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Prediction of recurrent course of respiratory infections in premature infants

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The problem of prevention of frequent respiratory diseases for children remains relevant. Among premature infants, the most vulnerable group are children with very low and extremely low birth weight. Therefore, the development of a clinical prognostic model for the development of respiratory recurrent infections in premature infants may be the basis for creating a preventive program of early intervention.

Purpose — to determine the clinical and genetic determinants of the development of recurrent respiratory infections for children born with a body weight less than 1500 g and to develop an algorithm for early prediction of adverse effects.

Materials and methods. A cohort prospective study was conducted, which involved 155 children with very low and extremely low body weight. Prediction of the development of recurrent respiratory diseases was performed using simple and step-by-step multiple logistic regression analysis. Genetic methods included polymorphism studies of the GSTP1, GSTT1, GSTM1, ACE, AGT2R1 and eNOS genes.

Results. Important predictors of increased morbidity of the examined children in a simple logistic regression analysis were: body weight at 12 months <10 percentile, rickets in the first year of life and artificial feeding at discharge from the neonatal hospital. The study showed no effect of genes polymorphism of the glutathione-S-transferase family and genes of the renin-angiotensin system on the development of recurrent respiratory infections in children with born weight less than 1500 g.

Conclusions. The developed model for predicting the recurrent course of respiratory infections for children born with a body weight less than 1500 g has a high specificity (95.35%) and moderate sensitivity (76.90%), which indicates the possibility of its use for a personalized approach to prevention adverse effects.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: prediction, recurrent respiratory infections, premature infants.

Прогнозування рекурентного перебігу респіраторних інфекцій у передчасно народжених дітей

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Проблема профілактики частих респіраторних захворювань у дітей залишається актуальною. Серед недоношених новонароджених найбільш уразливу групу становлять діти з дуже малою та надзвичайно малою масою тіла при народженні. Тому розроблення клінічної прогностичної моделі розвитку респіраторних рекурентних інфекцій у передчасно народжених дітей може стати підґрунтям для створення профілактичної програми раннього втручання.

Мета — визначити клініко-генетичні детермінанти розвитку рекурентних респіраторних інфекцій у дітей, які народилися з масою тіла <1500 г; розробити алгоритм раннього прогнозування несприятливих наслідків.

Матеріали та методи. Проведено когортне проспективне дослідження, до якого залучено 155 дітей з дуже малою та надзвичайно малою масою тіла. Прогнозування розвитку рекурентних респіраторних захворювань виконано за допомогою простого та покрокового множинного логістичного регресійного аналізу. Генетичні методи включали дослідження поліморфізму генів GSTP1, GSTT1, GSTM1, ACE, AGT2R1 та eNOS.

Результати. Важливими предикторами підвищеної захворюваності обстежених дітей при простому логістичному регресійному аналізі виявилися: маса тіла у 12 місяців <10 перцентиль, перенесений рахіт на першому році життя та штучне вигодовування на момент виписки з неонатального стаціонару. Дослідження не виявило впливу поліморфізму генів сімейства глютатіон-S-трансфераз та генів ренін-ангіотензинової системи на розвиток рекурентних респіраторних інфекцій у дітей, які народилися з масою тіла <1500 г.

Висновки. Розроблена модель прогнозування рекурентного перебігу респіраторних інфекцій в дітей, які народилися з масою тіла <1500 г, має високу специфічність (95,35%) і помірну чутливість (76,90%), що свідчить про можливість її застосування для персоналізованого підходу до профілактики несприятливих наслідків.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: прогнозування, рекурентні респіраторні інфекції, передчасно народжені діти.

Introduction

The problem of frequent respiratory diseases prevention in pediatrics remains relevant. Respiratory diseases are the main reason for visiting a doctor, hospitalization and prescribing a wide range of drugs [5,16]. Particular attention is drawn by premature infants with recurrent respiratory infections (RRI), which are characterized by an unfavorable and prolonged

course [20,22]. Among premature infants, the most vulnerable group are children with a very low body weight and extremely low body weight at birth [7,18]. The World Health Organization recommends paying special attention to the development and implementation of measures for the prevention of acute respiratory infections in young children [19].

In scientific works various factors (influencers of the RRI formation) are investigated and various aspects of this problem are discussed: immunological, microbiological, physiological, infectious, social and hygienic [1,4,17]. However, the literature does not sufficiently highlight the role of individual factors and the importance of their combined effect on the immune status of children born with a very low body weight and extremely low body weight. Therefore, the development of a clinical prognostic model of RRI in premature infants may be the basis for creating a preventive program of early intervention [3,8,9].

