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Infection and Incidence of Herpes Viruses in Neonates in Aktobe Region of Kazakhstan

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Abstract

The aim of the study was to investigate the incidence and morbidity of herpes viruses in neonates in Aktobe region of Kazakhstan. Were analyzed The aggregate data of neonatal mortality in the Republic of Kazakhstan for the period 2010-2014 were analyzed, a retrospective analysis of medical records of 1,544 patients was conducted, 938 sera of blood of unhealthy newborns were surveyed for markers of intrauterine infection. Aktobe is a region with average neonatal mortality rates (1.33‰) due to late mortality (0.59‰) despite the low rate of early neonatal mortality (0.74‰). The infant mortality rate from congenital anomalies among children under one year in Aktobe region and in Aktobe city decreased in 2011 compared to 2010 (9.9 and 9.5 per 10,000 of live births, respectively) and increased again in 2012 (by 1.1 and 4.5, respectively). The proportion of mortality from cytomegalovirus infection (CMVI) in the general mortality rate amounted in 2010 to 50%; in 2011, 60%; and in 2012, 66.7%. The frequency of neonatal jaundice among newborns in Aktobe amounted to 4.9-7.5%. Intrauterine infectious viral hepatitis among newborns occurs at a frequency of 1.15 and 2.2%. The incidence rate of hepatitis per 1,000 babies is not equal—13.5, 21.9, 11.5. A high prevalence of cytomegalovirus (CMV) antibodies (99.0%) and herpes simplex virus (HSV) (92.5%) was detected. Prevalent was the detection of IgG (91.7%) in patients with clinical manifestations of CMVI. According to the infectious morbidity, the frequency of incidence of CMVI is 4.61, and the frequency of "infection" is 52.5 in general in 57.2 per 1,000 children in the first year of life. Similarly, the frequency of incidence of herpes infection is 0.35, and the frequency of "infection" is 20.97 in general in 21.3 per 1,000 children in the first year of life. The so-called infected with CMV children—234 (51%)—and infected with HSV—63 (34%)—had the obvious clinical manifestations, so they should be attributed to the illness.

Keywords: Intrauterine infection; Infection; Morbidity; Cytomegalovirus; Herpes simplex virus

Introduction

In the early twenty-first century, the World Health Organization's (WHO) experts predicted that it will be a century of opportunistic infections because of the increasing influence of adverse environmental factors on the human body, primarily on the immune system [1]. Among the many agents that have a direct impact on the immune system, those of a special note are the viruses of the herpes family, which are widespread in the human population. The herpes simplex virus (HSV) antibodies are found in 70-100% of the population; the cytomegalovirus (CMV) neutralizing antibodies, in 70-80% of adults' blood. The detection rate of anti-CMV antibodies increases with age. Specific antibodies are detected in 30-70% of children less than two years; and in 50-80% of persons, at the age of 15-19 [2]. The Epstein-Barr virus (EBV) is found in about 90-92% of the world's population; 60% of cases of infectious mononucleosis are 2-20 years old. And the primary EBV contamination occurs at an early age—less than three years [3].

Herpes viruses occupy a leading place in the perinatal pathology at the present stage. This is due to the prevalence of perinatal infection because of the growth of the infection in women of childbearing age, as well as opportunities (4-10%) of perinatal infection from mother to infant [4,5]. Among the pregnant women, they account for 42.6 of 94.5%. In 4-5% of pregnant women, the virus is excreted with the urine; in 10% of the women, it is found in scrapings from the cervix; in 5-15% of lactating mothers it is found in the milk [6]. An intrauterine infection accounted for one-third of perinatal mortality and its prevalence ranges from 1:3,000 to 1:100. 63% of children with intrauterine infection are born with no signs of infection; 24%, with questionable signs of infection; and only 13%, with clinical manifestations [7]. Among neonatal deaths from various causes a clinic of generalized CMVI is seen in 5-15%. In newborns, CMVI is found in 0.5-2.5% of cases—occurs, as a rule—latent. According to the autopsies, the frequency of CMVI ranges from 2.2% in children dying within the first month of life to 63.4% of deaths in the second half of their life, with the maximum mortality falling within 1-5 months of age. Clinically distinct forms of intrauterine CMVI can cause severe pathology and even the death of the child [8,9].

