FEATURES OF CELLULAR IMMUNITY IN NEWBORN INFANTS WITH CYTOMEGALOVIRUS INFECTION

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Cytomegalovirus infection (CMVI) is gaining increasing significance in modern clinical medicine [1-8]. As a cause of mortality in cases of monospecific disease origin or as a competing condition, CMVI ranks fourth after influenza, herpes, and adenovirus infections. According to World Health Organization (WHO) data, in developing countries, 90-100% of the population becomes infected with cytomegalovirus (CMV) during childhood [9]. The European regional bureau of WHO categorizes CMVI as a group of diseases that determine the future of infectious pathology. The relevance of CMVI is attributed to its widespread prevalence among pregnant women, high morbidity, and mortality among children, as well as a wide spectrum of clinical and pathological variants. The frequency of generalized forms of this disease, according to autopsy data, varies from 2.2% among children who died between 7 and 30 days of age to 63.4% among children who died in the first year of life. CMV infection is classified as an "opportunistic" infection, the clinical manifestation of which becomes possible only in the presence of primary or secondary immunodeficiency. In terms of impact, CMV infection is second only to the HIV virus. CMV infection often progresses asymptomatically, which is particularly dangerous during pregnancy. It is possible that this asymptomatic infection can have serious consequences for the fetus, including antenatal fetal death, spontaneous miscarriages, perinatal mortality, and congenital malformations and abnormalities in development. Barton, M.; Forrester, A.M.; McDonald, J. (2020) draw attention to a significant number of cases of asymptomatic infection at birth and potential long-term consequences for children, such as hearing and vision problems, and delays in psychomotor development [3]. Literature indicates that perinatal CMV infection may be a cause of intellectual disability and a decrease in the coefficient of intellectual development in children. It is also known that the virus can persist lifelong in the body of an infected individual. It is quite possible that clinically manifest chronic pathology in the mother leads to intrauterine infection, which may be the cause of CMV infection in newborns. Many complications and mortality are associated with primary maternal infection as well. During primary cytomegalovirus infection (CMVI) in pregnancy, the transmission rate of cytomegalovirus to the fetus varies from 15% to 50% of cases. The mechanisms of immune system disturbances during CMVI are of significant interest. It is well known that the immune system protects the body from genetically foreign antigens through immunological reactions. In the course of these reactions, antigens are recognized, and specific responses (production of antibodies) occur, leading to their neutralization, destruction, and elimination from the body. In our view, disruptions in the immune system determine the course of CMV disease and the formation of the "clinical mask" of the infectious process. It is considered that a high titer of anti-CMV antibodies in pregnant women may have an unfavorable prognostic value for the fetus and, by crossing the placenta, protect the fetus from infection.

Thus, the aim of this study was to investigate the state of cellular immunity in newborns with cytomegalovirus infection.

Materials and Methods: We examined 284 newborns, including 228 (80.3%) full-term infants, 2 (0.7%) post-term infants (with a gestational age exceeding 42 weeks), and 54 (19%) preterm infants. Among preterm infants, 31 (57.4%) were classified as preterm of I degree, 10 (18.5%) as preterm of II degree, 11 (20.3%) as preterm of III degree, and 2 (3.8%) as preterm of IV degree. The research utilized clinical, laboratory-diagnostic, and instrumental methods. Laboratory methods included blood and urine tests, bacteriological examinations of blood and stool, swabs from the throat, and biochemical blood

