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Clinical Correlation of Risk Factors for the development of Bilirubin Encephalopathy in Neonatal and Postneonatal Children

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Abstract
Jaundice and its pathological manifestations cause neurological disorders in children in the neonatal and post-neonatal period. According to the World Health Organization, the prolongation of neonatal jaundice or its pathological forms are developing, even among developed countries. sometimes causing neurological complications.In order to study the risk factors for the development of bilirubin encephalopathy in children in the neonatal and post-neonatal period, 80 babies with hyperbilirubinemia in the neonatal and post-neonatal period were selected from the department of infant resuscitation and pathology of newborn babies of the Perinatal Center of Surkhandarya Region. In order to determine the cause and development factors of bilirubin encephalopathy, the mother's age, hereditary diseases, epidemiological history, as well as somatic diseases of the mother, obstetric-gynecological history, the course of pregnancy and childbirth complications, the course of childbirth were studied. General blood analysis, biochemical analysis of blood: bilirubin and its fractions determine the level and course of complications of bilirubin intoxication. Bilirubin and its fractions in the blood analysis of each examinee were checked and monitored several times, because bilirubin and its fractions are important for the acute or chronic course of the disease and neurological disorders. evaluates the condition. Diagnosis of bilirubin encephalopathy, clinical-neurological status, prognosis and complications are inextricably linked with clinical-laboratory aspects. Pathological course of pregnancy: severe level of anemia, severe form of toxicosis, numerous abortions and urogenital diseases, maternal hypertension, endocrinopathies, intra-fetal infection and long-lasting gestosis create conditions for bilirubin intoxication and aggravate damage to the hematoencephalic barrier of the brain. resulting in increased toxic effects of bilirubin.

Keywords: Jaundice, Bilirubin Encephalopathy, Cerebral Palsy, Retrocollis, Postneonatal.

1. INTRODUCTION

Jaundice and its pathological manifestations cause neurological disorders in children in the neonatal and post-neonatal periods. [1]According to the World Health Organization, the prolongation of neonatal jaundice or its pathological forms is the most common in developing and even developed countries. Zan is causing neurological complications.[31],[3]Jaundice in newborns is still a serious issue in the modern world. The clinic and prognosis of the pathogenesis of bilirubin encephalopathy are being thoroughly researched. In particular, through an investigation of the literature on bilirubin encephalopathy, through an in-depth research of the reasons of disability, ideas are investigated, and the characteristics of the condition are explored in practice. In hyperbilirubinemia, the nature of the accumulation of the main amount of bilirubin in the deep roots of the brain has not yet been fully determined[2]. As a result of the accumulation of bilirubin, the basal ganglia, hypothalamus, nuclei of the brain column (e.g. oculomotor, cochlear, vestibular and olivary nuclei) and the brain acquire a yellow colour.[32],[5] Neonatal jaundice causes morbid and premorbid conditions as a result of acute bilirubin encephalopathy and complicated chorio-athetoid cerebral palsy[4]. Children are killed by acute bilirubin encephalopathy (ABE), a global illness that is most prevalent in the post-neonatal and neonatal periods. It is still unclear how this potentially fatal acute infantile episode and its progression to kernicterus are pathophysiologically explained. The classification of hyperbilirubinemia and its clinical implications, OBE, and subsequently, the nomenclature of kernicterus spectrum disorder (KSD) will all be covered in this study. After that, we go into the pathophysiology of OBE and talk about the clinical variables that affect it. We go into OBE and KSD's clinical correlations in great depth. In order to assist in lowering the occurrence of this mainly preventable condition, we offer a thorough approach to its diagnosis and end with a set of straightforward

