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Immunological Aspects of Intrauterine Infection in Newborns

Omonova Guzal Zarifovna
Samarkand state medical university, Department of clinical pharmacology

Abstract: Intrauterine infection (IUI) is the main cause of death in 37.5% of newborns or is a complication of the course of the main disease, and occupies one of the leading positions in the structure of neonatal death.

There is no reliable data on the actual prevalence of IUI. However, according to a number of studies, infectious diseases are detected in 50-60% of full-term hospitalizations and 70% of premature babies [1]. The main cause of IUI is infectious urogenital diseases of the mother, the frequency of which has remained high among pregnant women in the last 10 years and is 88-100 per 1000 pregnant women. Unfortunately, at the moment we do not have reliable information about the probability of the fetus being infected from an infected mother, but the risk of infection of the fetus with various microorganisms isolated from the mother is from 5 to 70%, data on frequency. The prevalence of infection in newborns is insufficient and highly contradictory [2, 3].

Key points: Immunological indicators, immune defects, intrauterine infections, diagnosis of intrauterine infections.

Early diagnosis of infectious and inflammatory diseases in newborns remains relevant to this day, and therefore new informative diagnostic methods have been used in recent years. These include the study of cytokine status [4, 5], detection of acute phase proteins (C-reactive protein) [6, 7] and procalcitonin (PCT) [8, 9], as well as other diagnostic tests characterized by identification. one or another reliable parameter [10-14].

The study of the role of pro- and anti-inflammatory cytokines in the pathogenesis of infectious diseases in newborns is of great interest [15-17]. Many studies [18-20] report the high diagnostic and prognostic value of TNF and IL-8 levels in neonatal sepsis. Some authors [21, 22] suggest using a combination of IL-6, which plays an important role in triggering the synthesis of C-reactive protein by hepatocytes, to increase the information content of the test for C-reactive protein. in the diagnosis of neonatal bacterial infections.

PCT has been proven to be a sensitive marker of systemic inflammatory response in newborns on the 3-7th day of life, and the diagnostic value of anti-inflammatory cytokines increases after the 14th day of life. However, PCT may be superior to CRP in detecting and evaluating the severity of infection, as confirmed by many studies. Despite many publications on the diagnostic value of PCT in systemic infections, including in newborns, there is no clear opinion about the possibility of using this indicator in the diagnosis of infectious and inflammatory diseases in the first 2 days of life. a wide spread of its reference ranges at this age [8, 23, 24].

The aim of this study is to improve the quality of IUI diagnosis and to optimize the management of newborns at high infectious risk in the early neonatal period by applying a screening algorithm using available and informative tests.

Materials and methods

A study was conducted on 240 full-term and 10 premature babies born to mothers with infectious and inflammatory diseases of the genitourinary tract. Among pregnant women, mainly viral

infections were observed in 35 (14%), bacterial infections in 30 (12%), mixed viral-bacterial infections in 185 (74%) cases. Urogenital chlamydia was detected in 85 (34%) patients, ureaplasma in 75 (30%) cases, mycoplasma - in 30 (12%) cases. HSV-2 infection was detected in 135 (54%) mothers, cytomegalovirus infection (CMVI) - in 180 (72%). 45 (18%) women had chronic kidney and urinary tract diseases;

The course of this pregnancy was complicated by the addition of preeclampsia in 50 (20%) mothers, anemia of pregnant women was diagnosed with the same frequency, and about half of the patients (46%) had a risk of pregnancy. According to the results of a comprehensive assessment, dysfunction of the fetoplacental complex was diagnosed in 100 (40%) pregnant women, polyhydramnios in 30 (12%) cases.

Childbirth occurred spontaneously in 160 (64%) cases, 86 (34.4%) pregnant women gave birth spontaneously, during labor 4 (1 .6%) in a woman vacuum extraction of the fetus was used. The duration of labor was from 2.75 to 18 hours, the duration of the waterless interval - from 2.5 to 24 hours, labor was complicated by weak labor in 40 (16%) cases, prenatal rupture of amniotic fluid in 30 (12%) observed.) women in labor. 20 (8%) patients developed chorioamnionitis during labor.

To determine clinical and laboratory correlation, newborns were divided into 6 groups based on the main clinical diagnosis.

Group 1 included 45 (18%) newborns with generalized and severe localized forms of IUI, including sepsis, meningoencephalitis, pneumonia, and gastroenterocolitis.

Group 2 consisted of 30 (12%) newborns with moderate local infectious processes, in particular: vesiculopustulosis, conjunctivitis, rhinitis, omphalitis, vulvovaginitis, local forms of candidiasis.

Group 3 included 25 (10%) newborns with morphological changes in the central nervous system (CNS) and internal organs detected by ultrasound, indicating that they were infected with IUI.

