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Immunology of Neonates and Clinical Applications-An Overview

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Abstract

Congenital viral infections in neonates cause severe damage. However, these same viruses cause minor damage if infected after the neonatal period. This rapid response change from fetal immunotolerance to immune activation is very interesting and necessary for survival. Immunity is immature and non-focused in neonates, particularly in preterm neonates. If we introduce a foreign body in the form of formula milk to preterm neonates with an improper innate immunity barrier, the neonate will respond aggressively, causing self-damage in the form of necrotizing enterocolitis (NEC). Due to underdeveloped innate immunity barriers, skin allergens are also common in infants. Immunotolerance is a necessary phenomenon of the fetus and early infancy; it is an adaptive response to nature, not an exact weakness. Neonatal immunity lacks memory, which is why repeated doses of immunization are necessary. Neonates will not respond to the polysaccharide vaccine, as carbohydrates are less antegenic than fat and protein. Placental immunology plays a major role in maintaining and protecting the half-matched fetus in many ways. This review discusses the clinical and practical aspects of neonatal immunology.

Keywords: Congenital Viral Infections; Innate Immunity; Natural Killer Cells; Neonatal Microbiomes; Antigenicity

Abbreviations: NEC: Necrotizing Enterocolitis; HLA: Human Leucocyte Antigen; Treg: Regulatory T; BPD: Broncho Pulmonary Dysplasia; ROP: Retinopathy of Prematurity; TLR: Toll-like Receptors; PAF: Platelet-Activating Factor

Introduction

Immunity in neonates is underdeveloped, posing challenges in fighting infections. However, certain unique aspects of the neonatal immune system can help mitigate these limitations. For instance, maternal antibodies can provide protection against intracellular bacteria, compensating for the deficiency in cell-mediated immunity. The presence of B-1 lymphocytes and poly specific antibodies are two examples of adaptive mechanisms in which adaptive immunity acts like innate immunity. B-1 lymphocytes create antibodies to multiple antigens that are not specific, like innate immunity [1]. While innate immunity components like vernix and skin barriers are advantageous in full-term neonates, premature infants lack these defenses. They are also vulnerable to infections and inflammation's due to a weaker intestinal epithelial barrier. Although neonatal neutrophils can effectively kill bacteria, their ability to adhere to and migrate toward infection sites is compromised.

Additionally, inadequate complement activity hinders the production of essential chemo attractants C5a and C3b, which are crucial for opsonization and phagocytosis [2]. The depletion of neutrophil storage pools can lead to systemic infections when bacterial replication surpasses innate defense mechanisms. Qualitative and quantitative deficiencies will be noted in adaptive immunity, with neonatal T and B cells exhibiting a naive phenotype. while B cell activity is impaired but partially compensated for by maternal antibodies. The effector functions of CD8 T cells and natural killer cells are less potent, and antigen-presenting cells produce fewer inflammatory cytokines. These physiological immunodeficiencies, acquired by nature, prevent autoimmune-aggressive inflamation. In the subsequent discussion, we aim to explore the adverse effects and limited advantages of this immunological immaturity.

Discussion

Babies usually have immunological tolerance in the fetal stage. Immediately after birth, a baby should be able to face various pathogens and distinguish between its own cells and invading bodies. Though some antigen recognition will be possible with genetic programming, as recognized, is definitely a good challenge. In the human placenta, fetal trophoblast cells do not express

human leucocyte antigen (HLA-A and B) molecules responsible for rejecting allografts in humans. TH1-to-Th2 skewing also drives the system toward immune tolerance rather than defense from microbial infections. Regulatory T (Treg) cells play a vital role in embryo implantation and pregnancy maintenance after allogeneic mating. Implantation failure, miscarriage, and preeclampsia are associated with decreased numbers of or dysfunctional Treg cells [3]. Scharschmidt and colleagues examine host responses following colonization with a prototypic commensal *S. epidermis* or a pathobiont *S. aureus*. In doing so, they find that rather than passively applying the same tolerance program to all bacterial inhabitants, the cutaneous immune system actively discriminates between a pathogen and commensal, Treg cells, more with *S. epidermis* than *S. aureus* [4].

Pattern recognition receptor function increases over time, and the increase in capacity occurs in proportion to time since birth rather than gestational age, suggesting that it is controlled by exposure to the environment. Another cause of tolerance is fetuses' slow growth, like tumors, which creates immune tolerance. Mother chimeric cells will transfer from mother to baby, causing immunotolerance. The whole pregnancy will be an anti-inflammatory phase, and at the time of pregnancy, it will become a pro-inflammatory phase. After birth, there are up to three months of immunotolerance, during which time the microbiome will develop. For this, breast milk will be helpful. After which, immunity will last for the rest of the individual's life as a pro-inflammatory phase [5]. Telologically, Fc receptors will be higher in the first 2 days of the neonatal intestine, when the mother will produce colostrum [6].