clinical procedures that fall between these preventative and rehabilitative measures.A pathological condition resulting from necrosis of neurons and deep yellowing of neurons of the basal ganglia and brainstem nuclei is considered.[7] Acute bilirubin encephalopathy (ABE) is a worldwide morbidity and mortality, especially in newborns and young children. The pathophysiology of this life-threatening acute infantile event and its progression to kernicterus are still poorly understood. Bilirubin encephalopathy is rare but persists despite universal newborn screening.[8,9] According to scientific studies, studies have been conducted on the risk factors for the development of bilirubin encephalopathy and the causes of its complications, but information about some of the causes and pathophysiology remains unknown.[12,14] Developmental risk factors include prematurity, diseased or damaged erythrocyte breakdown, often incompatibility of the mother's blood group with the baby's blood group, i.e., hemolytic diseases of infants, pregnancy or increased production of bilirubin before 37 weeks of gestation (Gilbert's syndrome), which is a condition this leads to high bilirubin levels. Factors at riskNewborns frequently experience mild jaundice, but there are specific circumstances that greatly raise the risk of severe jaundice and kernicterus. A decrease in the enzyme glucose-6-phosphate dehydrogenase (G6PD), which is necessary for the proper functioning of erythrocytes and does not share a blood group with the mother, is one risk factor for kernicterusNewborn babies cannot metabolise and eliminate bilirubin.[14,16]] Bilirubin metabolism is carried out by uridine diphosphate glucuronyltransferase isoform 1A1 (UGT1A1) proteins, which carry out a reaction called "glucuronidation" (SN2 conjugation). [18]This reaction binds bilirubin with glucose, making it water-soluble, so it is more easily excreted in the urine or feces. UGT1A1 enzymes are present but inactive in the liver until several months after birth, as the maternal liver performs glucuronidation in the fetus.[19] Individual UGT isoform development in infants and young children was analysed, including fetal liver sampling, and demonstrated that pediatric mRNA and protein levels for URT1A1 did not differ from adults, but activity was lower.Although mild jaundice is very common in newborns, certain factors are known to increase the risk of severe jaundice and kernicterus significantly.[20,21] Risk factors for kernicterus include: deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), which does not share the blood group of the mother and child, this enzyme ensures the normal functioning of erythrocytes, hypotrophy, premature birth, sepsis, meningitis, yellowing of the skin due to improper nutrition, family history. [22,28] A history of jaundice or trauma during birth can increase the baby's risk of severe jaundice in most of these cases, but prompt treatment of high bilirubin levels will almost always prevent kernectura. Babies are also prone to severe jaundice and kernicterus because their livers are not fully developed and are not able to eliminate bilirubin from the blood[29]. Other risk factors include hypotrophy, premature birth, sepsis, meningitis, inadequate nutrition, a family history of jaundice, or birth trauma. The majority of these ailments can make the infant more susceptible to severe jaundice.However, kernectura is nearly always avoided with early treatment of elevated bilirubin levels.[30] Although there have been a few documented cases of kernicterus in adults, these are uncommon. It is widely believed that newborns are more susceptible to kernicterus because of the immature blood-brain barrier. Because their livers are still developing and unable to remove bilirubin from the blood, babies are also susceptible to severe jaundice and kernicterus.[31] The exact mechanism underlying the harm that bilirubin causes to neurons is unknown.However, it seems to involve multiple pathways, such as neuronal inflammation, excitotoxicity, bilirubin-related lipid peroxidation, and prolonged energy shortage. Microglial cell activation has been demonstrated in vivo; TNF-α and IL regulate pro-inflammatory cytokines, which in turn cause inflammation and necrosis of impacted cells. [25,26]

2. RESEARCH MATERIAL

To study the risk factors for the development of bilirubin encephalopathy in children in the neonatal and post-neonatal period, 80 babies with hyperbilirubinemia in the neonatal and post-neonatal period were selected from the department of infant resuscitation and pathology of newborn babies of the Perinatal Center of Surkhandarya Region. Out of 80 patients, 35 are girls and 45 are boys. For the examination, full-term babies with 4-5 points on the Kramer scale, with a total amount of bilirubin in the blood biochemical analysis of more than 256 μmol/l, with a duration of jaundice lasting longer than 2 weeks, were selected. Physiological development of newborns was evaluated based on the "Newborn development percentile table".

3. RESEARCH METHODS

In order to determine the cause and development factors of bilirubin encephalopathy, the mother's age, hereditary diseases, epidemiological history, as well as somatic diseases of the mother, obstetric-gynecological history, the course of pregnancy and childbirth complications, the course of childbirth were studied.

