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CLINICAL AND PARACLINICAL FEATURES AND PATHOPHYSIOLOGICAL MECHANISMS OF DIGESTIVE SYSTEM DISORDERS IN PREMATURE INFANTS WITH PERINATAL PATHOLOGY

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Summary

Introduction. *According to the World Health Organization (WHO), the incidence of preterm birth is 10-15%, or about 15 million newborns worldwide, and this number is increasing. The highest incidence of morbidity and mortality is observed in infants born before 32 weeks of gestation. Among other things, preterm infants have an immature digestive system, which leads to food intolerance. The formation of cumulative nutrient deficiencies in the digestive system from birth puts children at risk of delayed psychophysical development and contributes to the development of negative long-term neurological consequences. Many of these complications have lifelong consequences for health, growth and development, both in infancy and later in life.*

Aim of the study. *To improve the diagnosis of intestinal dysfunction in perinatal pathology in premature infants based on the study of risk factors and clinical and laboratory parameters.*

Materials and methods of the study. *A comprehensive clinical and paraclinical examination of 91 premature infants with clinical manifestations of moderate and severe perinatal pathology with signs of disturbances of the functional state of the digestive system (group I, gestational age 29 (0/7) – 36 (6/7) weeks) and 57 conditionally healthy newborns (group II, gestational age 35 (0/7) – 36 (6/7) weeks) was performed. The total number of children studied was 148. Exclusion criteria were children with congenital malformations and septic conditions.*

The list of laboratory parameters used included: levels of α-1-antitrypsin (A1AT), PMN-elastase, albumin, fecal calprotectin (FC) and fecal elastase-1 (FE-1) in children's stool using enzyme-linked immunosorbent assay (ELISA), reagents from Immundiagnostic AG (Germany) on the basis of the German-Ukrainian laboratory "BUKINMED" (Chernivtsi, Ukraine).

The scientific work was carried out on the basis of neonatology departments of the Chernivtsi City Clinical Maternity Hospital in 2014-2018. Informed consent of the parents of the child was obtained with adequate explanation of the purpose, objectives, methods and scope of laboratory and instrumental research methods. The study protocol was approved by the Biomedical Ethics Commission of the Bukovinian State Medical University, 2015.

The studies were conducted in accordance with the basic provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (April 4, 1997), the World Medical Association Declaration of Helsinki on Ethical Principles for Research Involving Human Subjects (1964-2008), Order of the Ministry of Health of Ukraine ¹ 690 dated September 23, 2009 (as amended by Order of the Ministry of Health of Ukraine ¹ 523 dated July 12, 2012).

Statistical processing of data was performed using the software "STATISTICA" (StatSoft Inc., USA, version 10), program MedCalc (https://www.medcalc. org/index.php). Comparison of quantitative indicators with normal distribution was performed using Student's t-test. The difference in parameters was considered statistically significant at $p<0.05$.

The thesis was carried out within the framework of the scientific topics of the Department of Pediatrics, Neonatology and Perinatal Medicine of the Bukovinian State Medical University: Research work on "Improvement of directions of prognosis, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation" (State registration number 0115U002768, term of execution 01. 2015-12. 2019); Research work on "Chronobiological and adaptive aspects and features of autonomic regulation in pathological conditions in children of different age groups" (State registration number 0122U002245, term of execution 01.2020-12.2024).

Results and discussion. *The studied laboratory parameters of stool in premature infants with signs of food intolerance in perinatal pathology revealed certain pathophysiological mechanisms of its development, including acute inflammation, increased permeability of the intestinal mucosa, and exocrine insufficiency. Dysfunction of the digestive system is a consequence of complex autonomic and visceral dysfunction of the child's body against the background of hypoxia and morphological and functional immaturity at birth. An increase in the level of A1AT, PMN-elastase, albumin and a decrease in the concentration of FE-1 in feces are interdependent criteria of digestive system dysfunction. Increased permeability of the intestinal mucosa in conditions of local inflammation leads to translocation of pathogenic and opportunistic microorganisms into the bloodstream, which probably exacerbates the clinical manifestations of endotoxemia in perinatal pathology of premature infants. The above justifies the need to continue scientific research to develop a refinement of comprehensive diagnosis and correction of digestive function in preterm infants.*

Conclusions.

1. Premature birth of children causes a high risk of adaptation disorders in newborns, which is due to the morphological and functional immaturity of the body and the realization of perinatal risk factors.

2. In the complex of vegetative-visceral dysfunction in conditions of perinatal pathology in newborns, there are signs of combined dysfunction of the digestive system, which is characterized by weakening or absence of sucking reflex, regurgitation, intestinal stasis and paresis, delayed passage of meconium and transitional stools, flatulence; in the most severe cases, persistent and prolonged decrease in tolerance to enteral nutrition is one of the characteristic manifestations of SIDS.

