INTERNATIONAL MULTIDISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
SJIF 2019: 5.222 2020: 5.552 2021: 5.637 2022:5.479 2023:6.563
eISSN 2394-6334 https://www.ijmrd.in/index.php/imjrd Volume 11, issue 02 (2024)

CYTOKINE PROFILE IN PREMATURE NEWBORNS WITH PERINATAL NERVOUS SYSTEM PATHOLOGY

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Key words: Premature newborns, perinatal pathology of the nervous system, cytokines.

Improvement of modern methods of caring for premature newborns has led to a decrease in the number of deaths in this group. At the same time, an important medical and social problem remains the increase in morbidity and disability in children born prematurely, associated with perinatal lesions of the central nervous system of hypoxic, traumatic, metabolic, toxic and infectious origin [1–6]. In connection with the transition to WHO-recommended live birth criteria, methods of safe motherhood, a unified system of primary resuscitation and nursing of premature infants are being introduced, extended and high-frequency mechanical ventilation, replacement therapy with surfactant preparations and immunoglobulins are increasingly used in the treatment of the most severe conditions of the neonatal period. All this increases the possibilities of management and survival of premature infants [5].

Despite significant studies of the results associated with the use of modern technologies for the care, diagnosis and treatment of premature newborns, a number of issues related to the disclosure of ontogenetic aspects of neonatal adaptation remain poorly understood to date. In addition, the latest requirements for assessing the adaptation processes of a newborn child provide for an integrated approach that allows us to describe the totality of data that defines ontogenesis as a single process of individual development of a child, taking into account the heterochrony, unevenness and systematicity of various functional units [6, 7]. In connection with Therefore, the purpose of the following analysis of literary data was to describe the etiological factors and pathogenetic mechanisms of damage to the central nervous system in the perinatal period.

Premature infants are most susceptible to the damaging effects of chronic intrauterine hypoxia and acute intrapartum asphyxia, due to morpho-functional immaturity of the brain, impaired cerebrovascular autoregulation, decreased activity of antioxidant systems, characteristics of metabolic processes, energy deficiency and low level of plastic processes [7–9] . Thus, if the frequency of perinatal lesions of the central nervous system, depending on the nature of the ante- and intranatal periods, in full-term children ranges from 15 to 60%, then in premature infants this figure increases to 65–85%. Lesions of the central nervous system of various origins in premature infants, due to predisposing circumstances, can lead to the formation of persistent neurological disorders with subsequent chronicity of the process, disability, social maladjustment and a decrease in the quality of life in general. The perinatal origin of neurological pathology in the structure of childhood disability is 70–80% [9–12].

The interaction of organs and systems in the conditions of a whole organism in premature infants during the first months of life is manifested by lability of regulation, exhaustion and disunity of adaptation mechanisms [8]. The immune system of the newborn is decisive and responsible for maintaining the homeostasis of the body, especially in conditions of postnatal adaptation. The state of the immune system, according to N.N. Volodina et al. [9], taking into account effective therapeutic and rehabilitation measures, determines the survival of the child. It is known that the mobilization of factors of innate and adaptive immunity in newborns is subject to general laws of adaptation, but their characteristics in various pathological conditions in premature infants remain insufficiently studied [10, 11].

The main indicators of cytokine status in children born prematurely are considered to be quite informative markers that reflect the system of adaptive mechanisms of the body [12, 13]. However, in clinical practice, the criteria that determine the degree, nature and depth of damage to adaptive mechanisms in premature newborns have not been sufficiently studied. The immunological aspects that contribute to the emergence of local or generalized forms of pathological processes in premature infants have not been fully deciphered. In this context, a comprehensive study of the ontogenetic features of adaptation in premature infants is of particular relevance, which makes it possible to develop criteria for early diagnosis and give a prognostic assessment of the implementation of pathological conditions in the postnatal period. The activity of the immune response in premature newborns with congenital infections depends on a decrease in the production of immune factors, which may be due to polymorphism of the corresponding genes. The vascular endothelial growth factor (VEGF) gene encodes the synthesis of endothelial growth factor, which is responsible for angiogenesis and plays an important role in the pathogenesis of the severe condition due to the formation of capillary leakage. VEGF is involved in the development of many diseases. Combinations of polymorphisms, in particular VEGF and the gene encoding β1-adrenergic receptors (ADRB1), can worsen the course of the pathological process [11].

Modern publications do not present many studies that would be devoted to the search for a set of markers, taking into account the presence of polymorphisms of the corresponding genes, which allows timely diagnosis and, therefore, prevention of the development of undesirable outcomes in the early stages of the pathological process in premature newborns. It should be noted that at present there is no proposed universal set of markers (taking into account genetic predisposition) that would allow timely diagnosis of the development of severe conditions, and, consequently, prevent adverse outcomes in the early stages of the pathological process in premature infants.

In recent years, a general understanding of the development of the immune system in newborns has emerged. When born before 32 weeks, preterm infants are considered immunologically immature. The innate immune system is considered the first line of defense. The cells of the innate immune system consist mainly of myeloid cells such as macrophages, neutrophils, basophils, eosinophils, monocytes and lymphoid cells [6]. Neutrophils play a very important role in protecting newborns from infections. However, before 32 weeks they make up a low percentage of blood cells [12]. In premature newborns, neutrophils do not have the ability to form neutrophil extracellular traps. These decoys are strands of extracellular DNA, chromatin, and antibacterial proteins that kill microorganisms through the generation of reactive oxygen species [14]. Like other types of immune cells, monocytes recognize antigens.

