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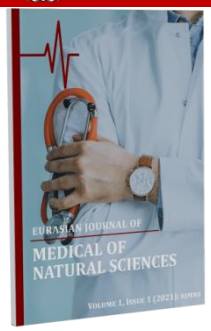

PATHOGENETIC ASPECTS AND ETIOLOGICAL STRUCTURE OF HYPERBILIRUBINEMIA SYNDROME IN THE NEONATAL PERIOD

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ABSTRACT

Hyperbilirubinemia in newborns is a complex clinical and biochemical syndrome caused by multifactorial disorders of bilirubin metabolism in the early postnatal period. The modern understanding of the pathophysiology of this condition is based on the integration of fundamental knowledge about the molecular and cellular mechanisms of formation, transport, conjugation, and elimination of bilirubin.

Introduction: The development of hyperbilirubinemia in newborns is determined by a combination of physiological features of the neonatal period and potential pathogenetic mechanisms. Key physiological prerequisites include increased bilirubin production due to shortened erythrocyte lifespan (70-90 days compared to 120 days in adults), limited activity of the UDP-glucuronosyltransferase enzyme in the liver, transient deficiency of transport proteins (ligandin, Y and Z proteins), as well as intensive reutilization of bilirubin through enterohepatic circulation.

Pathological hyperbilirubinemia forms when physiological mechanisms are exacerbated or additional pathogenetic factors are added, including: 1) hemolytic conditions (immune conflicts, erythrocyte membranopathies, and enzymopathies); 2) polymorphism of genes encoding bilirubin metabolism enzymes; 3) obstructive processes in the biliary system; 4) metabolic and endocrine disorders; 5) infectious and inflammatory diseases with liver damage.

At the molecular level, the key pathogenetic links are: intensification of oxidative stress with the formation of heme peroxidation products, disruption of hepatocyte transport protein expression (OATP, MRP2), dysregulation of glucuronosyltransferase system activity, and

decreased intestinal clearance of bilirubin due to modification of microbiota and intestinal enzymatic activity.

Integral analysis of etiopathogenetic mechanisms of hyperbilirubinemia allows individualization of therapeutic and preventive strategies aimed at modulating key pathogenetic links and preventing neurological complications associated with the toxic effects of indirect bilirubin on central nervous system structures.

Although most cases of neonatal jaundice have a benign course and resolve spontaneously, in 8-9% of cases, pathological hyperbilirubinemia occurs, requiring medical intervention. Special clinical significance is attributed to this condition due to the potential neurotoxicity of indirect (unconjugated) bilirubin, which under certain conditions can cross the blood-brain barrier and cause damage to the central nervous system – from transient bilirubin encephalopathy to kernicterus with the formation of persistent neurological disorders.

The modern understanding of neonatal hyperbilirubinemia pathogenesis goes far beyond traditional concepts of "physiological jaundice" in newborns. The formation of this condition represents a complex multifactorial process, including the interaction of physiological features of the neonatal period and numerous pathological mechanisms. Key physiological prerequisites are increased bilirubin production due to shortened erythrocyte lifespan, transient functional immaturity of liver enzyme systems responsible for bilirubin conjugation, limited activity of hepatocyte transport proteins, and intensive enterohepatic circulation of bilirubin. Pathological hyperbilirubinemia forms when these physiological mechanisms are exacerbated or additional pathogenetic factors are added, among which hemolytic conditions, genetic polymorphism of bilirubin metabolism enzymes, obstructive processes in the biliary system, metabolic disorders, and infectious-inflammatory diseases play a leading role.

Despite significant advances in understanding individual links in the pathogenesis of neonatal hyperbilirubinemia, questions remain unresolved regarding the integrative assessment of the interaction of various pathogenetic mechanisms and their relative contribution to the formation of the clinical picture. Molecular genetic aspects of regulating the expression of transport proteins and enzyme systems of bilirubin metabolism, mechanisms of neuronal damage in hyperbilirubinemia, and the influence of perinatal factors on the modification of the main pathogenetic links remain insufficiently studied. In addition, there are no clear prognostic markers that allow identification of newborns at high risk of developing severe hyperbilirubinemia and neurological complications.

In this regard, a comprehensive study of the etiopathogenetic mechanisms of hyperbilirubinemic conditions in newborns is relevant to identify prognostically significant markers of pathological hyperbilirubinemia development and to develop personalized approaches to the prevention and treatment of this condition. Special attention is paid to studying the relationship between the activity of key enzymes of bilirubin metabolism, genetic polymorphisms, and clinical manifestations of hyperbilirubinemia in newborns of different gestational ages.

The novelty of the presented research lies in the integrative analysis of pathogenetic mechanisms of neonatal hyperbilirubinemia, taking into account genetic, biochemical, and clinical parameters, which allows not only to deepen the understanding of the etiopathogenesis

of this condition but also to form a basis for the development of differentiated diagnostic algorithms and preventive strategies aimed at reducing the frequency of severe hyperbilirubinemia and its neurological complications.