tests. Instrumental studies of newborns included ultrasound examination of the brain, Doppler studies of the vascular system, and radiographic examinations of the respiratory organs. A cytological method was applied, utilizing materials such as urine, saliva, and breast milk for the research. This method allows the diagnosis of cytomegalovirus infection, as cytomegalic cells (CMC) are specific to this infection and are not found in other infections. Simultaneously, morphological studies of CMC were conducted. The essence of the method lies in the identification of virus-affected CMC, often of epithelial origin. We employed an enzyme-linked immunosorbent assay (ELISA) to detect specific IgM and IgG antibodies to CMV in the blood of newborns. For some patients, polymerase chain reaction (PCR) was used, based on the detection of CMV DNA in the blood. To determine the immunological status, the following methods were employed in the study: the spontaneous rosette formation reaction of lymphocytes (Jondal, 1971); T-lymphocyte subpopulation analysis (Kerman K., 1976); functional activity of T-lymphocytes (Boyum A, 1974). Examinations of newborns were conducted on days 1-3, 5-7, and again on days 10-14. The diagnosis was based on antenatal history data, the clinical symptom complex of the disease during the first 2-3 weeks of the child's life, identification of pathognomonic "owl eye" cells specific to CMV infection, detection of specific infection markers during the same period, as well as identification of viral DNA in the blood and urine.

The obtained results were subjected to statistical analysis using the software packages "STATISTICA-6," "Excel 2016," and "ORIGN-7."

Results and Discussions: A total of 284 newborns, aged 1 day to 1 month, were included in the study. Cytomegalovirus infection (CMVI) was identified in 110 (38.7%) newborns. Among them, 93 (84.6%) were full-term infants with a gestational age of 38-40 weeks (birth weight 3000±260 g, height 49±2.5 cm); 1 (0.9%) was a post-term infant with a gestational age of 42 weeks (birth weight 3100 g, height 51 cm); and 16 (14.5%) were preterm infants. Seventeen (15.5%) infants were born in asphyxia, and 11 (10%) had umbilical cord entanglement around the neck. Newborns were assessed on the Apgar scale, with 35 (31.8%) scoring 7/8 points, 47 (42.8%) scoring 7/7 points, and 28 (25.4%) scoring 5/6 points or less. Analysis of historical data showed that the majority of infants were born to mothers under 35 years old – 72 (65.5%), while the remaining were older than 35 years – 38 (34.5%). All mothers had a complicated obstetric history. Based on clinical and laboratory data, as well as considering maternal history, newborns were categorized into three groups. Group I included n=32 infants with an active form of CMVI; Group II comprised n=38 newborns with an inactive form of CMVI; and Group III included n=40 infants with a residual form of CMVI. Analysis of the clinical features of cytomegalovirus infection (CMVI) in newborns revealed that generalized CMVI with multi-organ involvement and polymorphism of clinical manifestations is typical for newborns. The manifestations include various degrees of severity of central nervous system (CNS) involvement (100%), hepatobiliary system (46.3%), respiratory tract organs (42.7%), ocular involvement (12.5%), cardiovascular system organs (12.5%), and congenital developmental abnormalities (10%) (Figure 1).