Herpes viruses, having a broad tissue tropism, are capable for lifelong persistence and latency in the body of an infected person. Moreover, the herpes virus is able to block and evade the immune levels of protection, to escape from the T-killers and Natural-killer cells, and to successfully modify the immune response of humans [10]. Herpesvirus infection can occur in the form of generalized and localized forms and in the form of a "slow" infection. There are well known facts that even for asymptomatic forms of 5-15% of children in the next 1-2 years and the following are registered at a later date: the disorders of the central nervous system (CNS) (60 to 100%), the diseases of the respiratory tract (from 15.4 to 69.2%), liver disorders (15.4%), and other forms of embryopathy and fetopathy [11-13]. Latent and persistent forms of herpesvirus infections that are not manifested clinically create a false opinion about the low level of their prevalence. The situation is complicated by the fact that serological markers of CMVI in children during the first five years of life, infected as both prenatal and postnatal, are detected in 40-60% of cases [14].

The etiologic spectrum of congenital infections of Toxoplasmosis Other diseases Rubella Cytomegalovirus Herpes simplex virus (TORCH)-complex, which is characterized by the veiling and the

effacement of clinical manifestations, and sometimes by a variety of clinical syndromes, is expanding [15]. The liver disorders in congenital infections were observed in 40-63.3%; and gastrointestinal tract disorders, in 48% of children [16]. CMV hepatitis in the structure of acute icteric hepatitis of viral etiology is observed in 1% [17]. The prenatal and acquired viral hepatitis caused by the CMV, an EBV, HSV I, II, VI types are intensively studied [18,19]. Children without clinical symptoms are most likely to develop serious complications up to cerebral palsy, delayed mental and physical development with sensory impairments, i.e., leading to a sharp decline in the quality of life of the child [20]. Therefore, taking into consideration the herpesvirus infection, "we must distinguish between the concept of 'infection' and 'morbidity', as in the case of infections (contamination), including the children of early age, pathology is not always developed or its formation is deferred"[21].

The prevalence of herpes viruses in the human population, especially among women of childbearing age, the ability for the lifelong persistence and latency in the body of an infected person, the ability for the blocking of and avoiding the levels of immune defence, to escape from the immunological control, successfully modifying the immune response of a person dictates the necessity of studying the occurrence of herpes viruses in a specific category of the child population. With their relevance in perinatal pathology, the lack of specific clinical signs of herpesvirus infections, particularly of the immune response in children of the first year of life impede the recognition of the time of infection and the manifestation of congenital infections, accompanied by a liver damage. Polymorphisms of the variants of the clinical course of hepatitis (from the nonjaundice to cholestatic) and a different duration of the disease dictate the need for early diagnosis and early therapy. Taking into consideration the lack of information about prenatal infections in newborn infants, the aim of the study was to investigate the incidence and morbidity of herpes viruses in neonates of the Aktobe region of Kazakhstan.

Materials and Methods

In the first stage of the study, the research material was presented by the aggregated data of children's deaths in the first 28 days because of the intrauterine infections (P23—congenital pneumonia, P35-39—infections that are specific to the perinatal period) in the Republic of Kazakhstan (RK) in terms of the areas for the period 2010-2014. Thus the dead were calculated according to the place of death. Data of the Committee of Statistics of the Ministry of National Economy of the Republic of Kazakhstan on the number of live births for 2010-2014 was used. As the main method in the study of neonatal mortality, a retrospective study using the descriptive and analytical methods of medical statistics and epidemiology [22] was used. In the second phase, a retrospective analysis of medical records in the history of child development of 1,544 patients (form No. 112/y) for the period 2012-2014 was carried out in urban hospitals for further diagnosis of "neonatal jaundice". The diagnosis "neonatal jaundice" is set in accordance with the provisions of the Clinical Protocol for diagnosis and treatment of "Neonatal jaundice", approved by Ministry of Health of the Republic of Kazhakstan dated January 21, 2014.

In the third stage of the etiological verification of intrauterine infections 938 sera of blood of unhealthy children at the age of three days to 12 months of life who were hospitalized in the city's and regional children's clinical hospitals in Aktobe in 2013 were examined. Antibodies IgM and IgG to the antigens of CMV, HSV, toxoplasmosis, and chlamydia were determined by enzyme immunoassay analysis (EIA). The authors performed a prospective analysis of 403 patients with the diagnosis "infectious viral hepatitis." Infectious viral hepatitis was verified on the basis of anamnestic and clinical data and the results of laboratory tests. The viral etiology of infectious hepatitis was verified by the results of enzyme immunoassay analyzer "BioRad" with reagents from "Vector-best" (Russia), if necessary in parallel with the determination by polymerase chain reaction (PCR) for CMV DNA in various biological substrates (blood, urine). Clinical and laboratory parameters of liver injury were assessed by jaundice with coverage of zones according to Kramer, and the size of the liver and spleen. The content of total bilirubin with fractions and the activity of hepatic-cellular enzymes were determined with the Cobas 6000 analyzer using reagents of "C6000 Roche" (Switzerland). The study was performed in a licensed clinical diagnostic laboratory "OLYMP" (license No. 30, LP00545DM, series 0007678; on March 11, 2008, the international accreditation ISO 15189:2012) was passed. A statistical processing was performed using the standard software package Statistica 7.0.