3. Increased levels of A1AT, PMN-elastase, albumin and decreased concentration of FE-1 in feces of children with nutritional dysfunction in the complex of signs of perinatal pathology are laboratory confirmation of digestive system disorders in premature birth.

4. The pathophysiological mechanisms of transient disorders of the functional state of the digestive system, which cause clinical signs of food intolerance, are: acute inflammation, increased permeability of the intestinal mucosa and exocrine insufficiency. Increased permeability of the intestinal mucosal barrier leads to increased translocation of pathogenic and opportunistic microorganisms into the bloodstream, which contributes to the growth of endotoxemia in perinatal pathology of premature infants.

5. Harmonization of clinical and paraclinical criteria for disorders of the functional state of the digestive tract in the complex of perinatal pathology will increase the effectiveness of diagnostic measures in the neonatal period, especially in premature infants, and improve approaches to medical care by improving the range of diagnostic and therapeutic measures.

Key words: *newborn; digestive system; food tolerance disorders; α-1-antitrypsin level; PMN-elastase; albumin; fecal calprotectin; fecal elastase-1.*

Introduction

Preterm birth is one of the leading causes of neonatal mortality and morbidity worldwide. According to the World Health Organization (WHO), the rate of preterm birth is 10-15%, or approximately 15 million newborns worldwide, and this number is steadily increasing. The highest incidence of morbidity and mortality is observed in infants born before 32 weeks of gestation. [1,2]

Among other organ systems, preterm infants have an immature digestive system, leading to manifestations of food intolerance and, in the most severe cases, the development of necrotizing enterocolitis (NEC). [3] The formation of cumulative nutrient deficiencies in the digestive system from birth puts children at risk for delayed psychophysical development and contributes to the development of negative long-term neurological consequences. Many of these complications have lifelong consequences for health, growth and development, both in infancy and later in life.

The imperfection of the motor-evacuation function of the gastrointestinal tract (GIT) in premature infants is combined with insufficient activity of enzyme systems, peculiarities of the intestinal microbial landscape, which contributes to the development of digestive dysfunction and complicates enteral feeding, especially in very premature infants. [4] Disturbances in cavernous and parietal (membrane) digestion, absorption, and intestinal motility are the causes of food intolerance in preterm infants. At the same time, preterm infants need timely and sufficient intake of a complex of macro- and micronutrients to ensure "catch-up growth" and progressive psychophysical development. [5] Intestinal immaturity and the associated increased risk of morbidity and food intolerance make it important to select appropriate enteral nutrition for preterm infants.

Timely diagnosis and correction of digestive system disorders requires the development of a differentiated approach to the assessment of clinical and laboratory criteria for nutritional dysfunction in premature infants, to prescribe appropriate drug correction, taking into account the leading mechanisms of its development.

Aim of the study. To improve the diagnosis of intestinal dysfunction in perinatal pathology in premature infants based on the study of risk factors and clinical and laboratory parameters.

Materials and methods of the study

A comprehensive clinical and paraclinical examination of 91 premature infants with clinical manifestations of moderate and severe perinatal pathology with signs of disturbances of the functional state of the digestive system (group I, gestational age 29 (0/7) – 36 (6/7) weeks) and 57 conditionally healthy newborns (group II, gestational age 35 (0/7) – 36 (6/7) weeks) was performed. The total number of children studied was 148. Exclusion criteria were children with congenital malformations and septic conditions.

The list of diseases of early neonatal period included clinical diagnoses according to ICD X revision. To study the course of pregnancy, childbirth, somatic status of mothers, to determine perinatal risk factors for the development of disorders of the functional state of the digestive system in children, an analysis of pregnancy exchange cards (F № 113/0), birth histories (F № 096/0), newborn development cards (F № 097/0) was conducted.

The general condition of the children at birth and in the dynamics was assessed according to generally accepted methods. The correspondence of development to gestational age at birth was determined using the Ballard scale and percentile tables. Severity of neonatal condition was determined taking into account peculiarities of adaptation according to Apgar scale at 1 and 5 minutes of life and further dynamic clinical and laboratory observation. Due to the diversity of nosological forms of diseases, for the correct interpretation of the results, a methodological approach was used, which included the division of children into groups based on the severity of the general condition of the newborn. Clinical assessment of the functional state of the digestive system was carried out according to classical methods, taking into account the age characteristics of the newborn period.

The list of laboratory parameters used included α-1-antitrypsin (A1AT), PMN-elastase, albumin, fecal calprotectin (FC), and fecal elastase-1 (FE-1) levels in children's stool by enzyme-linked immunosorbent assay (ELISA), reagents from Immundiagnostic AG (Germany) on the basis of German-Ukrainian laboratory "BUKINMED" (Chernivtsi, Ukraine). Chernivtsi, Ukraine).

The scientific work was carried out on the basis of neonatology departments of the Chernivtsi City Clinical Maternity Hospital in 2014-2018. Informed consent of the parents of the child was obtained with adequate explanation of the purpose, objectives, methods and scope of laboratory and instrumental research methods. The study protocol was approved by the Biomedical Ethics Commission of the Bukovinian State Medical University, 2015.