Group 4 consisted of 30 (12%) newborns with various degrees of hypoxic damage to the central nervous system.

Group 5 included 28 (11.2%) newborns with intrauterine growth retardation (IUGR).

Group 6 consisted of 92 (36.8%) clinically healthy newborns.

In addition to the standard clinical and laboratory examination performed for all newborns, 158 children underwent an ultrasound examination of the thymus gland (UG) - immunological examination, study of interferon status in 90 newborns; (IFS) and cytokine concentrations (TNF-α, IL-1 , IL-4 , IL-6 , IL-8 , α- and γ-IFN) in blood serum, spontaneous and stimulated blood cell cultures, 50 The level of PCT in a child was determined using an express method.

The frequency of isolation of representatives of aerobic microflora in smears from the mucous membrane of the nasopharynx and anus in newborns at high risk of infection at birth ranges from 40.2% (in clinically healthy newborns) to 62.2% (in children with severe forms) IUI). Severe forms of IUI are characterized by a high frequency of contamination of newborns with representatives of sexually transmitted infections: HSV-2 - 43.6%, CMV - 58.2%, chlamydia - 41.8%, ureaplasma - 52.7%, mycoplasma - 32.7%.

Research results

Based on clinical data and evaluation of immune parameters using the percentile scale of the main immunological parameters in the examined newborns, the following variants of the immune response and cytokine status in the early neonatal period were determined.

Two types of immune response were detected in newborns with severe forms of IUI (14 children were examined). The first variant (8 newborns) is characterized by the activation of innate and adaptive immune cells together with their maturation, the increase of IFN in the blood serum and the ability of leukocytes to produce α-IFN with a low ability of lymphocytes to produce γ. -IFN. The most pronounced inhibition of interferonogenesis α-(4-8 IU/ml) and γ-(<4 IU/ml) in 2

newborns who died in the early neonatal period was determined at low concentrations of IFN in blood serum. <4 IU / ml), which allows us to consider these indicators as predictors of adverse outcomes in newborns with IUI (p = 0.03). IL-8 was detected in the blood serum of all children (its amount exceeded 50 pkg/ml in 75% of cases) and a decrease in the production of IL-6, IL-1 and TNF-α was observed.

The second variant (6 newborns) was characterized by lack of immune activation and increased IFN, lack of phagocytes, mature T- and B-lymphocytes. The ability of leukocytes to produce α-IFN was within normal values, and the ability of lymphocytes to produce γ-IFN was slightly higher than in the first variant. IL-8 was detected in blood serum in 30% of cases (the level did not exceed 50 pkg/ml). This variant of the immune response was characteristic of such forms of the disease, which appeared as a result of aspiration and ingestion of amniotic fluid, with the development of aspiration pneumonia, which was more indicative of intrapartum infection and was confirmed by a high frequency of complications during childbirth. , later periods of IUI manifestations in the early neonatal period, the absence of common forms of infection and death.

The specific characteristics of the immune response in newborns with local infectious and inflammatory diseases of moderate severity (10 newborns were examined) are as follows: the predominance of the anti-inflammatory immune response There are no changes in the number and maturation of ma and adaptive immune cells. The pattern of increased levels of IgM and serum IFN, high ability to produce α-IFN, IL-4 (<10). pkg/ml) without immunological criteria of systemic infection (absence of IL-8 and anti-inflammatory cytokines in blood serum, unchanged production of lymphokines and monokines).

The immune status of newborns with morphological changes in the central nervous system and internal organs detected in ultrasound examinations (8 children were examined) characterizes the infectious process completed at the time of birth. The immune response was characterized by an increase in the number of mature immunocompetent cells, and IgG values did not differ from normal values; The production of IL-1 and TNF-α decreased, the production of α-IFN and IL-4 increased, and the anti-inflammatory direction of the immune response prevailed.

The results of microbiological research in combination with disruption of the cytokine status in the form of mothers (herpes virus etiology of infection in 90.9% of cases) and their newborns (isolation of HSV-2 in 43.6%, CMV infection in 58.2%). Increased production of α-IFN, decreased production of IL-1 and TNF-α confirmed the viral etiology of the disease. Changes in the central nervous system and internal organs detected at birth, together with immune indicators, indicate an early intrauterine infection, mainly of viral etiology, a favorable outcome for fetal viability against the background of etiotropic therapy in the antenatal period, but with this. formation of permanent structural changes during birth, mainly CNS.

In newborns with hypoxic lesions of the central nervous system (15 newborns were examined), hypoxia is an additional damaging factor contributing to an increase in antigen load, and in conditions with a low risk of intrauterine infection (8 children) led to its activation. innate immune cells with no change in cytokine status. In 7 newborns, when hypoxia was combined with microbial contamination, the immune response was characterized by an increase in macrophages from the blood stream, an increase in the level of IgM in the blood serum, an increase in the production of anti-inflammatory cytokines, and a decrease in blood flow. the ability of lymphocytes to produce γ-IFN did not exclude the manifestation of IUI, the clinical manifestation of which could be canceled against the background of symptoms of damage to the central nervous system and ongoing anti-infective therapy.