Many scientific reports draw attention to the role of polymorphism of genes of the glutathione-S-transferase family and renin-angiotensin system in the development of chronic diseases, disorders of physical, speech and psycho-emotional development of premature infants [8–11]. Therefore, we suggested that the polymorphism of these genes may affect the development of RRI in this cohort of children.

Purpose of the study — to determine the clinical and genetic determinants of the development of recurrent respiratory infections for children born with a body weight less than 1500 g and to develop an algorithm for early prediction of adverse effects.

The study was carried out as part of the research project: To develop clinical and laboratory criteria, methods of prediction and prevention of metabolic disorders in young children. State registration number 0120U102856.

Materials and methods of the research

In order to assess the impact of socio-hygienic, medical and genetic factors on the development of recurrent respiratory pathology, a cohort prospective study was conducted, which involved 155 children weight less than 1500 g. All children were observed at the Child Development Center of Poltava Regional Children's Clinical hospitals. In the process of information processing, all children recorded the total number of episodes of acute respiratory pathology of infectious origin [15].

Depending on the frequency of acute respiratory diseases, two clinical groups were identified: the Group 1 included children who occasionally (no more than 2 times in six months) suffered from acute respiratory viral infections (ARVI), (n=117); the Group 2 included children with frequent respiratory diseases who had more than 2 episodes of ARVI, acute or obstructive bronchitis, and at least one episode of pneumonia within six months (n=38).

The material for the genetic study was peripheral venous blood. To determine the polymorphic variants after the procedure of isolating DNA samples from the obtained material, a molecular genetic study was performed using polymerase chain reaction methods according to M. Arand [2]. The contribution to the increased morbidity of genetic models was investigated: the comparison «+» vs. «-» genes GSTT1 and GSTM1; dominant models: (GG + AG vs. AA) GSTP1 gene, (DD + DI vs. II) ACE gene; (CA + AA vs. AA) gene AGT2R1 and (aa + ab vs. bb) gene e NOS.

The influence of the following factors on the development of RRI was analyzed: socioeconomic status of the family, features of antenatal and intranatal periods, duration of artificial lung ventilation, diagnoses and treatment at the inpatient and outpatient stages, nutrition, birth weight, gestational age, postponed disease at an early age.

Statistical analysis was performed using STATA version 11 for Windows (StataCorp, Texas, USA). In order to predict the development of RRI in premature infants, a step-by-step multiple logistic regression analysis was performed. The odds ratio (OR) with 95% confidence intervals (CI) was used to identify risk factors.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution mentioned in the work. Informed consent of children' parents was obtained for the research.

Results of researches and discussion

The results of the study show that during the first 6 months of life, 39 (25.0%) of children had at least one episode of ARVI, 2 episodes — 3 (1.8%) of infants, and one (0.6%) child had even 3 episodes of the disease (Fig. 1). Over the next six months, the incidence of ARVI was much higher. Thus, 54 (34.7%) of infants already had 1 episode of ARVI. The number of children with 2 episodes of ARVI probably increased from 3 (1.8%) to 32 (20.4%),