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Statistical processing of data was performed using the software "STATISTICA" (StatSoft Inc., USA, version 10), program MedCalc (https://www.medcalc. org/index.php). Comparison of quantitative indicators with normal distribution was performed using Student's t-test. The difference in parameters was considered statistically significant at $p<0.05$.

The thesis was carried out within the framework of the scientific topics of the Department of Pediatrics, Neonatology and Perinatal Medicine of the Bukovinian State Medical University: Research work on "Improvement of directions of prognosis, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation" (State registration number 0115U002768, term of execution 01. 2015-12. 2019); Research work on "Chronobiological and adaptive aspects and features of autonomic regulation in pathological conditions in children of different age groups" (State registration number 0122U002245, term of execution 01.2020-12.2024).

Results and Discussion

The analysis of the gestational age of the newborns in the observation groups showed that in group I, 25

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(27.5%) children were born at a gestational age of 29 (0/7) – 31 (6/7) weeks, with a birth weight of 1500 grams or less; 35 (38. 5%) children – 32 (0/7) – 34 (6/7) weeks of gestation, with a birth weight of 1501-2000 grams; and 31 (34.1%) newborns – 35 (0/7) – 36 (6/7) weeks of gestation, with a birth weight of 2001-2499 grams. Both groups were dominated by boys – 49 (53.8%) and 32 (56.1%), respectively, and girls – 42 (46.2%) and 25 (43.9%), respectively. Comparative assessment of anthropometric parameters in newborns of observation groups I and II: birth weight 1809.34±437.36 g and 2266.1±232.98 g, body length 42.8±2.97 cm and 45.5±1.30 cm, head circumference 29.8±3.10 cm and 31.6±1.17 cm, trunk circumference 27.9±2.63 cm and 29.5±1.32 cm ($p<0.0001$).

Problems of adaptation of newborns of group I were caused both by morphological and functional immaturity of the child's body due to premature birth and realization of unfavorable ante/perinatal risk factors. Intrauterine development of children occurred against the background of combined somatic and obstetric and gynecological pathology during pregnancy in the mother. Thus, in 39 (42.9%) women of group I and 13 (22.8%) women of group II ($p=0.01$), pathology of the endocrine system was detected, namely diffuse nontoxic goiter was diagnosed in 33 (36.3%) and 11 (19.3%) cases, respectively ($p=0.03$). Grade II-III anemia was detected in 9 (9.9%) and 1 (1.8%) cases, respectively ($p=0.05$); urinary system pathology was detected in 49 (53.9%) and 22 (36.8%) cases, respectively ($p=0.04$). Analyzing the frequency of gynecological pathology in the anamnesis of mothers of the observation groups, it was found that it was significantly higher in women of group I compared to group II – 48 women (52.7%) and 20 (35.1%), respectively ($p=0.04$); a higher percentage of contamination with opportunistic pathogens (OP) was also noted in women of group I – 55 (60.4%), and in women of group II – 13 (22.8%) ($p<0.0001$). The presence of complicated obstetric and gynecological history in mothers significantly increases the risk of severe perinatal pathology in children, which confirms the multifactorial nature of its development. Complicated obstetric history was found in 68 (74.7%) mothers of group I and 29 (50.9%) women of group II ($p<0.003$), especially perinatal losses in 17 (18.7%) and 2 (3.5%) cases, respectively ($p=0.007$). Complications of pregnancy, especially gestosis of the first and second half of pregnancy – in 25 (27.5%) cases in group I and in 6 (10.5%) cases in group II ($p=0.01$); placental dysfunction – in 28 (30.8%) and 12 (21.1%) cases, respectively ($p=0.20$); pathology of placental and umbilical cord attachment – in 28 (30.8%) and 4 (7.0%) cases, respectively ($p=0.0006$). The obtained statistically significant results of differences in comparison of somatic and obstetric-gynecological pathology in mothers of the observation groups, taking into account the frequency of perinatal pathology in children, confirm the fact of significant influence of maternal health on the nature of postpartum adaptation, which requires significant attention of obstetric-gynecological service. The evaluation of ante/perinatal risk factors plays an important role in the assessment of the adaptive capacity of the newborn's body and is one of the main aspects of the neonatologist's attention when formulating an individual plan of monitoring and medical care of young children.

Intrapartum complications were characterized by: fetal distress threatening life – in 16 (17.6%) of group I deliveries and in 5 (8.8%) of group II deliveries ($p=0.14$); premature rupture of membranes – in 36 (39.6%) and 23 (40.4%) cases, respectively ($p>0. 92$); umbilical cord wrapping around the fetal neck was observed in 4 (4.4%) and 1 (1.8%) cases, respectively ($p=0.40$); cesarean delivery was performed in 62 (68.1%) and 29 (50.9%) cases, respectively ($p=0.04$), including emergency cesarean delivery in 16 (17.6%) and 4 (7.0%) cases, respectively ($p=0.07$). Given the results, no significant differences were found when comparing intrapartum risk factors that influenced the type of neonatal adaptation in the comparison groups.