In newborns with IUGR (14 children were examined), the immune response is characterized by a decrease in the number of innate and adaptive immune cells (CD3+, CD20+, CD8+, CD16+, monocytes). Two types of IFS were installed. The characteristic features of the first type of IFS were the absence of IFN in the blood serum and the high ability of lymphocytes to produce γ-IF. The second type of IFS was associated with an increase in serum IFN (16 IU/ml) and a low ability of lymphocytes to produce γ-IFN (<4 IU/ml). There was a statistically significant correlation (p =

0.004) between the second type of IFS and the frequency of postpartum infection in newborns with IUGR, which was 64.3% (9 newborns were sick)

Indicators of immunity and cytokine status in clinically healthy newborns without microbial contamination (17 children were examined) did not differ from normal values. In clinically healthy newborns (12 children), microbial contamination increased the number of immunologically mature adaptive immune cells (CD3+, CD20+, CD4+, CD8+, CD16+), the level of IgG, the number of innate immune cells (neutrophils) characterized by a decrease. 1, Increase to 5. - 2 times. Production of γ-IFN, IL-6 and IL-4 did not differ from normal values; Changes in immune parameters in healthy newborns from mothers with urogenital infections depend on the presence of microbial contamination, which leads to an increase in the number of mature immune cells capable of producing pro-inflammatory and anti-inflammatory cytokines. characterized by, prevents maintaining their balance. Manifestation of IUI.

The immunological criteria for the early diagnosis of severe forms of IUI in newborns are as follows: an increase in the level of IgM in the blood serum of more than 1.0 g / l and a decrease in the level of IgG less than 6.6 g / l; An increase in peripheral blood flow of early precursors of T- and B-lymphocytes - more than 70.4%, immature T-lymphocytes - more than 19.4%; an increase in serum IFN of 16 IU / ml or more with a decrease in the ability of lymphocytes to produce γ-IFN to less than 4 IU / ml or less than 3.0 pkg / ml; serum IL-8 level exceeding 50 pg/ml and (or) low production of IL-4 combined with production of γ-IFN less than 3.0 pg/ml (less than 10 pg/ml).

Since the thymus is the main organ of the immune system of the fetus and newborn, the morphological features of IUI and the immune status of newborns at high infectious risk were compared to determine informative and available criteria for the early diagnosis of IUI and immunodeficiency. . Studies have shown a clear relationship between the volume of intravenous fluids, the presence and severity of clinical manifestations of IUI, and immune defects in newborns in the early neonatal period (Table 1).

Thymomegaly with an IV volume of more than 2.5 ml/kg determined by ultrasound is statistically significant for severe forms of IUI in which the immune response is impaired in the form of maturation and activation of innate and adaptive immune cells with profound impairment of their effector functions. was A decrease in the volume of intravenous fluid to less than 1 ml/kg is associated with immune dysfunction in the form of a lack of mature immunocompetent cells and a lack of anti-inflammatory immunity, which is clinically characterized by prolonged intrauterine infections. high rate of postpartum infectious and inflammatory diseases in newborns.

Taking into account the diagnostic value of PCT for systemic infections, including newborns, as well as the wide range of control ranges of this indicator in the first 2 days of life, a study of the level of PCT using the express method was conducted in 40 years. full term and 10 premature babies.

Newborns are divided into 4 groups based on the nature of the pathology.

Group 1 consisted of 21 newborns with intrauterine pneumonia.

Group 2 included 6 newborns who were diagnosed with clearly defined non-focal IUI based on the sum of the anamnesis, clinical symptoms and laboratory test results.

Group 3 included 13 newborns with non-infectious pathologies.

Group 4 included 10 clinically healthy newborns.

A PCT level exceeding 2 ng/ml on the first day of life was statistically significant for severe forms of IUI with signs of systemic inflammatory reaction and organ failure. At the same time, in newborns without signs of infectious and inflammatory diseases, there was no increase in the level of PCT in blood serum during the first 48 hours of life. The results of the study allow the use of an increase in the PCT level of more than 2 ng / ml as an early diagnostic criterion for severe forms of IUI in newborns from the first day of life.

Summary

Thus, our study shows a clear relationship between the presence and severity of clinical manifestations of IUI, immune defects, IUI status, and the results of a semi-quantitative rapid test to determine PCT. Suggested immunological indicators of cytokine disorder and ultrasound criteria of IV pathology, an increase of PCT more than 2 ng / ml from the first day of life can be used as criteria for early diagnosis and severity of IUI.

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