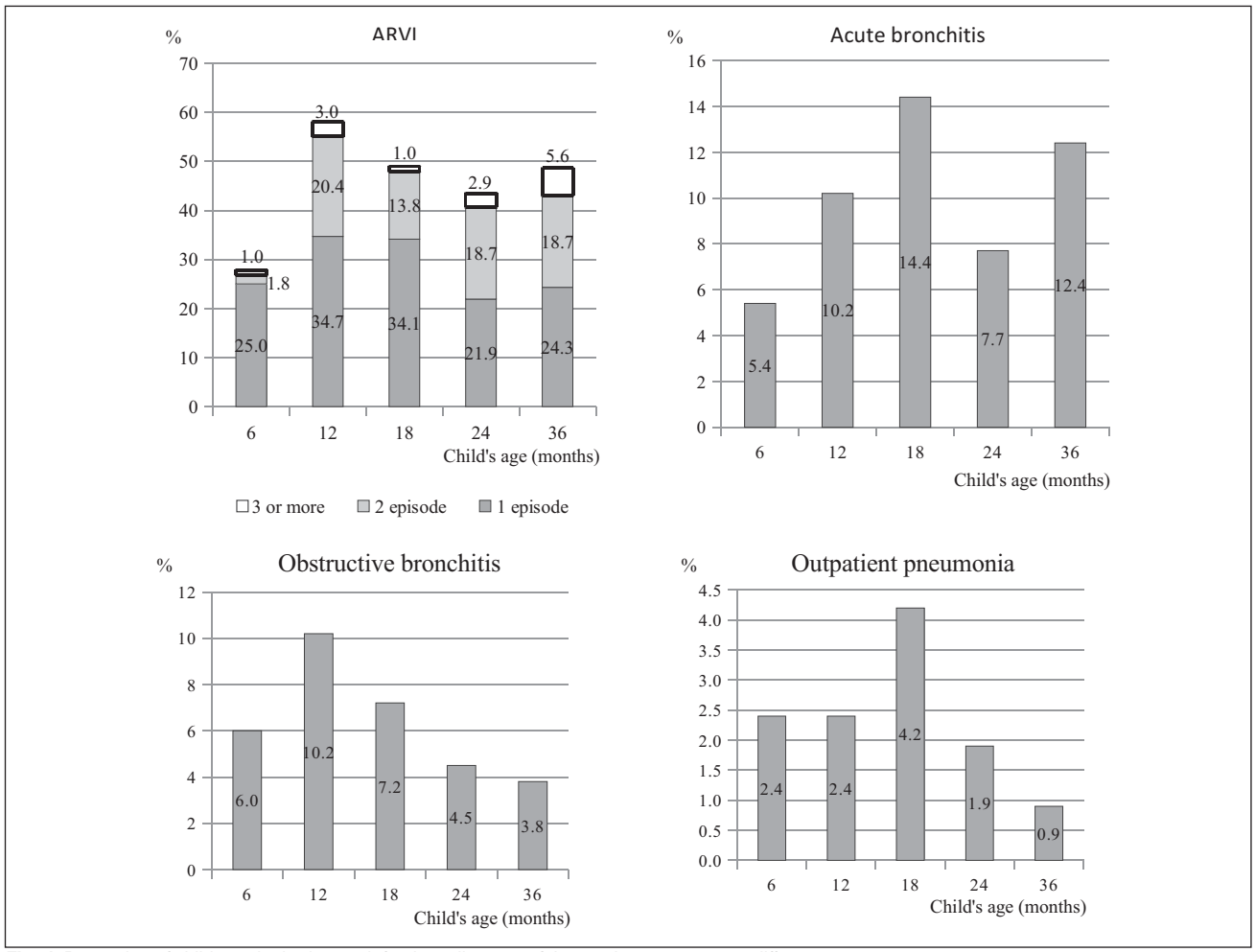

Fig. 1. Proportion of children who had acute infectious diseases of the respiratory system at different ages

p=0.000. The incidence of acute bronchitis — 8 (5.4%) and 16 (10.2%), p=0,152, obstructive bronchitis 9 (6.0%) and 16 (10.2%), p=0.229 and pneumonia — 4 (2.4%) and 4 (2.4%), p=0.229 respectively was almost the same in all age periods. According to the results of the analysis, no differences were found between the frequency of in ARVI children at 18, 24 and 36 months.

The results of the study showed no effect of infectious history of the mother during pregnancy and childbirth on the development of RRI in the examined children. However, attention should be paid to the relation with the probability of p=0.05 between the presence of gestational pyelonephritis in the mother during pregnancy and the development of RRI (Table 1).

Risk factors for the development of RRI in children, which characterize the course of the neonatal period, were the body mass index at birth and formula feeding at discharge from the neonatal hospital. Thus, according to the results of our study, formula feeding at discharge from the hospital increases the chances of having a RRI at an early age (OR=2.33).

This convincingly demonstrated the fundamental role of breastfeeding in the formation of the child's immunity.

Clinical and experimental studies show that vitamin D has a direct antiviral effect, low concentrations of vitamin D in the blood may increase the risk or severity of respiratory viral infections [6,12,21]. We proved that rickets in the first year of life significantly increases the risk for a child to have RRI (OR=2.36).

The role of iron in ensuring the normal functioning of the immune system should be noted. It is known that iron deficiency states lead to an acute weakening of immunity [13,14]. Almost 25% of the children with iron deficiency we examined were classified as children with RRI. It is established that the presence of anemia directly in the first year of life of the child is reliably associated with the development of RRI at an early age (p=0.042). Body weight less than 10 percen-

Table 1

Relation between the development of recurrent respiratory infections and individual clinical factors by simple logistic regression analysis