The score of early neonatal adaptation according to the Apgar scale in the 1st and 5th minute of life in children of group I was 5.53±0.97 and 6.73±0.80 points ($p<0.0001$), in newborns of group II – 6.90±0.59 and 7.67±0.58 points ($p<0.0001$). According to the results of the evaluation we can speak about more significant disorders of acute adaptation in children of group I in comparison with group II. Newborns in group I required resuscitation at birth, in particular: tracheal cleaning was performed in 57 children (62.6%); free-flow oxygen therapy in 51 children (56.0%); mechanical ventilation with mask and bag in 53 children (58.2%); mechanical ventilation with endotracheal intubation tube and bag in 46 children (50.5%). At the same time, among the children who underwent tracheal intubation, there was a significant predominance of children with gestational age from 29 (0/7) to 31 (6/7) weeks – 20 children (22.0%). According to the obtained data, the severity of the neonatal condition directly depends on the gestational age and the degree of morphological and functional maturity at birth. In particular, children of younger gestational age have a higher risk of adaptation disorders and development of perinatal pathology.

Clinical signs of maladaptation in children of group I in the early neonatal period were characterized by a significant frequency of respiratory distress syndrome (RDS) (respiratory distress according to the Downes scale 1-3 points – in 21 children (23.1%), 4-6 points – in 27 children (29. 7%), more than 7 points – in 43 children (47.3%)); moderate and severe asphyxia was diagnosed in 25 cases (27.5%); hypoxic-ischemic injury (HI)/neonatal encephalopathy – in 80 cases (87.9%); diabetic fetopathy – in 2 cases (2.2%); antenatal fetal damage – in 13 cases (14.3%). All children showed signs of morphological and functional immaturity. Newborns were at risk of intrauterine infection in 84 cases (92.3%). Twenty-nine infants (31.9%) were born as a result of multiple pregnancies. During the first week of life, 42 children (46.2%) developed multiple organ dysfunction syndrome (MODS), including cardiovascular failure in 29 children (31.9%), hemorrhagic syndrome in 11 children (12.1%), anemia in 12 children (13.2%), convulsive syndrome in 2 children (2.2%), and coma in 2 children (2.20%). The condition of newborns in group II (control) during the period of postnatal adaptation was satisfactory, the children were in wards with their mothers and were exclusively breastfed.

Clinical symptoms in children of group I in the early neonatal period were accompanied by a combined syndrome of autonomic and visceral dysfunction, including signs of food intolerance. In particular, all patients had a weakened or absent sucking reflex. In 81 (89.0%) cases

a significant decrease in food tolerance was observed, accompanied by regurgitation and stasis in 64 cases (70.3%); intestinal paresis with delayed meconium and transient stools in 57 cases (62.6%); flatulence in 43 cases (47.3%). In general, 42 newborns (46.2%) with severe forms of perinatal pathology had persistent and prolonged manifestations of digestive system dysfunction, which was considered one of the manifestations of MODS.

In accordance with current recommendations, complete parenteral nutrition (CPN) was used in 88 cases (96.7%) and minimal enteral nutrition (MEN) was used in 56 cases (61.54%), which ensured the preservation of intestinal enterocytes with a gradual increase in the volume of enteral feeding.

At the laboratory examination of stools of newborns of group I (experimental), in comparison with indicators of children of group II (control), characteristic changes were noted, which to some extent allow to explain the mechanisms of development of food intolerance at vegetative-visceral dysfunction in conditions of perinatal pathology (Table 1).

Table 1

Fecal laboratory parameters in neonates of the observation groups on day 1-2 of life (M±m)

Indicators	Group I (experimental) (M±m)	Group II (control) (M±m)
A1AT (μg/g)	464,61±24,502*	196,80±10,196
PMN-elastase (ng/g)	85,21±4,535*	58,86±0,670
Albumin (μg/g)	49,17±2,768*	7,69±0,406
FC (μg/g)	384,88±0,599*	43,20±1,397
FE –1 (μg/g)	100,96±4,179*	207,50±7,434

*Note: * – significant difference between observation groups, p < 0.0001*

The results of the study showed that clinical signs of intestinal dysfunction in preterm infants are associated with a significant increase in fecal levels of A1AT, which is considered the primary inhibitor of acute phase serine proteases and is secreted during inflammation. A1AT neutralizes excess proteases produced by microorganisms and macrophage cells and plays an important role in the formation of an anti-inflammatory response. It is one of the markers of acute phase inflammation because its expression increases in response to acute inflammatory stimuli, which reduces the production of proinflammatory cytokines and, consequently, inflammatory cell infiltration and tissue damage. [6, 7]