Three major monocytic cell subsets were studied according to their expression of monocytic surface markers (membrane glycosylphosphatidylinositol-related protein 14 (CD14) and CD16). Before 29 weeks of gestation, most fetal monocytes have an immature phenotype, characterized by low expression of the CD14 marker. These monocytes are actively involved in tissue remodeling, but they are inactive in immune responses [8]. Determination of the characteristics of monocyte activity explains some of the reasons for the predominance of known pathogens in the etiology of infectious processes in premature infants. For example, monocyte toll-like receptor 2 (TLR2) activity, which plays a predominant role in recognizing coagulase-negative staphylococci, is prominent in late gestation. Accordingly, infections with this pathogen are most common in infants less than 30 weeks' gestational age. However, in preterm infants up to 29 weeks of gestation, monocytes and dendritic cells produce small amounts of IL-17-polarizing

cytokines by neonatal antigen-presenting cells, which increases the risk of gastrointestinal infections [10,11].

Breast milk is important in the formation of immunity in premature infants. Modern studies have published observations regarding the cellular composition and presence of antimicrobial peptides in breast milk. These findings explain the immune properties of breast milk and its influence on the maturation of the immune system. The main clinical significance of these results is that breast milk may be used to protect against neonatal sepsis. For example, studies have repeatedly proven that taking breast milk, as opposed to formula, significantly reduces the incidence of necrotizing enterocolitis in premature infants. Modern studies have shown that the intestine itself is a functionally separate immune organ [8]. It is known that the function of the immune system is also greatly influenced by hormones, in particular thyroid hormones [5].

Premature newborns have immaturity in the regulation of the hypothalamic-pituitary-thyroid system. It has been determined that low levels of triiodothyronine and thyroxine in critically ill children significantly increase the risk of poor prognosis due to the development of neonatal sepsis [11]. In their work, A. Patra et al. described that 65% of women who gave birth at 23–24 weeks had histologically detected signs of chorioamnionitis in the placenta, and at 29 weeks – in 30% of women. Therefore, the authors concluded that maternal chorioamnionitis, diagnosed clinically or histologically, is an important cause of preterm birth. Chorioamnionitis is one of the main risk factors for neonatal sepsis. Chorioamnionitis can cause pronounced immune reactions in the fetus, up to “immune paralysis,” which leads to a more severe course of the infectious process [10].

Early neonatal sepsis is usually caused by bacteria from the maternal genitourinary system. The baby can be infected in utero. The most common causative agents of early neonatal sepsis are Escherichia coli, Staphylococcus epidermidis, Streptococcus agalactiae, Proteus mirabilis, Haemophilus influenzae and Listeria monocytogenes. When the fetus is infected in utero with a pathogen such as Listeria monocytogenes, pregnancy can end in spontaneous miscarriage or early birth [12].

The level of perinatal morbidity and mortality is contributed by very early premature births at 22-27 weeks of pregnancy, leading to the birth of children with extremely low body weight. The high level of disability in very premature infants and the costs of caring for them are also of no small importance [2, 3]. Previous studies indicate a close connection between miscarriage (spontaneous pathological termination of pregnancy, premature birth) and infection. The body's defense against pathogens is carried out by components of the innate and acquired immune system. Modern studies at the molecular level have identified a number of polymorphisms in the genes of components of the human immune system that modify the immune response, which leads to a predisposition to a certain range of diseases associated with an infectious factor, such as infertility, spontaneous pathological termination of pregnancy at various stages of gestation, severe placental insufficiency and preeclampsia [4].

Immune mechanisms play a key role in the pathogenesis of preterm labor [4–7]. A very small number of works are devoted to determining the role of the receptor for advanced glycation end products (RAGE) and its ligands in the implementation of PR. RAGE is a multiligand cell surface receptor, one of the representatives of the immunoglobulin superfamily, which determines its properties [8–11]. Today, RAGE is considered a pattern recognition receptor (PRR), which has a large variability of ligands. The RAGE system takes part in many physiological and pathological processes, including acting as an activator of adaptive and innate

immunity [8, 9], but the significance of the components of this system during pregnancy has not been sufficiently studied.

Perinatal infectious pathology is one of the urgent and serious problems of modern neonatology and a leading factor in the development of the disease and deaths in newborns [1–4]. Intrauterine infections are the cause of death in premature newborns in 68.1% of cases, and in full-term newborns in 49.7% [5]. Despite modern achievements in studying the mechanisms of development of this pathology and the latest advances in its treatment in premature infants. But despite this, today perinatal infections continue to be one of the main causes of severe neurological disorders in the postnatal period [6, 7]. The difficulties of examining newborns necessitate the widespread use of paraclinical methods, in particular ultrasound scanning of the brain, which makes it possible to quickly identify and evaluate organic changes, including those associated with infectious pathology of the central nervous system (CNS).

One of the main diagnostic results is given to laboratory diagnostics, with the determination of neuron-specific proteins, in particular neuron specific enolase (NSE), which is a specific marker of neuronal damage and serves as an indicator for determining the severity of their damage, in addition to violations of the general integrity of the blood-brain barrier. Currently, determining the level of anti-inflammatory cytokines seems to be effective for diagnosing and predicting the course of intrauterine infections and neonatal sepsis, and therefore the possibility of using these indicators as informative criteria for assessing the severity of damage to the central nervous system [9–14]. Neuroinflammation plays an important pathogenetic role in cerebral lesions; identifying the level of proinflammatory cytokines allows them to be used as informative criteria for assessing the severity of damage to the brain and spinal cord. According to the results of the studies, high levels of pro-inflammatory cytokines during hypoxic-ischemic damage to the central nervous system make it possible to identify the severity of brain damage in premature newborns, being an additional damaging factor.

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