modulates cellular immunity and Th2 that stimulates humoral immunity.[1]

While B lymphocytes can recognize antigens directly with their antibodies, T lymphocytes can only recognize antigens that are presented by the antigen-presenting cells through class I and II major histocompatibility antigens.[4]

The fundamental properties of cellular immunity are the production of cytokines and cytotoxic activity. The most important cytokines in adaptive immunity are IL-2, 4, 5, 10, and 13 and INF γ and β and TGF β.[4]

The production of cytokines is diverted to the Th2 response profile until one year of age. The production of IL-12 that activates CD4 T lymphocytes to the Th1 profile is delayed in the newborn.[6] The Th1 response deficit seen in the neonate confers impairment in the cytotoxicity function.[7] Cytokines create an immunoinflammatory context that generates response amplification and recruitment of cells capable of interfering with the immune response. Thus, its deficiency causes problems throughout the immunity. The lowest production of cytokines (IL-2, IL-4, IL-6, and IL-10) in response to antigens occurs, in part, due to the low intrauterine exposure but also to the secretory and inhibitory function of the placenta.[4,7,8]

Humoral immunity

Humoral immunity is exerted by B lymphocytes, which stimulated by antigens, differentiate into antibody-producing plasmocytes. They are recognized for presenting the CD19 and CD20 markers on their surface.[4]

B lymphocytes precursors are in the liver at eight weeks where they begin their differentiation. After birth, the maturation of B cells occurs in the bone marrow. The production of fetal immunoglobulins already starts from the 10th week of gestation, reaching a peak in 26 weeks. From then on, it falls sharply until birth. This occurs due to the small intrauterine exposure to antigens and high levels of maternal immunoglobulins passively transferred to the fetus. Thus, at birth, the child presents low levels of immunoglobulins (IgM, IgA, and IgE), and the vast majority of IgG is of maternal origin.[1]

After birth, the self-production of immunoglobulins starts in response to food and environmental antigens. The period between the fall of maternal antibodies and the sustained production of antibodies is called transient or physiological hypogammaglobulinemia. It occurs between the third and fifth months of life, with full resolution between two and five years of age.[4]

Studies in humans and animals have shown that the effectiveness of antibodies produced by B cells in newborns differs from that observed in adults. The neonatal response is delayed, and antibodies show lower serum peaks and have a short duration. The reduced production of antibodies by B cells at this time is partially due to: maternal antibodies, B cells and T helper cells immaturity, their stimulant.[8]

For the class "switch" to occur, i.e. B lymphocytes presenting other classes of immunoglobulins on its surface, the interaction with CD4 T lymphocytes is necessary. Cytokine production occurs on the interaction between CD4 T lymphocytes Th2 pattern and B lymphocytes according to the predominance of some of them, B lymphocytes produce one or another class of immune globulin. This interaction is impaired in the newborn.[1]

The complete development of the lymphoid tissue microarchitecture happens after birth so that the germinal centers become apparent around the fourth month of life. It is likely that this development process can limit the antibody response in the neonatal period.[8]

Specific response to pathogens in the neonatal period

Group B Streptococci (EGB)

EGB is a major cause of bacterial infection in the neonatal period. Secondary mortality to this infection remains high in spite of advances in the intensive care of these patients. Colonization by pathogenic Group B streptococci is facilitated by their great capacity of adherence to mucosal epithelial cells in newborns and absence of secretory IgA in the first week of life.[6] In addition, the lack of specific maternal antibodies against the bacterial capsule polysaccharides combined with neonatal failure in the synthesis of specific antibodies are important contributing factors to the high mortality.[6]

Neutrophils are phagocytic cells present in circulation that significantly contribute to the death of EGBs. However, the limited genesis of chemotactic factors may delay the recruitment of neutrophils, whose adhesion capacity is deficient.[9] INF γ appears to increase protection in newborns promoting activation of neutrophils, however, their production is impaired in these patients. In addition, a deficiency in interleukin-12 production by phagocytic cells has been proposed recently as another mechanism associated with bad immune response to EGB.[7]

E. coli

E. coli is one of the main gram-negative bacteria that cause meningitis and sepsis in the neonatal period. The survival of the bacteria within the host's cells such as macrophages and monocytes in peripheral blood represents an important bacterium pathogenic mechanism.[7]

It is known that IgG cannot efficiently adhere to the bacteria surface thus, allowing the same escape to the mechanism of immune system recognition. The deficiency in the complement cascade observed in the cord blood of newborns also contributes to the defect in opsonization in neonates against E. coli. Therefore, the bacteria survival within macrophages may have an important role in the emergence of clinical conditions such as sepsis and meningitis.[7]

Listeria monocytogenes

Listeria infection in humans most commonly occurs in infants and young children or immunocompromised adults. Perinatal infection is usually caused by colonization or infection from the mother. Listeria monocytogenes causes a fulminant infection usually when acquired in utero or in the early neonatal period, whereas, when acquired later, it manifests as a meningeal infection of an insidious nature.[9]