According to the literature, A1AT is synthesized primarily in the endoplasmic reticulum of the liver and by polymorphonuclear neutrophils, alveolar macrophages, monocytes, enterocytes, and Paneth cells. Because of its relatively low molecular weight, it penetrates well into tissues, performs a transport function, and returns to the circulation with bound protease, where it is exposed to other inhibitors and the reticuloendothelial system. [8] An increase in A1AT levels results in inhibition of the activity of many proteolytic enzymes, such as trypsin, chymotrypsin, plasmin, thrombin, elastase, hyaluronidase, leukocyte proteases, macrophages, microorganisms, etc. [9, 10] Due to its antiproteolytic activity, it is highly resistant to pancreatic enzymes and bacteria in the intestine, is not absorbed in the intestine and is excreted unchanged in the feces.

Studies have shown a significant increase in the level of PMN-elastase in the feces of the main group of newborns, which indicates the migration of leukocytes and activation of the mechanisms of inflammation of the intestinal mucosa. Recent scientific literature shows that the meconium of preterm infants contains a higher level of PMN-elastase than that of term infants, which is directly related to the incidence of intestinal inflammation. [11]

PMN-elastase is a serine protease glycoprotein secreted by activated neutrophils. Polymorphonuclear neutrophils are the major component of the acute inflammatory response, are the first cells recruited to sites of inflammation, and form the first line of defense against invading microorganisms. PMN-elastase is stored in significant amounts in the cytoplasmic azurophilic granules of neutrophils and is released upon activation of these cells in response to inflammatory triggers and is one of the mediators of inflammation. Polymorphonuclear neutrophils are very effective in killing invading pathogens by releasing microbicidal products, but excessive release of these substances can cause significant damage to the intestinal epithelium and local tissue injury. [12, 13]

Enzymatically active PMN-elastase acts in combination with reactive oxygen species (O_2 radicals, H_2O_2, OH radicals) and helps to degrade microorganisms engulfed by lysosomes. This protease is also externalized in an active form during neutrophil activation at sites of inflammation, thus contributing to the regulation of the inflammatory and immune response. As a multifunctional protease, it also has a regulatory function in the body's response to non-infectious inflammatory diseases. [14] During inflammation, a certain amount of protein produced by neutrophils is released into the intestinal lumen. [15] This protease, which is overexpressed in the feces of patients with inflammatory bowel disease, may contribute to tissue destruction. [16]

In premature infants of group I, a significant increase in the level of albumin in feces was found, which also confirms the presence of parietal absorption disorders and indicates an increase in mucosal permeability. At the same time, these processes are characterized by increased translocation of OP and endotoxins from the intestinal lumen into the bloodstream. [According to the literature, an increase in fecal albumin in preterm infants is evidence of protein loss and intestinal inflammation. When plasma proteins enter the intestinal lumen, they are rapidly degraded into amino acids and reabsorbed into the portal circulation. Loss of serum proteins in the intestine occurs regardless of molecular weight. Serum proteins (albumin, immunoglobulin A), which have a longer half-life (i.e., lower rate of catabolism), are most affected by the imbalance. Plasma protein leakage occurs due to damage to the intestinal mucosa resulting in inflammatory exudation of protein-rich fluid across the altered epithelium and increased mucosal permeability due to inflammatory infiltrates, resulting in protein leakage into the lumen.

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Newborns of the study group with signs of food intolerance against the background of perinatal pathology showed a significant increase in the level of FC in stool, which confirms the presence of acute neutrophilic inflammation in the intestine accompanied by granulocyte migration and neutrophil infiltration due to increased mucosal permeability and immaturity of the immune system in the early neonatal period.

FC is a heterocomplex calcium/zinc-binding protein consisting of two heavy chain proteins and one light chain protein; it belongs to the S100 protein family, constitutes 60% of the total cytosolic protein content of neutrophils and 5% of the total neutrophil protein. Since FC has many biological activities, including bactericidal, fungicidal and immunomodulatory effects, and performs regulatory functions in inflammatory reactions, it can be assumed that this protein affects the protection of the physiological environment of the body, in particular the preservation of the intestinal ecosystem, which is important for the establishment of adaptation and formation of newborn health during the first weeks of life [18, 19, 20, 21].