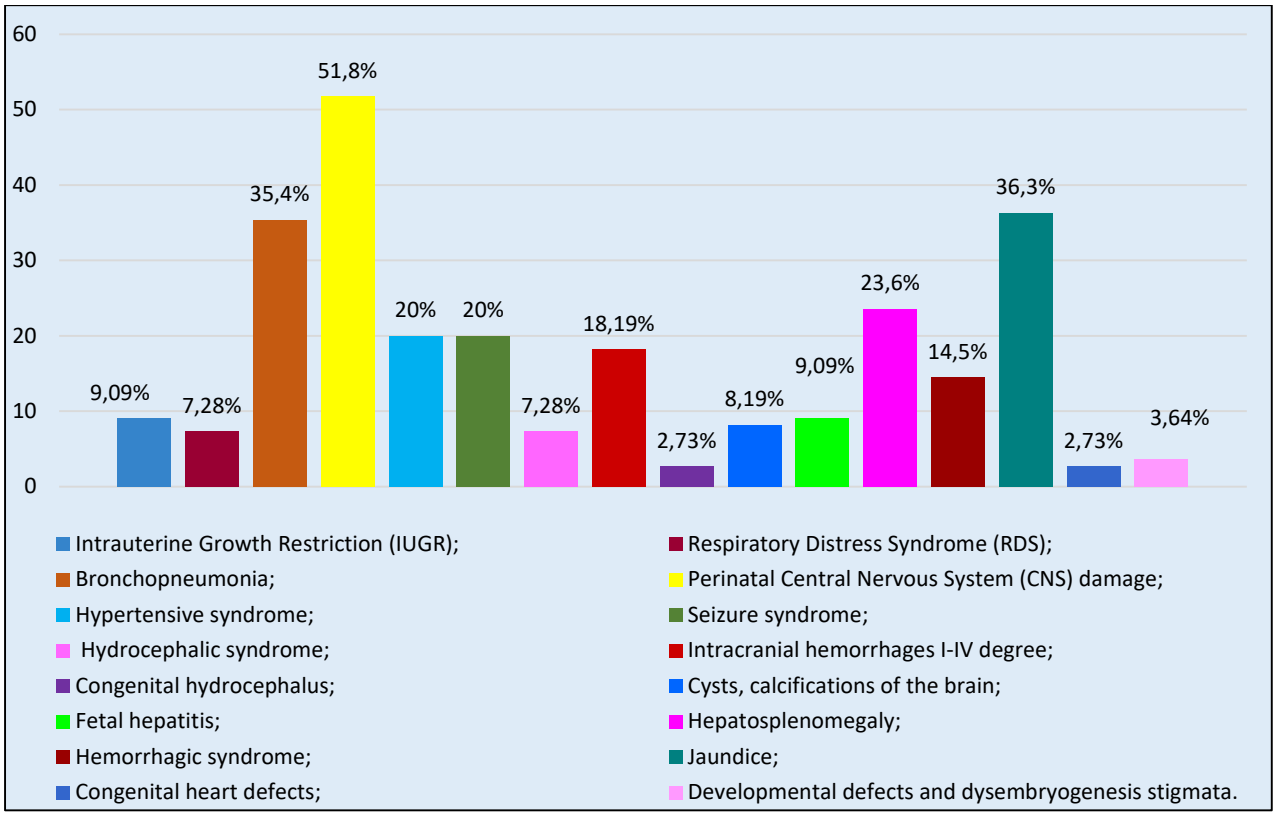

Fig.1. *Clinical characteristics of newborns born to mothers with CMVI.*

It is well known that the immune system provides protection to the body against genetically foreign antigens through immunological reactions. During these reactions, antigens are recognized, and specific responses occur, leading to the production of antibodies that result in their neutralization, destruction, and elimination from the body. In our view, disruptions in the immune system determine the course of cytomegalovirus infection (CMVI) and the formation of the "clinical mask" of the infectious process.

With the aim of identifying disturbances and determining immunological features in CMVI, we assessed the immune status of all newborns. We examined cellular immunity. The analysis of indicators of the state of the cellular component of the immune system in newborns revealed significant differences between the main and control groups.

In newborns with cytomegalovirus infection (CMVI), a reduction in the CD3+ subpopulations (T lymphocytes) was observed in all groups compared to the control group (Figure 1). The content of T lymphocytes (CD3+) in newborns in Group I was within 36.2%, in Group II – 41.1%, in Group III - 35.3%, while in the control group (CG), these values were significantly higher at 61.1% ($p>0.05$). The decrease in the number of CD3+ lymphocytes in infected newborns may be indirect evidence of the suppressive effect of CMV on lymphocytopoiesis.

A statistically significant difference was also found between the groups of children regarding the values of T-helper/inducer lymphocytes (CD4+). In our view, this indicator is of great importance since, in addition to performing the functions of immune response inducers and helpers, they possess cytotoxic activity against cells infected with cytomegalovirus. Thus, children with an active form of CMVI had a low level of CD4+ - 22.4%, with an inactive form of CMVI – 24.3%, with a residual form – 21.9%, compared to the control group 41.2% ($p>0.05$) (Figure 2). Comparative analysis revealed a significant reduction in the number of cytotoxic suppressor T lymphocytes (CD8+). Thus, in Group I, this indicator was 14.8%, in Group II – 14.2%, Group III – 13.6%, compared to the control group's 20.5% ($p>0.05$). The depression of CD8+ T lymphocyte subpopulations may be a consequence of the direct and selective action of CMV on these cells or serve as a background on which CMV infection occurs. There is information in the literature that the virus itself integrates between CD4+/CD8+ (IRI).