Dependent variables	OR	95% CI	P
Gestational pyelonephritis (yes, no)	13.0	0.77–215.1	0.05
Gestational age (weeks)	0.92	0.79–1.07	0.307
Body weight at birth (g)	0.99	0.996–1.000	0.058
Body mass index (units)	0.69	0.50–0.96	0.029
Artificial lung ventilation (yes, no)	1.35	0.96–1.03	0.942
Formula feeding at discharge (yes, no)	2.33	1.13–4.84	0.022
Severe intraventricular hemorrhage (yes, no)	1.82	0.71–4.65	0.209
Body weight less than 10 percentiles at 12 months	3.06	1.42–6.58	0.004
Exclusively breast milk at 6 months	0.38	0.15–0.97	0.043
Body weight less than 10 percentiles in 24 months	2.42	1.14–5.12	0.021
Rickets at 0–12 months	2.36	1.09–5.11	0.029
Anemia at 0–12 months	1.53	1.03–5.25	0.042

Table 2

Associations between the development of recurrent respiratory infections and polymorphism GSTP1, GSTT1, GSTM1 ACE, AGT2R1, eNOS genes

Genetic models	OR	95% CI	P
GSTPl GG+AG	1.33	0.311–5.77	0.751
GSTT1 «-»	0.75	0.01–13.69	0.670
GSTM1 «-»	2.0	0.11–28.28	0.472
ACE DD+lD	0.54	(0.02–42.79)	0.579
AGT2R1 CC+CA	4.5	0.14–31.3	0.357
eNOS4ab+4bb	0.45	0.007–6.78	0.479

Table 3

Prognostic model of development of recurrent respiratory infections in examined children and its operational characteristics

Prognostic variable	β	m	OR (95% CI)	P	ROC
Rickets at 0–12 months	0.76	0.39	2.13 (1.01–4.61)	0.052	
Body weight at 12 months less than 10 percentiles	0.92	0.46	2.5 (1.13–5.52)	0.023	
Formula feeding at discharge	0.82	0.39	2.26 (1.05–4.86)	0.036	
_const	-1.49	0.38			0.7030

Notes: β — coefficient is the degree of change in the outcome variable for every 1-unit of change in the predictor variable; m — estimated slope.

tiles at an early age also significantly increases the chances of a child to have frequent infectious diseases of the respiratory system, reduces-exclusively breastfeeding in the first 6 months of life (p=0.043).

The study revealed no effect of polymorphism of genes of the glutathione-S-transferase family and genes of the renin-angiotensin system on increased morbidity in children born with a body weight less than 1500 g (Table 2).

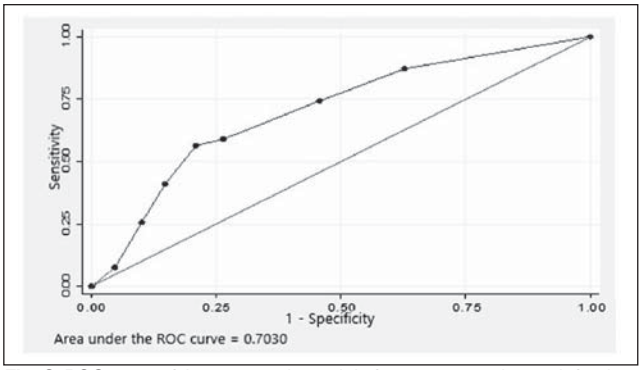

Fig. 2. ROC curve of the prognostic model of recurrent respiratory infection, which includes 3 risk factors

After correction of confudings in multiple regression analysis it was found that the most significant predictors of RRI development at an early age can be considered: body weight at 12 months <10 percentile, rickets in the first year of life and formula feeding at discharge from the neonatal hospital. Therefore, these prognostic variables are included in the prognostic model, which served as the basis for the creation of an algorithm for identifying high-risk individuals with regard to the occurrence of RRI (Table 3).

The operational characteristics of the model developed by us are quite high, in particular the sensitivity was 76.9%, specificity 95.35%, positive predictive value — 33.33%, negative predictive value 77.36%, area under the curve (AUC) — 0.7030 (Fig. 2).

Conclusions

Important predictors of the development of recurrent respiratory infections at an early age in children born with very low and extremely low body weight can be considered: body weight at 12 months <10 percentile, rickets in the first year of life and formula feeding at discharge from the neonatal hospital.

Developed a model for predicting the development of RRI, has a high specificity — 95.35%, moderate sensitivity — 76.9%, which allows with high accuracy to identify a group of children in need of in-depth examination and timely preventive measures. This will overcome the imbalance of immune responses and reduce the incidence of respiratory infections.

Prospects for further research. A promising direction of further research is an in-depth study of possible relationships between gene polymorphisms and the development of recurrent respiratory diseases in a larger cohort of premature children. Such studies will make it possible to determine the risk group for the development of the specified condition.

No conflict of interests was declared by the authors.

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