FC is found in the cytoplasm of neutrophils and macrophages, to a lesser extent in monocytes and epithelial cells, is secreted extracellularly, and is expressed in some mucosal epithelial cells. [22] FC is released from cells under stress or injury and enters the feces. It reflects the transepithelial migration of neutrophils into the intestinal lumen; its levels are quantitatively related to the migration of granulocytes into the intestine. FC is a marker of intestinal inflammation and allows differentiation of irritable bowel syndrome from inflammatory bowel disease. It provides a highly sensitive, specific, and non-invasive alternative for assessing inflammatory activity, predicting relapse, and monitoring disease progression. [19, 22] Calprotectin is found in body fluids at concentrations proportional to the degree of inflammation, including feces at levels approximately six times higher than blood levels, highlighting its potential as an accurate biomarker of intestinal inflammation. [23, 24] As an inflammatory marker, FC is likely to play an important role in the detection of food intolerance as a trigger that increases the cascading response associated with allergy and inflammation. In response to food allergens, eosinophils and neutrophils are activated, leading to an increase in the level of the indicator. This allows it to be used as a marker to monitor intestinal hypersensitivity in infants. [13, 24, 25] However, it should be noted that there are certain peculiarities in the proper collection of fecal samples from children's diapers. As water is absorbed into the diaper, the FC concentration may increase by up to 30%, leading to a higher than actual level of FC determination, so attention should be paid to direct collection of feces at the time of voiding. [19, 24, 26]

Published studies by various authors have examined a wide range of age groups for FC in children. It has been found that there is significant individual variability of the index in infancy. [27] The level of FC also depends on the gestational and postnatal age of the child, and some discrepancies in the presented levels are noted. In particular, in very premature infants the level of FC is low, in healthy premature infants the indicators are higher than in adults and children over 4 years of age. [21, 28] There are reports of increased levels of FC in the meconium of preterm infants [29]; there are no significant differences between preterm and term infants. [1] In infants in the first year of life, normal levels of FC can be more than 10 times higher than in healthy older children. FC levels may be high in the first months of life due to the active development of the digestive system, the immaturity of the adaptive immunity of the intestinal mucosa [26] and the barrier function of the intestinal epithelium. [18] FC is mainly derived from granulocytes and its concentration is directly proportional to the degree of transepithelial migration of granulocytes or newly recruited macrophages into the intestinal tract. It has been suggested that active intestinal colonization during the first weeks of life and potent chemotactic agents play an important role in stimulating transepithelial migration of granulocytes across the mucosa to develop food tolerance and establish the intestinal microbiocenosis, which is the reason for high FC concentrations. Thus, the reason for the high concentration of FC in the stool of infants within a few months of birth is that subclinical physiological inflammation may occur in the digestive tract, and such inflammation promotes granulocyte migration into the intestinal lumen. Low expression of inflammatory markers such as IL-17, IL-1β or macrophage inflammatory protein-1 (MIP-1) in preterm infants confirms the presence of mild neutrophilic inflammation, i.e. neutrophil infiltration and luminal leakage, which resembles acute intestinal inflammation. The severity of inflammatory markers is usually lower than in purely inflammatory conditions such as necrotizing enterocolitis (NEC). [1]

There are conflicting data on the effect of breastfeeding on the level of FC. Most authors note that FC is significantly higher in the group of children who were exclusively breastfed. This may be a confirmation that immunomodulatory factors of breast milk affect the intestinal mucosa. [19, 30] The ESPGHAN expert group recommends that FC levels should be used to differentiate functional abdominal pain from organic disease and that the use of serial FC measurements should be considered as a non-invasive screening tool for situational assessment of the risks and benefits of stopping enteral feeding and for timely diagnosis and prevention of NEC. [21] According to the results of Rodríguez-Benítez MV et al. 2021, inflammatory parameters in meconium (PMN-elastase, FC) were increased in preterm infants with gastrointestinal, respiratory or neurological diseases. [1]

Pancreatic activity plays an important role in maintaining the physiological process of digestion. A decrease in the number and/or activity of pancreatic enzymes to a level insufficient to maintain normal digestion is one of the main causes of decreased food tolerance. [31, 32] The exocrine function of the pancreas develops more slowly in premature infants than in full-term infants, which obviously affects weight gain and may have a negative impact on further physical and psycho-nervous development of the child. The index of the level of FE-1 in children of group I, who had manifestations of food intolerance, was significantly lower in comparison with the indexes of group II, which confirms a certain insufficiency of the exocrine function of the pancreas and intestines in conditions of perinatal pathology and morphological and functional immaturity of newborns.

Functionally, FE-1 is a pancreatic-specific serine carboxyendopeptidase that digests peptides to alanine, glycine and serine residues and catalyzes the hydrolysis of

natural elastin. Like other pancreatic proteinases, elastase is synthesized as an inactive precursor called proelastase, which is stored in the acinar cells of the pancreas. Proelastase is activated by trypsin in the duodenum, binds to bile salts, and is minimally degraded during passage through the gastrointestinal tract. [22, 33, 34] Preterm infants have low transient levels of FE-1 up to 48 hours after birth, and the lower the gestational age and birth weight, the longer it takes to reach normal levels. [35]

Thus, the studied laboratory parameters of stool in premature infants with signs of food intolerance in perinatal pathology showed certain pathophysiological mechanisms of its development, including acute inflammation, increased permeability of the intestinal mucosa and exocrine insufficiency. Dysfunction of the digestive system is a consequence of complex autonomic and visceral dysfunction of the child's body against the background of hypoxia and morphological and functional immaturity at birth. Increased levels of A1AT, PMN-elastase, albumin and decreased stool concentrations of FE-1 are interdependent criteria of digestive system dysfunction. Increased permeability of the intestinal mucosa under conditions of local inflammation leads to translocation of pathogenic and opportunistic microorganisms into the bloodstream, which probably exacerbates the clinical manifestations of endotoxemia in perinatal pathology in preterm infants. The above justifies the need to continue research to develop a refinement of the comprehensive diagnosis and correction of digestive function in preterm infants.