Sepsis

Newborns are particularly susceptible to acute respiratory and diarrheal infections because of their immature B cell differentiation, insufficient Th1 responses, and innate predisposition toward Th2 cell polarizing cytokines [1]. Neonates lack cell-mediated immunity, which causes fungal and viral infections that are more severe in neonates. They usually have neutropenia and thrombocytopenia due to a lower reserve of bone marrow proliferative cells. There is a significant difference between male and female neonates, as female neonates will have more immunological factors in quantity and quality. Gram-negative sepsis is more severe due to the immaturity of the neonatal immune system, which is unable to respond properly to lipopolysacheride. Antenatal steroids cause increased natural killer cells and decreased T cell immunity; repeated doses may increase the chances of sepsis [7].

Neonatal Response to Maternal Infections and Inflammations

Antibodies are transferred to infants by pinocytosis, which is why they are more common in newborns than mothers. Consider this point when evaluating TORCH infections: because IgM is a large molecule, the likelihood of a false-positive reaction is greater. Therefore, increasing or lowering the IgG titer is more valuable. If IgM is negative, we can rule out a recent infection. Sometimes IgM may be negative in congenital infections due to a delay in response. Antibodies are only transferred after 30-32 weeks, so we can predict the increased risk of rhesus incompatibility after this gestational age [8]. Most of the connective tissue disease antibodies, including systemic lupus erythematous and autoimmune thyroid diseases are IgG-type, which causes a permanent conduction blockade in the neonatal heart. IgG2 will not transfer from mother to baby. At nine months of age, the baby adequately forms IgM. IgG3 transfers from the placenta to the baby [8]. IgA decreases the enterobacteria HMOs and increases the bifedobacteria in the neonatal intestine. Secretory IgA is usually resistant to proteolysis. IgA will transfer from milk to the baby. In the human placenta, there are usually no barriers, which is why antibodies will transfer to babies. However, in other mammals, there are many layers in the placenta preventing the transfer, so in animals, only the colostrum is the source of the antibodies. HIV antibodies will be present for up to 18 months, which is why PCR is needed for an accurate diagnosis.

Retinopathy of Prematurity and Bronchopulmonary Dysplasia

There is substantial evidence to implicate activated macrophages as the primary leukocytes involved in the development of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). IL-1β has also been shown to play a key role in the pathogenesis of BPD and ROP. Cord blood samples demonstrated an increase in TNF-α concentration and IL-6 at 24 hours post-birth in babies who developed ROP. There is a link between intrauterine inflammatory events and the subsequent development of severe ROP. Packed Red Blood cells (PRBC) transfusions in the first ten days of life are associated with an almost four-fold increased risk of severe ROP, independent of gestational age at birth or BPD status [9].

Increased concentrations of proinflammatory cytokines were found for variants in genes, and some of them are related to cell adhesion. The human neonatal Broncho alveolar lavage neutrophil influx and imbalance between elastase and alpha-proteinase inhibitors contribute to BPD development. Upregulated monocyte and neutrophil chemotaxis genes and T cell receptor signaling pathways are involved in the pathogenesis of BPD. Both genetic and epigenetic factors that control the inflammatory mediators will play a major role in BPD [10].

Allergy

Important factors are transferred from mother to baby, including low levels of complement and commensal bacteria, which may protect against asthma and allergies in later life. Neonatal microbiomes usually positively stimulate the immune system and give signals to the immune system [7]. Microbiomes typically reside in the mucosa. In the first 1,000 days, disruption

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of immunity not only affects the acute immune response but also long-term immunity in the form of allergies and autoimmune infections. Mothers' allergic behaviors will transfer to babies. As usual, Th2 skewing is prone to allergy in neonates [1].

Necrotizing Enterocolitis

Age-dependent maturation of Toll-like receptors (TLR) will occur. Unlike adults, neonates' TLR receptors are above the epithelial lining. In particular, uncontrolled TLR-4 signaling is thought to play a major role in the NEC. Notably, platelet-activating factor (PAF) is also an important acute mediator in the pathogenesis of NEC, which is not only a chemokine that induces inflammatory signaling but also can increase the expression of TLR-4. Meanwhile, TLR-9 may play a protective role [11]. Maternal transfer of immune defenses is significantly reduced in preterm infants (especially formula-fed infants), thus placing them at greater risk for inflammatory disorders such as NEC. Early initiation of breast milk will create the proper microbiome, which has long-term positive outcomes.

Neonatal Blood Transfusions: Acute and Chronic Effects

Blood transfusions are irradiated and leucodepleted to prevent inflammatory diseases like ROP, BPD, and fulminant NEC. Graft-versus-host disease and HLH are the major problems after multiple blood transfusions. That's why it's better to give maximum volumes at a time. Repeated and relative transfusions may hinder future transplantations [12].