The organism ability to defend from infection involves a large number of integrated responses, greatly influenced by the adaptive immunity, mainly determined by T lymphocytes and antibodies in which specificity, memory, and recognition of what is not self (non-self) are important features. Despite the innate immunity being effective in promoting some protection against bacteria, an adequate immune response is only possible with the emergence of acquired immunity.[7]

The bacteria initially induce a humoral immune response that consists in the synthesis and release of antibodies in the blood, from circulating plasma cells, which neutralize the exotoxins from the bacteria and promote their phagocytosis. The cellular response that follows is more important in this type of bacteria, which multiply intracellularly.[6] The macrophage activation is of paramount importance for an efficient destruction of bacteria and the activation by INF γ is fundamental in this process; its deficit production is related to scarcity and delay in the development of memory T cells in the neonatal period.[7,9]

Herpes-virus

The herpes virus is a pathogen capable of causing widespread and systemic infection or central nervous system disease with high mortality rates in the first few weeks of life. Congenital infection is usually caused by the herpes-virus type 2 present in the birth canal. Specific maternal antibodies in the newborn have an important role in the protection against disease development after exposure. Thus, it is known that the rates of infection in newborns to mothers with primary disease are higher than those observed in newborns to mothers with recurrent infections.[10]

Both cellular and humoral responses are involved in the control of herpes infection.[7] The cellular response by T lymphocytes, compromised in neonates, may be responsible for a rapid disease progression. The fatal evolution after the neonatal period is rare and affects children with T-cell related immunodeficiency, or in use of chemotherapy or radiation.[7] The delay in the response to the infection from Th 1 cells, proliferation of CD4 T lymphocytes, secretion of INF γ and tumor necrosis factor, and poor production of specific antibodies against the virus allow the infection to become widespread causing significant damage to all organs.[7]

Some studies show that there is significant production of IL-6 and IL-8 in term and pre-term newborns in response to infection by the herpes-virus. However, the overproduction of inflammatory cytokines seems to be associated with greater intensity in the clinical manifestations of the disease compared to those in adults.[7,10]

Cytomegalovirus (CMV)

CMV is the main cause of intrauterine infection, affecting 0.3 to 2.2% live newborns. Congenital infection is an important cause of hearing and visual deficiencies, or cerebral palsy in newborns. The virus can be transmitted to the fetus during the mother's primary infection and may also be transmitted years after the mother acquired the infection. Maternal antibodies do not prevent viral transmission but seem to protect the fetus from a massive infection reducing the intensity of symptoms.[9]

The host's immune response to CMV infection plays an important role as limiting the infection and clinical manifestations of the disease. Studies show that the great susceptibility of the fetus to CMV infection may be related to problems in cellular immunity, either innate (natural killer cells) or adaptive (T lymphocytes).

The specific response of CD4 and CD8 T cells to primary cytomegalovirus infection seems to be reduced when compared to the response observed in adults. The poor response of CD4 T cells is associated with prolonged elimination of the virus in infected patients urine, which suggests its fundamental role in the control of viral replication in mucosal surfaces.[10]

Recently, T cytotoxic lymphocytes (T CD8) have been described in newborns with congenital CMV infection. This finding suggests that intrauterine antigenic stimulation has the potential to stimulate a protective immunological response in the fetus and that, unlike CD4 T lymphocytes, the CD8 T lymphocytes response can be preserved. However, the efficiency of the response mediated by these cells in the newborn is not clear yet.[7,10]

Ebstein-Barr virus (EBV)

EBV infection occurring in early childhood is not associated to any specific clinical picture. However, when it occurs in the adolescence or in adults, a high proportion of individuals develop the clinical picture of mononucleosis, which occurs when the primary infection by EBV is not adequately controlled, leading to excessive stimulation of CD8 T cells by infected B lymphocytes. These findings suggest that the infection is better controlled in newborns and infants than in adults. This occurs because the CD8 T lymphocytes response seems to be reduced in newborns and infants, which explains the absence of disease clinical manifestations.[9]

Varicella-zoster virus

Fetal varicella syndrome occurs in about 2% of patients whose mothers develop chickenpox in the first

20 weeks of gestation. Chickenpox in the newborn may result from vertical or horizontal infection. Chickenpox acquired in the perinatal period (between five days before and two days after childbirth) occurs as the result of maternal viremia with virus transmission before the transmission of maternal antibodies. The visceral involvement and high mortality are characteristics of this disease presentation. Thus, innate immunity during the period in which the child is without maternal antibodies is critical for the control of infection.[7]

During pregnancy, maternal antibodies transmitted via trans-placenta to the child whose mother acquired chickenpox until six days before childbirth play an important role in protecting the newborn against disease manifestations.[7]

The exact role of humoral and cellular responses in the neonate for protection against the varicella-zoster virus has been continuously studied. However, the humoral response appears to not perform complete protection against the virus. Cell-mediated immunity and secretory immunity exert important roles.[7]

The large production of INF γ observed in patients with congenital varicella virus infection suggests that the Th 1 lymphocytes response is important as the first defense mechanism even if it is not effective to control the infection.[2] The failure to develop an adequate cellular immune response from T cells, macrophages, and natural killer cells has been correlated with the death of infected patients.[11]

Respiratory syncytial virus (RSV)

RSV infection is one of the most common diseases in the world, and it is estimated that every child is infected until the third year of life. The virus does not replicate outside the respiratory tree, being restricted to the respiratory mucosa infection. The clinical spectrum of the disease is extremely variable, from mild upper respiratory tract infections to severe pneumonia.