Results and Discussion

One of the leading methods of scientific analysis of the epidemiological situation is mapping [23], which allows analyzing the spatial distribution of the frequency of neonatal deaths. The mapping was carried out on the basis of indicators of neonatal mortality (overall, early, and late) after a preliminary determination of average annual performance in individual medico-geographical regions, then the arithmetic mean (M) coefficients and standard deviation (sigma) were calculated, and on this basis a scale of levels of cartogram, grids with grouping mortality was defined. It should be noted that the data of the Republican organizations were excluded from the calculation. On the cartogram of neonatal mortality in general were determined the following groups of regions (Figure 1a):

1. Regions with low rates (up to 1.28‰)—South Kazakhstan region (0.83‰), North Kazakhstan region (0.93‰), West Kazakhstan region (1.20‰), Pavlodar region (1.21‰), and Astana (0.93‰);
2. Regions with average rates (from 1.28 to 2.12‰)—Almaty region (1.28‰), Aktobe region (1.33‰), Karaganda region (1.48‰), Atyrau region (1.50‰), Zhambyl region (1.53‰), Kyzylorda region (1.89‰), Mangystau region (1.96‰), and East Kazakhstan region (1.96‰);
3. Regions with high rates (from 2.12‰ and above)—Kostanay (2.39‰), Akmola (2.66‰) regions, and Almaty (4.18‰).

Spatial assessment of early neonatal mortality identified the following regions (Figure 1b):

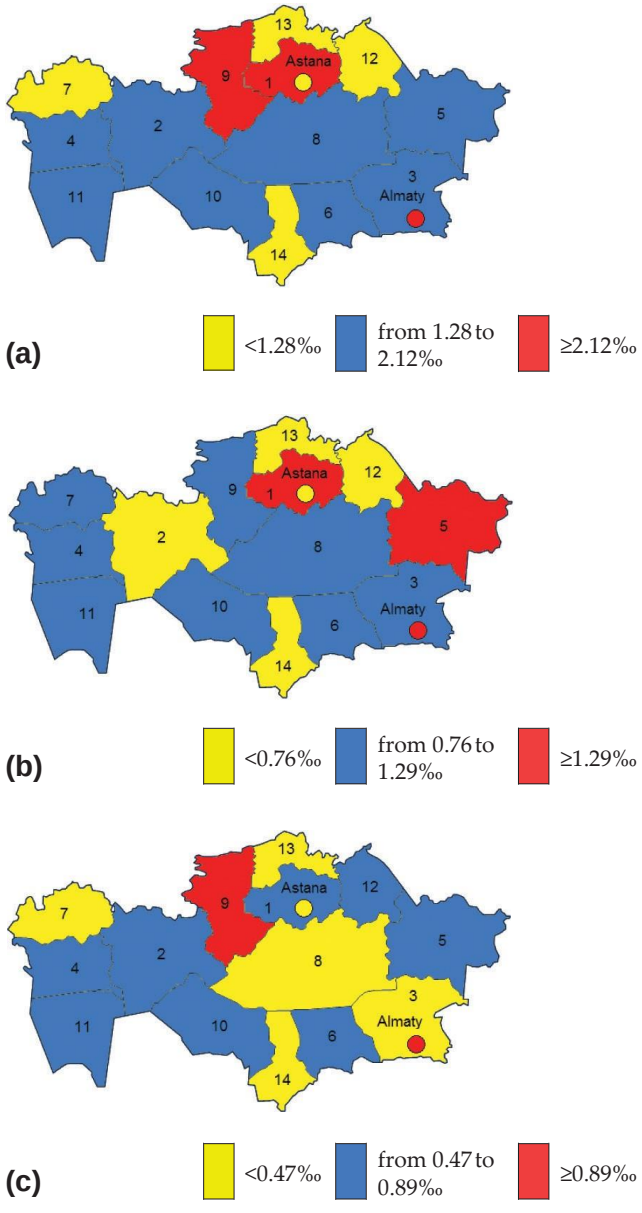
1. With low rates (up to 0.76‰)—South Kazakhstan region (0.38‰), Pavlodar region (0.51‰), North Kazakhstan region (0.52‰), Aktobe region (0.74‰), and Astana (0.66‰);
2. With average rates (from 0.76 to 1.29‰)—Atyrau region (0.85‰), West Kazakhstan region (0.85‰), Zhambyl region (0.90‰), Almaty region (0.90‰), Kostanay region (0.96‰), Karaganda region (1.07‰), Mangystau region (1.11‰), and Kyzylorda region (1.26‰);
3. With high levels (from 1.29‰ and higher)—East Kazakhstan region (1.29‰), Akmola region (2.11‰), and Almaty (2.30‰).