Conclusions

1. Premature birth of children causes a high risk of adaptation disorders in newborns, which is due to the morphological and functional immaturity of the body and the realization of perinatal risk factors.

2. In the complex of vegetative-visceral dysfunction in conditions of perinatal pathology in newborns, there are signs of combined dysfunction of the digestive system, which is characterized by weakening or absence of sucking reflex, regurgitation, intestinal stasis and paresis, delayed passage of meconium and transitional stools, flatulence; in the most severe cases, persistent and prolonged decrease in tolerance to enteral nutrition is one of the characteristic manifestations of SIDS.

3. Increased levels of A1AT, PMN-elastase, albumin and decreased concentration of FE-1 in feces of children with nutritional dysfunction in the complex of signs of perinatal pathology are laboratory confirmation of digestive system disorders in premature birth.

4. The pathophysiological mechanisms of transient disorders of the functional state of the digestive system, which cause clinical signs of food intolerance, are: acute inflammation, increased permeability of the intestinal mucosa and exocrine insufficiency. Increased permeability of the intestinal mucosal barrier leads to increased translocation of pathogenic and opportunistic microorganisms into the bloodstream, which contributes to the growth of endotoxemia in perinatal pathology of premature infants.

5. Harmonization of clinical and paraclinical criteria for disorders of the functional state of the digestive tract in the complex of perinatal pathology will increase the effectiveness of diagnostic measures in the neonatal period, especially in premature infants, and improve approaches to medical care by improving the range of diagnostic and therapeutic measures.

Prospects for further research. Prospects for further research are the study of laboratory criteria for the functional state of the pancreas to develop generalized recommendations for clinical and laboratory examination of preterm infants with signs of food tolerance disorders in perinatal pathology.

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КЛІНІКО-ПАРАКЛІНІЧНІ ОСОБЛИВОСТІ ТА ПАТОФІЗІОЛОГІЧНІ МЕХАНІЗМИ ПОРУШЕНЬ СИСТЕМИ ТРАВЛЕННЯ У НЕДОНОШЕНИХ НОВОНАРОДЖЕНИХ ДІТЕЙ ПРИ ПЕРИНАТАЛЬНІЙ ПАТОЛОГІЇ

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Резюме.

Вступ. За даними ВООЗ, частота передчасних пологів коливається від 10 до 15 %, що становить близько 15 мільйонів новонароджених у світі, і цей показник стабільно зростає. Найбільша частота захворюваності і смертності відмічається у дітей, народжених до 32-го тижня гестації. Поряд з іншим, передчасно народжені діти мають незрілість травної системи, що обумовлює прояви харчової непереносимості. Формування кумулятивного дефіциту поживних речовин при порушеннях системи травлення від народження спричиняють у дітей ризик затримки психофізичного розвитку, сприяють розвитку негативних віддалених неврологічних наслідків. Багато з таких ускладнень мають довічні наслідки для здоров'я, росту й розвитку як у немовлячому віці, так і в подальші роки життя.

Мета дослідження. Удосконалити діагностику порушень функціонального стану кишечника при перинатальній патології у недоношених новонароджених дітей на основі вивчення факторів ризику та клініко-лабораторних показників.

Матеріали та методи дослідження. Проведено комплексне клініко-параклінічне обстеження 91 передчасно народженої дитини, у яких відмічались клінічні прояви перинатальної патології середнього та важкого ступеню з ознаками порушень функціонального стану системи травлення (I група, термін гестації 29 (0/7) – 36 (6/7) тижнів) та 57 умовно здорових новонароджених (II група, термін гестації 35 (0/7) – 36 (6/7). Загальна кількість обстежених дітей склала 148 осіб. Критеріями виключення були діти, які мали вроджені вади розвитку та септичні стани.

Перелік лабораторних показників, які використовувалися, включали: рівень α-1-антитрипсину (А1АТ), PMN-еластази, альбуміну, фекального кальпротектину (ФК) та фекальної еластази-1 (ФЕ-1) у випорожненнях дітей за допомогою ензим-зв'язаного імуносор-

бентного методу (ELISA), реактиви фірми «Immundiagnostic AG» (Німеччина) на базі Німецько-Української лабораторії «БУКІНМЕД» (м. Чернівці, Україна).