Immune Hemolytic Anemia

Rh antigenicity is greater than A and B antigens, and they reside only on red blood cells. Because of that, Rh immunological reactions were severe. ABO antigens, which develop late and have low antigenicity, will be present in all systems of the human body. IgG antibodies usually last two months, which is why we should follow up for anemia after two months of any incompatibility. As we know, both Rh incompatibility and ABO incompatibility are present, so the severity of Rh immunity will decrease. Every baby's delivery will increase the antigenicity and severity of Rh incompatibility. Fetal demise usually occurs at a younger gestational age as the number of pregnancies increases. This is unlike syphilis, where the neonatal gestational age of delivery will increase due to immunotolerance. But both scenarios are less common due to Rh immunoglobulin and Syphillius are very sensitive to pencillins after many years of usage. Rh antibodies are incomplete antibodies, like brucella; they are unable to form agglutination when their antigen antibodies are mixed on a slide. If we add antibody, which is a coombs reagent, to a newborn with Rh incompatibility, in which the Rh antigen and antibody complex already exist, immediate agglutination will form; this is called the direct coombs test [13].

Role of Immunity in the Severity of Alloimmune Thrombocytopenia

Thromboplasts will escape alloimmunization because HLA-1 is not present in thromboblasts. Hemorrhage is more common in allimmune thrombocytopenia than immune thrombocytopenea because α-v β-3-specific anti-HPA-1a antibodies induce endothelial cell apoptosis, which affects fetal vessel wall integrity, a critical factor in fetal intracranial hemorrhage development [14].

Acquired Hemophagocytic Syndrome

NK T cell imbalances in this system produced by chronic inflammation may be involved in the presentation of the acquired forms of hemophagocytic lymphohistiocytosis in the neonatal period. The main pathophysiological events in HLH are cytokine dysfunction and generalized histiocytosis resulting from the uncontrollable accumulation of macrophages processing active T-lymphocytes and antibodies [12].

Neonatal COVID-19 and Immunity

The COVID vaccination of the mother will protect the baby and decrease the MIS-C. Due to the immaturity of immunity, neonates and children will develop MIS-C [15].

Vaccination

As mentioned earlier, neonates currently lack T-cell-dependent immunity to polysaccharides, which is why we add proteins to vaccines. Measles and rubella antibodies wean over 6-12 months, which is why we usually vaccinate after six months. . After adding protein to the vaccine, it stimulates T-cell-dependent immunity. Proteins will act like adjuvants, which increase immunogenicity without increasing antigenicity. The mother's immunizations, tetanus and pertusis, will be transferred to the baby as immunoglobulins, causing the first immunization; breast milk is the second immunization. In babies with malnutrition, the epithelial lining will be blunted, decreasing the vaccination effect. In hepatitis B, if there is no immunoglobulin, it is better to administer another dose of the vaccine. As the hepatitis B virus takes a long time to develop disease, vaccines produce a good immune response. The vaccinevirus incubation period is shorter than the wild virus vaccine; this is the principle of postexposure prophylaxis [16]. The postnatal age appears to be a more important determinant of antibody response than the gestational age. Thats why we can give vaccinations early to preterm babies except for hepatitis B, as proper immunity is not noticed for hepatitis B. In varicella, immunoglobulin is more important than the vaccine because of the short incubation period.

Role of Immunity in Future Neurological Disorders

Dating back to the 1960s, researchers have documented an increase in neuropsychological disorders such as autism spectrum disorder and schizophrenia following outbreaks of rubella from

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less than 1-13% and 20%, respectively, because the inflammation-induced changes in the immune system shift towards TL17 and IL-6 [17]. The study suggests maternal immune stimulation during pregnancy influences fetal immune programming, leading to a proinflammatory phenotype in offspring. This is consistent with the "multiple hit" concept of mental disorders, as seen in the offspring of immunostimulant mothers.

Hypersensitivity Reactions in Neonates

Hypersensitivity reactions are rare in the neonatal period due to the immaturity of the immunological system. Anaphylactoid reactions were uncommon, though some case reports are noted [18-20]. This is an advantage in the neonatal period. If medications are not diluted properly, some drug particles may block the vessels and mimic anaphylactoid reactions.

Conclusion

The neonatal immune system, specifically its cell-mediated immunity, is relatively weak, making newborns more vulnerable to infections. Conversely, the occurrence of a blood transfusion reactions, drug reactions, and anaphalactic reactions are less likely. But there is a risk of graft-versus-host reactions. It is better to call it an adaptation to the environment rather than a weakness. To ensure the well-being of premature infants, it is crucial to provide them with proper asepsis and nutrition, surely in the form of their mothers' milk. This will supply them with nonplacental transverse antibodies and specific immune cells, which are essential for their care. Neonatal immune systems require adequate and appropriate exposure to antigens to prevent future autoimmune, allergic, and metabolic disorders.

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