On the cartogram of a late neonatal mortality are represented regions (Figure 1c):

1. Regions with low rates (up to 0.47‰)—Astana region (0.27‰), West Kazakhstan region (0.34‰), Almaty region (0.38‰),

Karaganda region (0.42‰), North Kazakhstan region (0.45‰), and South Kazakhstan (0.45‰) region;

2. Regions with average rates (from 0.47 to 0.89‰)—Almaty region (0.55‰), Aktobe region (0.59‰), Kyzylorda region (0.64‰), Zhambyl region (0.64‰), Atyrau region (0.65‰), East Kazakhstan region (0.67‰), Pavlodar region (0.70‰), and Mangystau (0.80‰) region;
3. Regions with high rates (from 0.89‰ and above)—Kostanay region (1.43‰) and Almaty (1.88‰).



Regions: (1) Akmola. (2) Aktobe. (3) Almaty. (4) Atyrau. (5) East Kazakhstan. (6) Zhambyl. (7) West Kazakhstan. (8) Karaganda. (9) Kostanai. (10) Kyzylorda. (11) Mangistau. (12) Pavlodar. (13) North Kazakhstan. (14) South Kazakhstan

Figure 1: Map of the intrauterine mortality because of the neonatal infections in Kazakhstan in 2010-2014

Thus, Aktobe region is a region with average neonatal mortality rates (1.33‰) due to the late neonatal mortality index (0.59‰), despite of the low rate of early neonatal mortality (0.74‰). The results of spatial assessment (cartograms) of neonatal mortality because of the intrauterine infection dictate the need for focused studies of infection and the incidence of intrauterine infections in newborns, with the aim of reducing them.

According to the Statistics Board of Aktobe region, the infant mortality rate in the region tends to decrease, as in general throughout the territory of the Republic of Kazakhstan. A mortality rate (per 10,000 of live births) due to the congenital anomalies among children under one year of age, as in the region and in the city was mixed (Figure 2).

In 2011, the infant mortality rate decreased compared to 2010 (9.9 and 9.5, respectively) and increased again in 2012 (by 1.1 and 4.5, respectively). According to the variety of clinical syndromes and the development of multiple organ failure and adverse outcomes of severe generalized forms of intrauterine infection, we studied causes of mortality in infants in the city's children's clinical hospital in 2010-2012. Analysis of mortality structure showed the increased ratio of deaths from the CMVI in the general structure of mortality: in 2010—50%, in 2011—60%, and in 2012—66.7%.

It should be noted that the initial diagnoses at the time of the admission of patients were not intrauterine infections but conjugational and/or neonatal jaundice. With the diagnosis of "neonatal jaundice" from the city's polyclinics No. 2 and No. 4 of Aktobe in 2010, 199 newborns (5.6% of the total number of births of newborns, geographically fixed) were directed, in 2011—304 newborns (8.1%), in 2012—407 (9.8%), in 2013—433 (9.8%) newborns. The number of hospitalizations of newborns with diagnosed "neonatal jaundice" and infants over one month of living with a diagnosis of "conjugational jaundice" increased. Among them in 2011, 5.59% were hospitalized with a final confirmed diagnosis of "fetal hepatitis"; in 2012—1.47%. Only in a regional clinical hospital annually the number of patients with infectious viral hepatitis ranged from 4 to 4.8% of the total number of treated patients. This indicates the inconsistent trends in the prevalence of liver damage. And with the unpredictable development of neonatal jaundice, doctors of an outpatient segment, according to the strategy of integrated management of childhood illness in the identification of a "severe jaundice," immediately sent the newborn to the hospital. According to the prevailing diagnosis of "neonatal jaundice" in newborns, the analysis of the rate of registration among children of the first year of life over the three years in urban health institutions have revealed the opposite trend, similarly as the incidence of infectious viral hepatitis (Table 1).