Наукова робота проводилась на базі неонатологічних відділень міського клінічного пологового будинку м. Чернівці впродовж 2014-2018 рр. Було передбачено інформаційну згоду батьків дитини при відповідному роз'ясненні мети, завдань, методів та обсягу лабораторних та інструментальних методів дослідження. Протокол дослідження схвалено Комісією з питань біомедичної етики Буковинського державного медичного університету, 2015.

Дослідження виконувалися із дотриманням основних положень GCP (1996 рік), Конвенції Ради Європи про права людини та біомедицину (від 4 квітня 1997 р.), Гельсінської декларації Всесвітньої медичної асоціації про етичні принципи проведення наукових медичних досліджень за участю людини (1964-2008 рр.), наказу МОЗ України № 690 від 23.09.2009 р. (із змінами, внесеними згідно з Наказом Міністерства охорони здоров'я України № 523 від 12.07.2012 р.).

Статистична обробка отриманих даних проведена з програмного забезпечення «STATISTICA» (StatSoft Inc., USA, Version 10), програми MedCalc (https://www.medcalc. org/index.php). Порівняння кількісних показників із нормальним розподілом проведено з використанням t-критерію Стьюдента. Різницю параметрів вважали статистично значущою при $p<0,05$.

Дисертаційна робота виконувалась в межах наукової тематики кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету: НДР на тему «Удосконалення напрямків прогнозування, діагностики і лікування перинатальної патології у новонароджених та дітей раннього віку, оптимізація схем катамнестичного спостереження та реабілітації» (Державний реєстраційний номер 0115U002768, термін виконання 01.2015 р. – 12.2019 р.); НДР на тему: «Хронобіологічні й адаптаційні аспекти та особливості вегетативної регуляції при патологічних станах у дітей різних вікових груп» (Державний реєстраційний номер 0122U002245, термін виконання 01.2020 р. – 12.2024 р.)

Отримані результати та їх обговорення. Досліджені лабораторні показники випорожнень у недоношених новонароджених, які мали ознаки харчової інтолерантності при перинатальній патології, засвідчили певні патофізіологічні механізми її розвитку, серед яких: гостре запалення, підвищення проникливості слизової оболонки кишечника та екзокринна недостатність. Порушення функцій системи травлення є наслідком комплексної вегетативно-вісцеральної дисфункції організму дітей на фоні гіпоксії та морфо-функціональної незрілості при народженні. Підвищення рівня A1AT, PMN-еластази, альбуміну та зниження концентрації ФЕ-1 у стільці є взаємозалежними критеріями дисфункції травної системи. Підвищення проникливості слизової оболонки кишечника за умов місцевого запалення призводить до транслокації патогенних та умовно патогенних мікроорганізмів до кров'яного русла, що ймовірно підсилює клінічні прояви ендотоксикозу при перинатальній патології у недоношених. Вище зазначене обґрунтовує необхідність продовження наукових досліджень для розробки уточнення комплексної діагностики та корекції травної функції у передчасно народжених дітей.

Висновки

1. Передчасне народження дітей обумовлює високий ризик порушень адаптації у новонароджених, що обумовлено морфо-функціональною незрілістю організму та
2. реалізацією факторів перинатального ризику.
3. У комплексі вегето-вісцеральної дисфункції за умов перинатальної патології у новонароджених відмічаються ознаки поєднаної дисфункції системи травлення, ознаками якої є послаблення або відсутність смоктального рефлексу, зригування, стаз та парез кишечника, затримка відходження меконію та перехідного стільця, метеоризм; у найбільш важких випадках стійке й тривале зниження толерантності до ентерального харчування є одним з характерних проявів СПОН.
4. Підвищений рівень A1AT, PMN-еластази, альбуміну та зниження концентрації ФЕ-1 у стільці дітей за наявності харчової дисфункції в комплексі ознак перинатальної патології, є лабораторним підтвердженням розладів системи травлення при передчасному народженні.
5. Патофізіологічними механізмами транзиторних порушень функціонального стану травної системи, що обумовлюють клінічні ознаки харчової інтолерантності, є: гостре запалення, підвищення проникливості слизової оболонки кишечника та екзокринна недостатність. Підвищена проникливість слизового бр'єру кишечника призводить до зростання транслокації патогенних та умовно патогенних мікроорганізмів до кров'яного русла, що сприяє зростанню проявів ендотоксикозу при перинатальній патології у недоношених дітей.
6. Узгодження клініко-параклінічних критеріїв порушень функціонального стану травного тракту у комплексі перинатальної патології дадуть змогу підвищити ефективність діагностичних заходів в неонатальному періоді, зокрема у недоношених дітей, удосконалити підходи до надання медичної допомоги шляхом удосконалення комплексу діагностичних та лікувальних заходів.

Ключові слова: новонароджений; система травлення; порушення харчової толерантності; рівень α-1-антитрипсин; PMN-еластаза; альбумін; фекальний кальпротектин; фекальна еластаза-1.

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