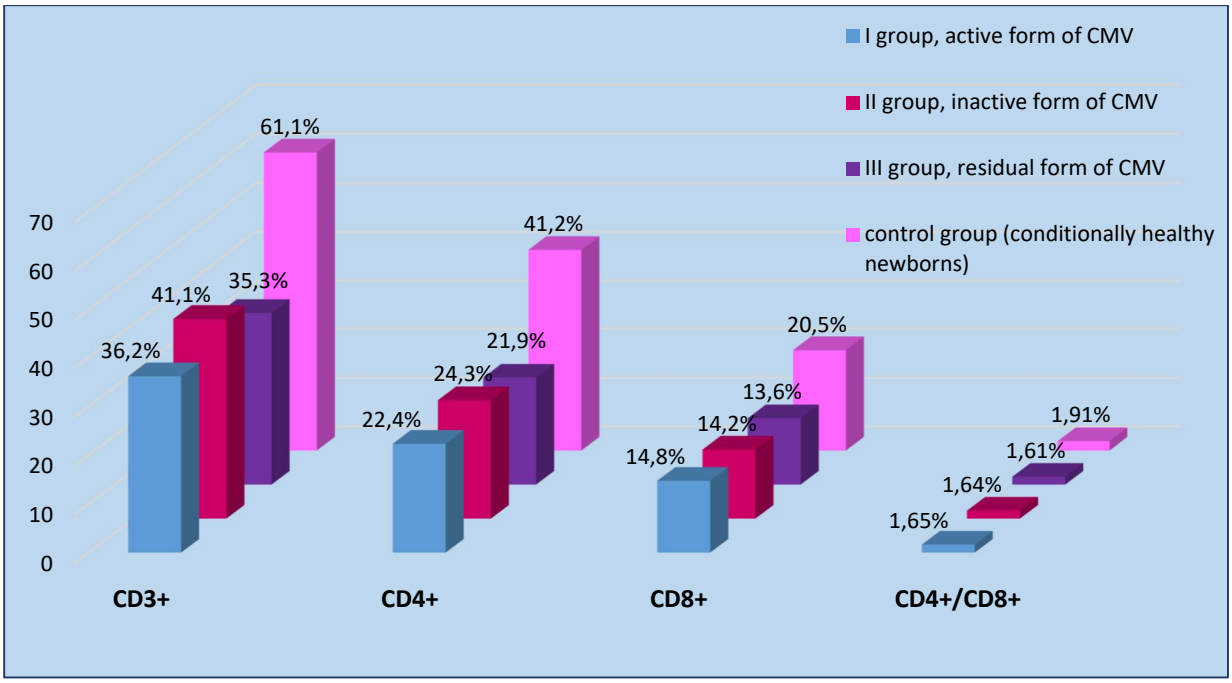

Fig. 2. *Comparative data on cellular immunity in newborns with CMV infection*

In newborns with an active form of cytomegalovirus infection (CMVI), the IRI level decreased to 1.65% in Group I, 1.64% in Group II, and 1.61% in Group III ($p>0.05$), due to a decrease in the values of T-suppressors and T-helpers, indicating immunosuppression. Thus, the comparative analysis of various T-lymphocyte populations in newborns with CMVI in the main groups indicates significant disruptions in the cellular component of immunity. It should be noted that in the induction of a specific immune response, a crucial regulatory role belongs directly to T-cells, specifically their regulatory subpopulations. According to literature data, T-cells produce a range of biologically active substances (interferon, suppressing the activity of viruses and serving as a powerful regulator of the proliferation and differentiation of all blood-forming cellular elements). Given the above and based on our research, it can be concluded that the reduction of T-cells contributes to the formation of disruptions in the mentioned biologically active substances. Thus, the state of immunosuppression underlying the pathogenesis of CMVI involves a sharp suppression of T-lymphocyte functions. Statistically significant reduction in T-lymphocyte function indicates the need for the development of a comprehensive therapy using immunomodulatory agents. Our research shows that the reduction of CD4+ leads to a decrease in the phagocytic activity of macrophages and neutrophils, and, in turn, CD4+ is capable of suppressing the immune response. The assessment of the cellular immune status allows us to conclude that newborns with CMVI experience immunosuppression of the T-cell component of immunity, which ultimately leads to the formation of immune deficiency of varying severity.