The following examination plans were provided for mother and child:

1. Genetic pathology observed in the mother before pregnancy, pathology of the hepatobiliary system, proportionality and somatic diseases of the parents' blood group were evaluated.
2. Maternal anamnesis during pregnancy, chronic genital pathology, iron deficiency anemia, gestosis, chronic fetoplacental insufficiency were studied by methods of general clinical examination of the factors causing intra-fetal infection and hypoxia of the fetus.

3. Objective assessment of newborns: general condition anthropometric indicators and adaptation to the external environment were assessed.
The degree of jaundice in the examination of newborns was evaluated based on the Kramer scale. Clinical anamnestic and laboratory examinations of all newborns were carefully observed. Accurate diagnosis and examination in newborns is more complicated than in other groups of diseases. Based on the examination plan, each newborn and premature In children aged 10 years old, the obstetric anamnesis and neurological status indicating the direct factors causing the pathological condition and the risk factors for the development of the disease were checked. Evaluation of the neurological status of newborns was performed using the traditional neurological examination and the Bayley scale of psychomotor development. BIND scale - The identification and assessment of the clinical and neurological status of encephalopathy caused by bilirubin intoxication was checked by the BIND scale. The clinical evaluation of those in the control group was carried out regularly. The general neurological examination of newborns and early-aged children was carried out several times during the day. The children in the control group were re-evaluated every month from the clinical and neurological examination up to one year of age. General blood analysis, blood biochemical analysis: bilirubin and its fractions determine the level and complications of bilirubin intoxication. Bilirubin and its fractions in the blood analysis of each subject were checked and monitored several times, because bilirubin and its fractions evaluate the acute or chronic course of the disease and the state of neurological disorders.

4. RESEARCH RESULTS AND DISCUSSIONS

The role of ante and intranatal factors in the origin of bilirubin encephalopathy was investigated and evaluated. According to obstetrical anamnestic surveys, most of them had mild and moderate acute respiratory infections during pregnancy (60-70%), and 60% of them had 2-3 repeated episodes. 8% had a relapsing and persistent type of ARVI, with persistent bilirubinemia. Anemia was observed in 70-80% of those examined. 1-2 levels of anemia were observed in the first trimester and the last trimester of pregnancy and there were 15 mothers who did not take blood-enhancing drugs, and 4 of them were born with fermentopathy with a high level of hyperbilirubinemia in their children. 3 levels of anemia (Hb 60-70 g/l) were observed in 2 pregnant women and the child was born with asphyxia. According to the examination analysis, diseases of the endocrine system were 26%, endemic goiter 9 (18%), teriotoxicosis 2 (4%) and diabetes were observed in 2 (4%) people. Cardiovascular system diseases were detected in 16%: the main group 10% in the comparison group 6 %. Arterial hypertension was observed in 6 people with coronary heart disease 2 (35 years old). Diseases of organs of the digestive system were found in 1/5 cases, mainly chronic gastritis 4 (8%) dysbacteriosis 3 (6%) chronic cholecystitis and biliary tract dyskinesia 6 %. Diseases of kidneys and urinary tract 21 (26%). Mainly chronic pyelonephritis, cystitis, kidney stone diseases were detected, and 6 (12%) cases of fetal swelling, preeclampsia and asphyxia in the child were found. It should be noted that systemic diseases were recorded in 4% of cases and neurological diseases in 2% of cases. Somatic diseases reduce the reactivity of the resistance of the mother's body, thus creating conditions for the development of this pathological condition in the fetus.

Table 1: Indicators of extragenital and genital diseases observed in mothers of newborns and infants in the study

№	Indicators Indicators of extragenital and genital diseases observed in mothers of newborns and infants in the study	Proportion of extragenital and genital diseases observed in mothers of newborns in the study
1	Anemia (2-3 degreeof anemia)	65 (81,25%)
2	ARVI	41 (51,25%)
3	Diseases of the endocrine system	17 (21,25%)
4	Diseases of the cardiovascular system	11(13,75%)
5	Genital diseases	43 (53,75%)
6	Kidney and urinary tract diseases	52 (65%)
7	Digestive tract diseases	4 (5%)
8	Systemic diseases	6 (7,5%)
9	Neurological diseases	7 (8,75%)