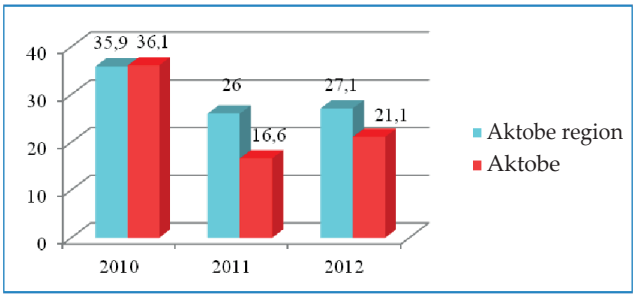


Figure 2: The congenital anomalies's mortality rate in the age of less than one year per 10,000 of live births

Treatment-and-prophylactic companies	In 2012		In 2013		In 2014	
	The number of children under one year	The number of children with neonatal jaundice	The number of children under one year	The number of children with neonatal jaundice	The number of children under one year	The number of children with neonatal jaundice
Municipal polyclinic No. 1	1,651	75	1,589	67	1,678	43
Municipal polyclinic No. 2	2,880	178	2,287	147	2,584	148
Municipal polyclinic No. 3	860	32	841	48	942	43
Municipal polyclinic "Bolashak"	201	23	219	45	228	14
Municipal polyclinic No. 4	1,258	28	1,646	57	1,663	77
Municipal polyclinic No. 5	903	83	880	86	1,032	67
Advisory-diagnostic center	–	21	–	2	–	6
Clinic of a family medicine	308	22	300	24	379	31
Railway hospital	502	10	590	17	548	12
Total	8,563	472	8,352	631	9,054	441
%	–	5.5	–	7.5	–	4.9
The rate per 1,000	–	55.1	–	75.5	–	48.7

Table 1: The prevalence of neonatal jaundice in treatment-and-prophylactic companies of Aktobe

Category of children	In 2012	In 2013	In 2014
The number of children less than one year	8,563	8,352	9,054
The number of children with viral infectious hepatitis	116	183	104
%	1.35	2.2	1.15
The rate per 1,000	13.5	21.9	11.5

Table 2: The incidence of infectious viral hepatitis in Aktobe

The frequency of neonatal jaundice among the newborns in Aktobe in different years varies without trends from 4.9 to 7.5% (the rate per 1,000 children in the first year of life is 48.7-75.5).

A further testing by immunoenzyme analysis and PCR has detected the persistence of viruses in peripheral blood. The intrauterine infectious viral hepatitis among newborns occurs with a frequency of 1.15-2.2%, which is consistent with the literature data [17]. And the incidence rate of hepatitis per 1,000 babies is different: 13.5-21.9-11.5 (Table 2).

Statistical data of the incidence of individual nosology does not give a clear picture of the prevalence of congenital infections of TORCH-complex in infants and children of the first year of life, in particular causing liver damage. Due to the delayed formation of organic pathology with the infection in the system of "mother-fetus" there cannot be any certain parallels between infection and the manifestation of the pathological process in the herpesvirus infections. Taking into account the epidemiological characteristics, especially that the factors in the transmission of CMV can almost be all the biological substrates and secretions, which contain the virus, and different transmission paths, the main source of CMV infection of children was mother-carriers. Different variants of infectious process are possible.

Transplacental infection of the fetus may occur at the primary infection of the mother and in the reactivation of a chronic infection. The intrauterine infection of the fetus by CMV in women with primary infection reaches 30-50%. In the secondary infection (reactivation of latent persistent infection), risks of a fetal infection and the development of severe forms of CMVI are much lower and do not exceed 2%. In infected children, a congenital CMVI proceeds mainly asymptomatically. In those women who have undergone a primary infection, an anti-CMV immunity is formed, which protects fetuses from developing a severe CMVI. During childbirth the fetus may aspirate an infected amniotic fluid. Also the penetration of CMV is possible through the damaged skin of the child from the mother's vaginal secretions. CMVI is one of the most common diseases that can be transmitted by a transplacental route. The frequency of a fetal CMV infection ranges from 1 to 3%. During and after childbirth, another 5-30% of newborns are infected.

Infants often get infected through breast milk. CMV is excreted with milk in 30-40% of seropositive mothers, and 30-70% of children who drink this milk would be infected [24].