The hyperbilirubinemia syndrome in newborns is one of the most common pathological conditions of the perinatal period, characterized by an increase in bilirubin concentration in blood serum with the subsequent development of jaundice coloration of the skin and mucous membranes. Epidemiological studies indicate that clinically significant jaundice is recorded in 60-70% of full-term and more than 80% of premature newborns, which determines the high relevance of this problem in the structure of neonatal morbidity.

Of particular clinical significance is the potential neurotoxicity of indirect (unconjugated) bilirubin, which under certain conditions can cross the blood-brain barrier and have a damaging effect on the structures of the central nervous system. According to the World Health Organization, severe neonatal hyperbilirubinemia annually causes bilirubin encephalopathy in 114,000 newborns worldwide, of which about 63,000 die, and a significant proportion of survivors suffer from persistent neurological disorders requiring long-term rehabilitation and special medical and social support.

The modern concept of neonatal hyperbilirubinemia pathogenesis views this condition as the result of the interaction of many factors, including both physiological features of the neonatal period and pathological processes leading to an imbalance between bilirubin production and elimination. Physiological prerequisites for the development of jaundice in newborns include increased bilirubin production due to accelerated hemolysis of erythrocytes, transient insufficiency of liver enzyme systems responsible for bilirubin conjugation, limited expression of hepatocyte transport proteins, and intensive enterohepatic circulation.

The etiological structure of neonatal hyperbilirubinemia is characterized by significant heterogeneity. Depending on the predominant pathogenetic mechanism, hyperbilirubinemias are distinguished as caused by: 1) increased bilirubin production (hemolytic conditions, polycythemia, internal hemorrhages); 2) impaired uptake and conjugation of bilirubin in the liver (functional immaturity, genetic defects, drug inhibition); 3) impaired excretion of bilirubin (obstructive processes in the biliary system, infectious and inflammatory liver diseases); 4) combined mechanisms. The clinical picture and prognosis of the disease are largely determined not only by the degree of bilirubin level elevation but also by the rate of its increase, the ratio of fractions, accompanying metabolic disorders, and individual patient characteristics.

Despite the long history of studying the problem of neonatal hyperbilirubinemia, many aspects of its pathogenesis and etiological structure remain insufficiently studied. In particular, questions regarding the relationship between genetic polymorphisms of key enzymes of bilirubin metabolism and clinical manifestations of jaundice, mechanisms of blood-brain barrier disruption in hyperbilirubinemia, the role of oxidative stress and inflammatory mediators in the realization of bilirubin's neurotoxic effect, as well as factors determining individual susceptibility of neurons to bilirubin-induced damage, require clarification.

In-depth study of pathogenetic aspects and etiological structure of neonatal hyperbilirubinemia has both fundamental and applied significance. On one hand, it expands understanding of the molecular and cellular mechanisms of bilirubin metabolism and its

disorders in the perinatal period. On the other hand, the data obtained provide a basis for developing personalized approaches to the diagnosis, prevention, and treatment of this condition, allowing minimization of the risk of developing severe hyperbilirubinemia and its neurological complications.

Currently, an integrative approach to the study of neonatal hyperbilirubinemia, based on a comprehensive analysis of clinical, biochemical, genetic, and neurophysiological parameters, is acquiring special relevance. This approach allows not only to clarify the relative contribution of various pathogenetic mechanisms to the formation of the clinical picture but also to identify prognostically significant markers of severe disease course requiring intensive therapeutic correction.

Conclusions: Thus, a comprehensive study of pathogenetic aspects and etiological structure of hyperbilirubinemia syndrome in the neonatal period represents an important scientific and practical task, the solution of which will contribute to improving the system of medical care for newborns with this pathology and reducing the frequency of associated complications.

References:

1. Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage - mechanisms and management approaches. N Engl J Med. 2023;369(21):2021-2030.
2. Bhutani VK, Wong RJ. Bilirubin-induced neurologic dysfunction (BIND). Semin Fetal Neonatal Med. 2022;28(2):101291.
3. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. N Engl J Med. 2022;358(9):920-928.
4. Kaplan M, Bromiker R, Hammerman C. Hyperbilirubinemia, hemolysis, and increased bilirubin neurotoxicity. Semin Perinatol. 2023;38(7):429-437.
5. Blackburn S. Hyperbilirubinemia and neonatal jaundice. Neonatal Netw. 2022;14(7):15-25.
6. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Lancet Child Adolesc Health. 2023;2(8):610-620.
7. Nakamura H, Yonetani M, Uetani Y, et al. Determination of serum unbound bilirubin for prediction of kernicterus in low birthweight infants. Acta Paediatr Jpn. 2022;34(6):642-647.
8. Raimondi F, Crivaro V, Capasso L, et al. Unconjugated bilirubin modulates the intestinal epithelial barrier function in a human-derived in vitro model. Pediatr Res. 2023;79(2):394-400.