According to the results of the research, the development rate and frequency of bilirubin encephalopathy due to hyperbilirubinemia in hemolytic disease of newborns is high. Hemolytic disease is mainly caused by an imbalance between the parents' blood group or Rh factor. 60 (80%) of those examined had hemolytic disease. The following table shows the parents' blood groups and Rhesus factor according to the anamnesis analysis. According to the analysis of the table, the number of babies born from the marriage of father Rh(-) factor and mother Rh (+) factor was 38 (48%) with anemic and jaundice form of GK. The total amount of bilirubin in them was 400-500 μmol/l in the first week. The rate of meeting between the first and second groups of ABO

incompatibilities is high in babies born out of wedlock 15 (30%). Also, special risk factors for the development of bilirubin encephalopathy, a complication of BGK caused by ABO incommensurability: gestosis (25%) endocrinopathy (18%) OICs (10%) and 3 degrees of anemia (30%) STD infections (24%) and birth traumas (15%).

According to the analysis, gynecological diseases of mothers of babies born with bilirubin encephalopathy: non-specific inflammatory diseases: cervical erosion 4 (8%) chronic adnexitis 6 (12%) endometriosis 3 (6%) STD infection 10 (20%). STD: SMV toxoplasmosis and HPV.This gynecological pathology fetoplacental insufficiency causes the development of chronic intrauterine hypoxia and ischemic and hemorrhagic damage of the brain during the perinatal period, resulting in damage to the hematoencephalic barrier and increased sensitivity to bilirubin.

Pathological conditions observed in the first half of pregnancy: risk of miscarriage (22.3±4.7), preeclampsia I-III degree (30.1±5.1%), early toxicosis (46.4±5.2%). pregnancy gestosis (42.3±5.3%), acute infections were detected in 16 (36.4±5.2%) of pregnant women. 40.9±5.2% (18) of pregnant women had premature birth and 9.1±3.3% (4) had late birth. Chronic fetal hypoxia was observed in 15.9±3.8% of 7 newborns.

According to the observations, pathologies in the intra-natal period are also significant: premature discharge of the amniotic fluid (13, 29.1±5.1%), contamination of the amniotic fluid (10, 22.7±4.5%), entrapment of the umbilical cord around the neck of the fetus6 (13,6±3.3%) Early delivery 15 (34.1±5.1%), breech birth 6 (13.6±3.7%), breech birth - 3 (6.8±2.9%) Also, the pathological course of childbirth was observed in 50.3% of the risk factors for the development of bilirubin encephalopathy in newborns, in which 17.4% of unplanned cesarean sections were observed, 17.4% were vacuum extraction and 14.3% were traumatized by birth forceps.According to the anamnestic data, the main complaints are: jaundice of the body in 100% of children, restlessness 30 (60%) slowness of sucking 21 (41.5%) when sucking 23 (46.7%) sleep disturbance 35 (71%).

