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The role of gene polymorphism in the development of critical conditions of newborns of different etiology (literature review)

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In recent years, a key achievement of medical science in diagnostic and prognostic aspects has been the study of molecular-genetic mechanisms involved in developing critical conditions and various diseases in children, especially newborns.

The aim of the study was to evaluate modern concepts about the role of gene polymorphism in the development of critical conditions of newborns of various etiologies, as well as issues of early prediction of these pathological conditions.

This article presents a literature review addressing key issues related to the determination of a significant relationship between gene polymorphism and neonatal pathologies. The study of gene polymorphisms affecting the development of various diseases is currently considered relevant due to the lack of scientific research in this area among the pediatric population. Special attention is given to studies conducted using the Genome–Wide Association Studies (GWAS) method to identify gene loci associated with various pathological conditions occurring in the neonatal period. Understanding the genetic factors influencing fetal development is critical for comprehending diseases' complexities and severities. Summarizing the theories and hypotheses presented in the article, it can be concluded that studying gene polymorphism and applying an individualized approach to diagnosing neonatal diseases is of great importance.

Conclusions. According to modern concepts presented in the literature, it should be emphasized that the need for early genetic testing of newborns, especially those with risk factors for perinatal asphyxia, can play a decisive role in the timely detection of severe conditions. Various genetic loci and gene mutations contribute to the detailing of clinical manifestations of diseases and risk factors, indicating the importance of identifying gene polymorphisms.

The authors declare no conflict of interest.

Keywords: newborn, neonatal mortality, diagnostics, genetic markers.

Роль генетичного поліморфізму в розвитку критичних станів новонароджених різної етіології (огляд літератури)

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Протягом останніх років найважливішим досягненням медичної науки в діагностичному та прогностичному аспектах стало вивчення молекулярно-генетичних механізмів розвитку критичних станів та різних захворювань у дітей, особливо новонароджених.

Мета: оцінка сучасних поглядів на роль генетичного поліморфізму в розвитку критичних станів новонароджених різної етіології, і навіть питання раннього прогнозування цих патологічних станів.

У статті наведено огляд літератури, присвячений ключовим питанням, пов'язаним із визначенням значущого зв'язку між генетичним поліморфізмом та неонатальними патологіями. Нині вивчення генетичних поліморфізмів, що впливають на розвиток різних захворювань, вважається актуальним через відсутність наукових досліджень у цій галузі серед дитячої популяції. Особливу увагу приділено дослідженням, проведеним із використанням методу повногеномного асоціативного аналізу. Розуміння генетичних факторів, що впливають на розвиток плода, має вирішальне значення для розуміння складності та тяжкості захворювань. Підсумовуючи представлені у статті теорії та гіпотези, можна зробити висновок про неабияку важливість вивчення генетичного поліморфізму та застосування індивідуалізованого підходу до діагностики неонатальних захворювань.

Висновки. Згідно з сучасними підходами, представленими в літературі, слід наголосити, що необхідність раннього генетичного тестування новонароджених, особливо з факторами ризику перинатальної асфіксії, може відігравати вирішальну роль у своєчасному виявленні важких станів. Різні генетичні локуси та мутації генів сприяють деталізації клінічних проявів захворювань та факторів ризику, що свідчить про важливість виявлення генетичних поліморфізмів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: новонароджений, неонатальна смертність, діагностика, генетичні маркери.

One of the primary priorities of global healthcare in recent decades has been reducing infant and neonatal mortality. Advances in neonatology, including the establishment of perinatal centers and improvements in intensive care methods, have contributed to lower mortality rates. However, complications and long-term consequences for surviving children remain significant concerns [13]. Critical conditions in newborns arise from severe birth pathology or extreme immaturity, requiring artificial life support or replacement of vital functions. These conditions are often polyetiological and frequently lead to multiple organ failure (MOF), primarily triggered by hypoxia and systemic inflammation [14]. MOF, in turn, is the underlying mechanism for many neonatal diseases. Researchers are particularly interested in understanding the role of gene polymorphisms in the pathogenesis of various neonatal diseases and conditions [11,13,14].

The aim of the study was to evaluate modern concepts about the role of gene polymorphism in the development of critical conditions of newborns of various etiologies, as well as issues of early prediction of these pathological conditions.

In recent decades, discoveries in molecular genetics and the development of new genetic research methods have helped address various issues related to the etiology, pathogenesis, early diagnosis, and prevention of critical conditions and neonatal diseases [7,14]. Currently, neonatal diseases are considered polygenic, involving complex genetic traits. Many studies have been conducted to identify a wide range of phenotypes and clinical manifestations of neonatal pathological conditions. Numerous molecular mechanisms underlying these conditions have been discovered, significantly improving diagnostic capabilities. However, a substantial proportion of diseases remain genetically unexplored, necessitating further research [4]. Thus, molecular methods can become valuable tools for diagnosing critical conditions and other neonatal diseases. Genome–Wide Association Studies (GWAS) have expanded the understanding of genetic factors involved in the pathogenesis of various diseases, including those in children. These studies have identified different genetic loci and gene mutations contributing to distinct clinical manifestations of diseases [4,7].