Conclusion:

1. Newborns typically exhibit a generalized cytomegalovirus infection with multi-organ involvement and a variety of clinical manifestations.
2. Generalized cytomegalovirus infection is accompanied by immunosuppression of the cellular component (deficiency of T-lymphocytes carrying CD4+ and CD8+ markers; decrease in the immune-regulatory index), ultimately leading to the development of an immune-deficient state.
3. Newborns with generalized cytomegalovirus infection show lymphocytosis, monocytosis, anemia, and increased transaminase activity in peripheral blood.

XÜLASƏ

Sitomeqalovirus infeksiyası olan yeni doğulan uşaqlarda hücəriyyətli immunitetin xüsusiyyətləri

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Açar sözlər: *yeni doğulmuş uşaq, immun sistemi, viruslar, sitomeqalovirus infeksiyası, hüceyrə immuniteti*

Bizim apardığımız elmi tədqiqatda 284 sayda yenidoğulmuş uşaq daxil edilmişdir. 110 sayda (38,7%) yenidoğulmuş körpədə CMV infeksiyası aşkar olunmuşdur. Anamnestik məlumatların təhlili göstərdi ki, bütün analar fəsadlı mamalıq-ginekoloji anamnezə malikdirlər.

Tədqiqatların nəticələri göstərdi ki, yenidoğulmuş uşaqlarda CMV infeksiyası poliorqan və polimorf təzahürlərlə xarakterizə olunur. CMVİ-nın immunoloji xüsusiyyətlərini müəyyən etmək üçün yenidoğulmuş körpələrdə hüceyrə immuniteti araşdırılmışdır.

Qenerilizə şəklində gedən sitomeqalovirus infeksiyası hüceyrə immunosupressiyası ilə müşayiət olunur (CD4+; CD8+ markerləri daşıyan T-limfositlərin çatışmazlığı; immunorequlyator indeksinin azalması). Nəticədə bu immun çatışmazlığı vəziyyətinin inkişafına gətirib çıxarır. Periferik qanda CMVİ ilə olan yenidoğulmuş uşaqlarda limfositoz, monositoz, anemiya və transaminazların aktivliyinin artması müşahidə olunur.

РЕЗЮМЕ

Особенности клеточного иммунитета у новорожденных детей с цитомегаловирусной инфекцией

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Ключевые слова: *новорожденный, иммунная система, вирусы, цитомегаловирусная инфекция, клеточный иммунитет*

Нами были обследованы 284 новорожденных детей. У 110(38,7%) новорожденных детей выявлена ЦМВИ. Анализ анамнестических данных показал, что все матери имели отягощенный акушерский анамнез.

Результаты проведенных исследования показали, что для новорожденных характерна генерализованная ЦМВИ с полиорганностью и полиморфностью клинических проявлений. Для выявления нарушений и определения иммунологических особенностей при ЦМВИ новорожденным младенцам оценивали клеточный иммунитет. Генерализованная цитомегаловирсуная инфекция сопровождается иммуносупрессией клеточного звена (дефицит Т-лимфоцитов, несущих маркеры CD4+; CD8+; снижение иммунорегуляторного индекса), что в конечном итоге приводит к развитию иммунодефицитного состояния. Для новорожденных с генерализованной цитомегаловирусной инфекцией в периферической крови наблюдается лимфоцитоз, моноцитоз, анемия, повышение активности трансаминаз.

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