It is known that "CMV has a cytopathic effect, transforms the formation of giant cells, the genome of the virus contains DNA. CMV has an affinity to the secretory epithelium of the salivary glands, where it gets hematogenously in the result of viremia. The infected with the virus cells mutate, acquiring a characteristic pathologic appearance of giant cells with inclusions, representing clusters of the pathogen. Replication of the virus occurs in the leukocytes, cells of the mononuclear phagocyte system. The replication process ends with the formation of a subsidiary of viral particles, which after leaving the cell interact with the receptors on neighboring cells and penetrate inside, strike them. In a latent form is possible a life-long persistence of the virus" [25].

To identify the prevalence of infection and morbidity, we have analyzed the research results for the presence of antibodies to antigens of major pathogens of TORCH-complex in the peripheral blood of children in their first year of life, for markers of CMV—501 children, for markers of HSV—200 children, on markers—125, markers—112 (Table 3).

The immunoenzyme analysis showed a high detection rate of antibodies to CMV (99.0%) and HSV (92.5%) among 938 of the surveyed children of the first year of life compared to a slight detection of antibodies TOXO (17.6-10.2%) and chlamydia (5%). A detection of CMV IgG (91.7%) was prevalent, and CMV IgM was detected only in 8.0% of cases. CMV IgM, indicating an acute phase of the disease, was identified in the majority of the surveyed (29 infants) without any clinical manifestations of the disease. In a small number of patients with positive result of CMV IgM was associated with the clinic of conjugational jaundice (five patients), fetal hepatitis (three patients), intrauterine infection (two patients), intrauterine pneumonia (in two

Category of patients	Cytomegalovirus infection	Herpes infection	Toxoplasmosis	Chlamydia
The number of patients with positive IgM and IgG to antigens of the pathogen	40 (8.0%)	3 (1.5%)	1 (0.8%)	1 (0.89%)
The number of patients with a positive IgG to antigens of the pathogen	456 (91.0%)	182 (91%)	7 (5.6%)	4 (3.57%)
The number of patients with negative results	5 (1.0%)	15 (7.5%)	117 (93.6%)	107 (95.5%)
Total examined	501	200	125	112

Table 3: Detection of antibodies IgG and IgM to antigens of the causative agents of intrauterine infections among children in the first year of life

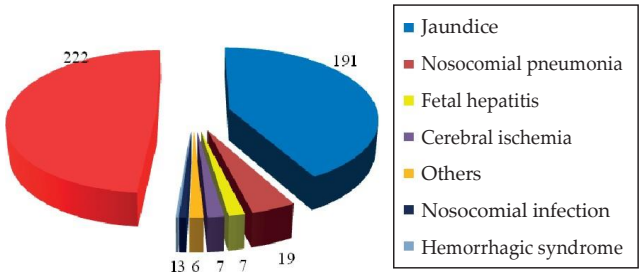


Figure 3: Detection of CMV IgG in children with various pathologies

patients). Conversely, CMV antibodies IgG, showing the nonactivation period of the virus and a repair, were observed in conjunction with the clinic overt diseases (Figure 3). Anti-CMV IgG were identified in infants with the clinic of jaundice (191 patients), the intrauterine pneumonia (19 patients), fetal hepatitis (seven patients), cerebral ischemia (seven patients), intrauterine infection (three patients), hemorrhagic syndrome (one patient), and other diseases (six patients).

The markers of HSV-IgM were detected in only three patients without any obvious clinical manifestations. HSV-IgG that is produced in the period of reconvalescence is revealed in the background of clinical manifestations: jaundice conjugational (42 patients), neonatal jaundice (three patients), fetal hepatitis (eight patients), cerebral ischemia (five patients), intrauterine infection (two patients), fetal pneumonia (one patient), anemia (one patient), and a purulent mastitis in one case. The results show the heterogeneity of the clinical manifestations of herpesvirus infections (CMV and HSV) and the lack of a correlation of different markers with the developed clinical picture. This is consistent with the literature data that the "detection of CMV in the first days of life of a newborn in any biological fluids by PCR is a proof of intrauterine infection. A detection of virus in the blood and a specific IgM indicates to an acute phase of infection, since the antibodies in this class do not penetrate across the placenta. At the same time, the absence of IgM, particularly in infants that were born from the infected mothers, cannot exclude the diagnosis because the IgM-response can be "masked" by the high concentration of IgG or immunological tolerance. The increase in IgG-antibodies to 5-6 months, also confirms the infection of the child" [26].