One of the primary mechanisms involved in the development of neonatal pathological conditions is hypoxia. Newborns experiencing asphyxia at birth belong to a high-risk group for hypoxic-ischemic encephalopathy, cerebral palsy (CP), and epilepsy. Y. Wang et al. conducted an exome sequencing study on a large cohort of 1,578 children to investigate the role of major genetic variants in the etiology of CP. They identified pathological genes related to nervous system disorders in 387 children. Notably, the genetic diagnostic frequency was higher among children with CP who had a history of perinatal asphyxia compared to those without asphyxia (P=0.0033) [12]. These findings emphasize the necessity of early genetic testing in children with CP, particularly those with perinatal asphyxia risk factors.

Another significant factor leading to neonatal neurological impairment and mortality is hyperbilirubinemia. Z. Cui et al. found that polymorphism of the G211A locus in the UGT1A1 gene, along with clinical risk factors, plays a crucial role in the development and progression of neonatal hyperbilirubinemia. This discovery has potential significance for the early prediction of this pathological condition [3].

The adverse effects of hyperoxia have been well-documented in numerous studies. High oxygen concentrations are the leading cause of retinopathy of prematurity (ROP). However, compelling evidence suggests that genetic factors also influence the development of ROP. H. Paradis et al. conducted a study on 30 newborns with ROP and identified 543 biallelic variants in 20 genes associated with ADRβ pathways. Large-scale multicenter studies investigating newly discovered risk factors may provide a novel approach for predicting and preventing severe ROP [9].

Neonatal respiratory distress syndrome (NRDS), characterized by surfactant deficiency, is the most common cause of respiratory failure in preterm newborns. M. Golshan-Tafti and colleagues investigated the association between variations in the surfactant protein-B (SFTPB) gene and NRDS risk. Their literature review revealed a strong correlation between SFTPB polymorphisms and NRDS [5].

The kidneys are among the most frequently affected organs in the neonatal period. Their development and function are regulated by multiple genes, including HNF1A, HNF1B, and PKHD1. Understanding the genetic factors influencing fetal kidney development is critical for comprehending renal disease complexities. M. Abdelwahed and colleagues conducted a study aimed at identifying pathological variants of the HNF1A, HNF1B, and PKHD1 genes in fetuses, infants, and their parents. The identification of these variants provided valuable insights into the genetic landscape of renal anomalies in affected patients, highlighting the importance of genetic screening [1].

L. Kastsiukevich and colleagues conducted a whole-exome sequencing study to identify gene sequences associated with pediatric inflammatory bowel diseases (IBD). Their findings indicated that certain IBD cases are linked to heterozygous variants in genes associated with congenital immune defects, enteropathies, and metabolic disorders [7].

Preterm birth is one of the major risk factors for neonatal diseases. M. Kadivnik and colleagues examined the association of interleukin-6 (IL-6) (rs1800796), interleukin-10 (IL-10) (rs1800896), and tumor necrosis factor-α (TNFα) (rs1800629) gene variants with spontaneous preterm birth. Analysis of blood samples from 199 women who had preterm deliveries and 200 controls revealed that TNFα (rs1800629) polymorphism was associated with preterm birth, whereas IL-10 (rs1800896)

polymorphism acted as a protective factor. No association was found between IL-6 (rs1800796) and preterm birth [6].

Neonatal sepsis is a major cause of neonatal mortality. A research team from Canada led by A.Y. An studied a cohort of 720 newborns and identified gene expression signatures (HSPH1, BORA, NCAPG2, PRIM1) that could predict sepsis development with 83% sensitivity and specificity [2].

In a cohort study by L.N. Sanchez-Pinto (2020), covering a six-year period and involving 20,827 critically ill neonates, four major phenotypes of multiple organ failure syndrome were identified based on disease severity and ICU duration: (1) severe encephalopathy (19.2%), (2) moderate hypoxemia (34.5%), (3) severe persistent hypoxemia with shock (19.1%), and (4) moderate persistent thrombocytopenia with shock (22.6%) [10].

A meta-analysis by J. Liang et al. (29 articles involving 3348 cases and 5183 controls) investigated the association between inflammatory cytokine SNPs and neonatal sepsis. Their findings indicated that specific polymorphisms in IL-1β, IL-6, IL-8, IL-10, and TNF-α genes are associated with either increased or decreased sepsis risk [8].

Conclusions

According to modern concepts presented in the literature, it should be emphasized that the need for early genetic testing of newborns, especially those with risk factors for perinatal asphyxia, can play a decisive role in the timely detection of severe conditions. Various genetic loci and gene mutations contribute to the detailing of clinical manifestations of diseases and risk factors, indicating the importance of identifying gene polymorphisms.

Thus, the identification of phenotypes and gene polymorphisms in neonatal critical conditions supports the necessity of further research in this field, opening new possibilities for disease diagnosis and prognosis in newborns.

The authors declare no conflict of interest.

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