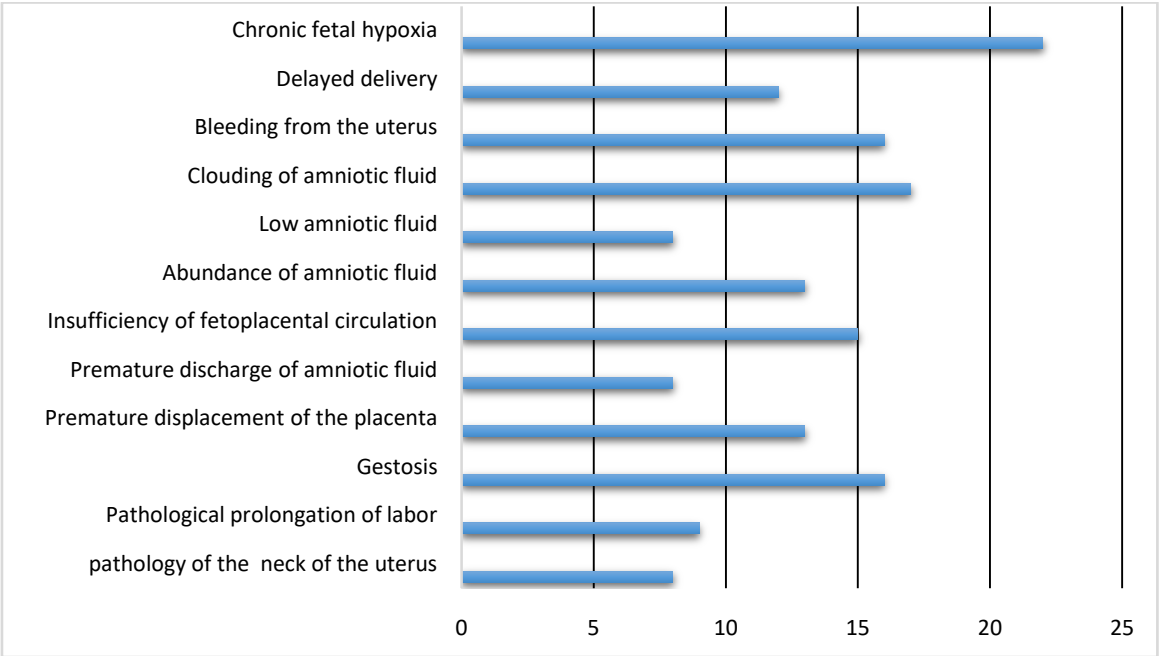

Diagram 1: Antenatal and intranatal risk factors during pregnancy of mothers of newborns with severe bilirubin encephalopathy

The onset of jaundice is on the first day of the newborn 24 (47.5%) and 367 ± 80.34 μmol/L of UB in blood, evaluated in 4-5 zones according to Kramer's scale. 26 (52.5%) babies with jaundice started on 2-3 days had 278 ± 50.35 μmol/L of 3-4 zones according to Kramer's scale. during the first week, the amount of UB increased intensively, and the maximum UB of 458±95.34μmol/l was observed. According to the analysis of the graphic diagram, UB and its fractions: BB and unbound bilirubin increase in peak amount in the first week of the neonatal period, as a result of which OBE develops. 30 (60%) babies born with the anemic and jaundiced form of bilirubin have a BB content of 448±68.34μmol/l in the 3rd of the neonatal period. It was observed on the 7th day. As a result of intensive treatment, the amount of BB decreased by 268±35.24μmol/l in the second half of the neonatal period. Babies born with fermentopathy 10 (20%) polycythemia 6 (12%) Liver disease + fetal infection 4(8%) amount of UB 358±55.34μmol/l BB 338±43.34μmol/l Unbound bilirubin 22±7.2 μmol/l OBE and SBE were determined.

Diagram 2: The amount of bilirubin and its fractions in the neonatal period in bilirubin encephalopathy of newborns

According to the results of laboratory analysis, the role of hypohemoglobinemia and hypoproteinemia is important in the development of bilirubin encephalopathy. According to observations, hypohemoglobinemia 52% of Hb was observed in 10 patients: 72.45±8.43 g/l, 16 patients: 94.45±14.43 g/l, 15 patients: 102.45±11.43 g/l. The amount of total protein among the examinees was 47.45±6.83 g/l, 42.45±5.43 g/l in 410 children and 45.25±3.43 g/l in 15 children. According to the indicators of the general blood analysis, the amount of erythrocytes in the examinees is 3.45±0.49 10*12 g/l. Color indicator of blood 0.77±0.04 EChT 8.8±5.43 mm/h. In general blood analysis, the amount of erythrocytes in 10 (20%) newborns was found to be 2.7 ±0.73 10*12 g/l EChT 22.45±2.43 g/l. In 60 (80%) subjects, no clinically significant changes were observed between the amount of erythrocytes, the color indicator, and the amount of erythrocyte sedimentation rate. However, it should be noted that the frequency of SBE is 3-4 times higher in infants with 2-3 degrees of anemia and various degrees of hypotrophy. showed.

5. CONCLUSION

Pathological course of pregnancy: severe level of anemia, severe form of toxicosis, numerous abortions and urogenital diseases, maternal hypertension, endocrinopathies, intra-fetal infection and long-lasting gestosis create conditions for bilirubin intoxication and aggravate damage to the hematoencephalic barrier of the brain. resulting in increased toxic effects of bilirubin. Neurological damage in hyperbilirubinemia of newborns depends on bilirubin intoxication and the reactive state of the body: sepsis, fermentopathy, complications of intrauterine infection.

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