Analysis of the Results

The immunoenzyme analysis among the examined children found a slight detection of antibodies TOXO (in 2010—17.6%; in 2011—9.4%; in 2012—10.2%) and chlamydia (5%). For the presence of antibodies to antigens of protozoa: TOXO and chlamydia were surveyed in 125 and 112 children in the first year of life, respectively. Antibodies TOXO-IgM showing an acute phase of infection were detected only in one case—in a child with the clinic of a conjugational jaundice. Among the 125 of investigated patients, in seven of them (5.6%) TOXO-IgG were positive, and most of them were without any clinical symptoms. And only in one child a clinic of conjugational jaundice was observed along with a positive result of TOXO-IgM. Chlamydia-positive IgM and IgG were detected in only one patient (0.89%). Four patients were infected with the presence of high titers of IgG antibodies in the blood.

Thus, the results show heterogeneity of clinical manifestations of congenital infections and the lack of correlation of detection of IgM and IgG to CMV and HSV between the clinical symptoms (hepatobiliary, respiratory, cardiovascular systems, CNS) and indicate the difficulties in the diagnosis of congenital herpes virus infections. Antibodies CMV-IgG always show the persistence of the virus in all stages: in the acute phase, in the period of activation, and out of activation CMVI; there's only one difference in the avidity of antibodies. The immaturity of the newborn's immune system contributes to this and also to the persistence of transplacentally received antibodies from the mother, the immunocompatibility of protective and compensatory mechanisms in the first year of a baby's life. Therefore, along with immunoenzyme analysis, it is necessary to conduct PCR.

According to the infectious morbidity the frequency of "morbidity" of CMVI is 4.61, and the frequency of "infection" of CMV is 52.5, in general, 57.2 per 1,000 children in the first year of life. Taking into consideration that among the so-called infected patients 234 (51%) of children had the obvious clinical manifestations; we should consider them as sick. Similarly, the frequency of "morbidity" of herpes infection is 0.35, and the frequency of "infection" of herpes simplex of the I and the II types is 20.97, in general, 21.3 per 1,000 children in the first year of life. Keeping in mind that among the so-called infected patients 63 (34%) of babies had a manifestation of a clinic; we should consider them also assick.

The study findings are consistent with literature data that the outcomes of CMV infection may range from asymptomatic forms with adequate immune response to the intrusion of the virus or the formation of a persistent infection to severe generalized forms and death. This is due to the different mechanisms of damage of hepatocytes in congenital hepatitis: from direct action of the virus on the liver—viral cytolysis—to indirect action through the immune system and a mixed form [27]. According to literature, the incidence rate of CMVI in Russia in 2003 among children under one year of age consisted of 11.58 per 100 thousand; 1-2 years—1.01; 3-5 years—0.44 per 100 thousand. In Moscow in 2006, the incidence rate of CMVI in children under the age of 14 was equal to 3.24 per 100 thousand of the children's population. In 20-30% of healthy pregnant women, CMV is presented in saliva; in 3-10%, in the urine; and in 5-20%, in the cervical canal or vaginal secretions. The virus is found in breast milk in 20-60% of seropositive mothers. The intrauterine liver damage in CMV is observed in 40-63.3% of the cases, but the clinical manifestation is registered in only 10-15% of cases [28].

The proposed criteria for the laboratory diagnosis according to the clinical protocol "Cytomegalovirus infection in children", approved by No. 23 on December 12, 2013, are not always considered by the neonatologists and paediatricians for the diagnosis of CMVI both in hospital and in primary health care. The lack of the competence of a physician in the interpretation of the obtained results of the serological study by the immunoenzyme analysis method leads to the incorrect diagnosis. A survey of a patient without the use of relevant protocols and methodological requirements leads to the fact that the doctors of practical public health, in the case of favorable clinical outcome discharge patients with a diagnosis of "neonatal or conjugational jaundice", do not take into account the presence of CMV IgG antibodies. However, recognizing that CMV is a hepatotropic agent, traditionally it is believed that this virus primarily affects the bile ducts with the development of cholestatic hepatitis and a congenital abnormality of the bile duct [29,30]. A severe liver damage with the development of cholestatic jaundice and the formation of fibrosis of the liver occurs with a frequency of 1:2,500 to 1:10,000 births [31]. There is a significant variability of the clinical course of congenital hepatitis from asymptomatic forms to severe cholestatic forms with the development of fibrosis and cirrhosis. The course of neonatal hepatitis of CMV etiology is "more severe and manifests with prolonged cholestatic jaundice in 91.7% with the development of acholia and urobilia in every third child, with a hepatomegaly, splenomegaly, and a formation of a severe fibrosis in 50.0% of children. At the same time, in patients with HSV infection, and HSV in a combination with a DNA infection (CMV, HBV) a liver fibrosis was not registered" [32]. In course of CMV hepatitis, the pathological and morphological changes rapidly progress in comparison with viral hepatitis C and B, which are traditionally believed to be slow infections with a gradual transition to a chronic form, and later with the outcome of liver cirrhosis.