In the first days of life, the newborn is able to develop an innate response to the virus; however, due to lack of intrauterine antigenic stimuli, the adaptive response is necessary for the proper control of infection.[7] The toll-like 4 receptor (TLR4) participates in RSV recognition by innate immunity. Premature newborns have small amounts of TLR4 and reduced production of cytokines after its activation, which means increased susceptibility to infection by this virus.[12]

The efficient adaptive response to viral pathogens is mediated by cytokines produced by Th1 cells. However, their production can be inhibited by cytokines secreted by Th2 lymphocytes. Therefore, a suitable balance between these two is essential for the eradication of RSV.[7]

Viral proteins such as glycoproteins and fusion proteins are important for viral penetration in the host's cells and the start of an immune response reaction. They are capable of inducing the formation of neutralizing antibodies; however the response can contribute to lung disease in newborns. Similarly, some studies show that maternal antibodies passively transferred in the first months of life may contribute to more serious disease conditions.[7]

Toxoplasma gondii

Toxoplasma is an obligatory intracellular pathogen that affects especially fetuses and newborns. About 60% of maternal infections are not transmitted to the fetus because the placenta can act as a barrier to the hematogenous passage of tachyzoites, which occurs particularly in the third trimester. The disease can result in brain or eye lesions; however, disseminated infection is rare in the neonate. It is suggested that the different transmission rates depend on placental blood flow, virulence of the toxoplasma strain, genetic susceptibility of the patient, and the number of parasites.[11]

As in other congenital diseases, the severity of infection acquired during pregnancy relates to the ability of intracellular parasites to damage human fetal organs in formation, immunological immaturity of the fetus, and placental barrier separating maternal and fetal humoral responses.[7] The balance between Th1 and Th2 responses influence the presence or absence of clinical manifestations.[9]

Parasitemia stimulates the immune response in the host, initially humoral, and cellular after a few days. The activation of T lymphocytes leads to the production of a great number of interleukins and reduced parasitemia.[9] However, it is known that survival in the intracellular environment promotes the parasite's protection against the immune system.[14] INF γ plays an important role in the control of infection as a strong activator of infected macrophages limiting the intracellular growth of tachyzoites. However, the production of INF γ is hampered in neonates, which is an important factor related to the high susceptibility of newborns.[9]

Candidiasis

Candida albicans is the main species causing fungal infection in newborns accounting for 40 to 70% of cases of candidemia in these children. The skin is colonized at birth by Candida species that reside in the birth canal, and the fungus proliferation leads to mucous or mucocutaneous disease.

The inability to locate, monitor, and eradicate infections by *Candida albicans* is characteristic in this age group and stems from the relative deficiency of specific and nonspecific defense mechanisms predisposing to invasive fungal infections.[9] The increased susceptibility to infection in the neonate, in particular in the oral cavity, results from the immature response from CD4 T lymphocytes commonly observed at that age.[7] In addition, it is known that the role of passively acquired antibodies in the defense of newborns is insignificant.[7]

Mycobacterium tuberculosis

Tuberculosis infection in neonates usually manifests itself in a disseminated form and results in severe clinical pictures such as miliary tuberculosis or tuberculous meningitis. Such demonstrations are accompanied by immune deficient T cells response observed in the negative responses to cutaneous sensitivity tests.

The exact mechanism by which the bacterium escapes from the elaborate response from the immune system has not yet been explained. The resistance of Bacillus to macrophages has been well-studied. Viable Mycobacteria appear to inhibit the fusion of phagosomes with lysosomes, which contain toxic substances that promote the death of Bacillus.[13]

Cell-mediated immunity has been primarily responsible for the immune response to tubercle bacilli. The T-cell-mediated response is crucial in the process of establishment of immunologic memory and protection. In addition, the produced cytokines are able to direct the cells of the macrophagic system in order to contain and destroy infectious bacilli.[13]

The newborn is able to develop a significant number of INF γ produced by CD4 T cells in response to stimulation by the BCG vaccine with live attenuated Bacillus. However, the T cells response to the virulent Bacillus in infections by *Mycobacterium bovis* or *Mycobacterium tuberculosis* is still deficient.[10]

CONCLUSION

Newborns have limited defense capability against aggressions from their environment resulting from characteristics in their immune system at birth. This knowledge sustains the prevention of infectious diseases, whether from the early recognition and appropriate treatment of diseases already installed or especially from constraining the exposure of children to antigens during this period of immune weakness.

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