Conclusion

The analysis of the spatial distribution of the frequency of mortality by the method of mapping revealed regions of Kazakhstan with low, medium, and high rates of neonatal, early, and late neonatal mortality. Aktobe region is a region with average neonatal mortality rates (1.33‰) due to the late neonatal mortality (0.59‰), despite the low rate of early neonatal mortality (0.74‰). The infant mortality rate in the region tends to decrease, as in general throughout the territory of the Republic of Kazakhstan. An infant mortality rate from congenital anomalies among children under one year in Aktobe region and in Aktobe city decreased in 2011 compared to 2010 (9.9 and 9.5 per 10,000 live births, respectively) and increased again in 2012 (by 1.1 and 4.5, respectively). The proportion of mortality from CMVI in the general mortality rate amounted in 2010, to 50%; in 2011, to 60%; and in 2012, to 66.7%.

The frequency of neonatal jaundice among newborns in Aktobe amounted to 4.9-7.5% (the rate per 1,000 children in the first year of life was 48.7-75.5). Intrauterine infectious viral hepatitis among newborns occurs with a frequency of 1.15 and 2.2%. The incidence rate of hepatitis per 1,000 babies is not equal 13.5, 21.9, and 11.5. A further testing by immunoenzyme analysis and PCR have detected the persistence of viruses in a peripheral blood. Intrauterine infectious viral hepatitis among newborns occurs at a frequency of 1.15 and 2.2%. And the incidence rate of hepatitis per 1,000 babies is different: 13.5, 21.9, and 11.5.

The analysis of studies of the presence of antibodies to antigens of major pathogens of TORCH-complex in the peripheral blood of children of the first year of life by the immunoenzyme analysis showed a high detection rate of antibodies to CMV (99.0%) and HSV (92.5%) among the children in the first year of life, when comparing with a slight detection of TOXO antibodies (17.6 to 10.2%) and chlamydia (5%). A detection of CMV IgG (91.7%) in patients with clinic of a symptomatic disease was prevalent. Similarly, HSV-IgG were detected on the background of clinical manifestations of hepatitis, cerebral ischemia, and pneumonia. The heterogeneity of the clinical manifestations of congenital infections, and the lack of correlation of detection of IgM and IgG to CMV and HSV between the clinical symptoms, indicates the difficulties in the diagnosis of congenital herpes virus infections.

According to the infectious morbidity, the frequency of "morbidity" of CMVI is 4.61, and the frequency of "infection" of CMV is 52.5, in general, 57.2 per 1,000 children in the first year of life. Taking into consideration that among the so-called "infected" patients, 234 (51%) of children had the obvious clinical manifestations, we should consider them as sick. Similarly, the frequency of "morbidity" of herpes infection is 0.35, and the frequency of "infection" of herpes simplex of the I and the II types is 20.97, in general, 21.3 per 1,000 children in the first year of life. Keeping in mind that among the so-called "infected" patients 63 (34%) of babies had a manifestation of a clinic, we should consider them also assick.

The lack of competence of a physician in the interpretation of the obtained results of the serological study by the immunoenzyme analysis method leads to incorrect diagnosis of the intrauterine infection. A survey of a patient without the use of relevant protocols and methodological requirements leads to the fact that the doctors of practical public health, in the case of a favorable clinical outcome discharge patients with a diagnosis of "neonatal or conjugational jaundice," do not take into account the presence of CMV IgG antibodies. But this does not exclude in catamnesis the development of liver fibrosis; the pathological and morphological changes rapidly progress in comparison with viral hepatitis C and B.

Therefore, we studied the incidence of intrauterine infections, in particular, herpesvirus infections are untrue and understated as a result of registration under other diagnoses. Consider herpes viruses as a relevant problem, causes of perinatal mortality, economic costs of causal treatment, and their development in the future of a child with a disability; they should be recorded in the registry of infectious diseases for the reliable registration of morbidity, monitoring in the dispensary with a view to their rehabilitation and the prevention of complications.

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