

The mathematical pathogenetic factors analysis of acute inflammatory diseases development of bronchopulmonary system among infants

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Key words:

pulmonary inflammation, infants, statistical factor analysis, disease clustering.

Zaporozhye medical journal 2017; 19 (5), 596–600

DOI: 10.14739/2310-1210.2017.5.110161

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The purpose. To study the factor structure and to establish the associative interaction of pathogenetic links of acute diseases development of the bronchopulmonary system in infants.

Materials and methods. The examination group consisted of 59 infants (average age 13.8 ± 1.4 months) sick with acute inflammatory bronchopulmonary diseases. Also we tested the level of 25-hydroxyvitamin D (25(OH)D), vitamin D-binding protein, hBPI, cathelicidin LL-37, β 1-defensins, lactoferrin in blood serum with the help of immunoenzymometric analysis. Selection of prognostically important pathogenetic factors of acute bronchopulmonary disease among infants was conducted using ROC-analysis. The procedure for classifying objects was carried out using Hierarchical Cluster Analysis by the method of Centroid-based clustering.

Results. Based on the results of the ROC-analysis were selected 15 potential predictors of the development of acute inflammatory diseases of the bronchopulmonary system among infants. The factor analysis made it possible to determine the 6 main components. The biggest influence in the development of the disease was made by “the anemia factor”, “the factor of inflammation”, “the maternal factor”, “the vitamin D supply factor”, “the immune factor” and “the phosphorus-calcium exchange factor” with a factor load of more than 0.6. The performed procedure of hierarchical cluster analysis confirmed the initial role of immuno-inflammatory components.

The conclusions. The highlighted factors allowed to define a group of parameters, that must be influenced to achieve a maximum effect in carrying out preventive and therapeutic measures. First of all, it is necessary to influence the “the anemia factor” and “the calcium exchange factor”, as well as the “the vitamin D supply factor”. In other words, to correct vitamin D deficiency and carry out measures aimed at preventing the development of anemia. The prevention and treatment of the pathological course of pregnancy will help stabilize the “the maternal factor” in the future.

Ключові слова:

запальні захворювання бронхолегеневої системи, діти раннього віку, факторний аналіз, кластерний аналіз.

Запорізький медичний журнал. – 2017. – Т. 19, № 5(104). – С. 596–600

Математичний аналіз патогенетичних факторів розвитку гострих запальних захворювань бронхолегеневої системи в дітей раннього віку

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Мета роботи – дослідити факторну структуру та встановити взаємозв'язок патогенетичних ланок розвитку гострих захворювань бронхолегеневої системи в дітей раннього віку.

Матеріали та методи. Обстежили 59 дітей раннього віку (середній вік – $13,8 \pm 1,4$ місяця), які хворі на гострі запальні бронхолегеневі захворювання. За допомогою імуноферментного аналізу досліджувався вміст у сироватці крові 25-гідроксівітаміну Д (25(OH)D), вітамін-Д-зв'язуючого білка, hBPI, кателіцидину LL-37, β 1-дефензину, лактоферину. Відбір прогностично значущих патогенетичних чинників розвитку гострої бронхолегеневої патології здійснювали за допомогою ROC-аналізу. Процедуру класифікації об'єктів виконували за допомогою ієрархічної кластеризації (Hierarchical Cluster Analysis) методом центроїдної кластеризації.

Результати. За результатами ROC-аналізу відібрано 15 потенційних предикторів розвитку гострих запальних захворювань бронхолегеневої системи в дітей раннього віку. Проведений факторний аналіз дав можливість виділити 6 головних компонент, з них найбільший внесок у розвиток захворювань із факторними навантаженнями понад 0,6 вносили «фактор анемії», «фактор запалення», «материнський фактор», «фактор забезпеченості вітаміном Д», «імуний фактор» і «фактор кальцієвого обміну». Процедура ієрархічного кластерного аналізу підтвердила ініціальну роль імунозапальних компонентів.

Висновки. Виділені фактори дали можливість визначити групу параметрів, на яку необхідно впливати для досягнення максимального ефекту при профілактичних та лікувальних заходах. Передовсім необхідно впливати на «фактор анемії» та «фактор фосфорно-кальцієвого обміну», «фактор забезпеченості вітаміном Д». Заходи, що спрямовані на запобігання та лікування патологічного перебігу станів вагітності, даватимуть змогу стабілізувати надалі «материнський фактор».

Ключевые слова:

воспалительные заболевания бронхолегочной системы, дети раннего возраста, факторный анализ, кластерный анализ.

Математический анализ патогенетических факторов развития острых воспалительных заболеваний бронхолегочной системы у детей раннего возраста

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Цель работы – провести исследование факторной структуры и установить взаимосвязь патогенетических звеньев развития острых заболеваний бронхолегочной системы у детей раннего возраста.

Материалы и методы. Обследовано 59 детей раннего возраста (средний возраст $13,8 \pm 1,4$ месяца), больных острыми воспалительными заболеваниями бронхолегочной системы. С помощью иммуноферментного анализа исследовалось содержание в сыворотке крови 25-гидроксивитамина Д (25(OH)D), витамин-Д-связывающего белка, hBPI, кателіцидина LL-37, β 1-дефензинов, лактоферрина. Отбор прогностически значимых патогенетических факторов развития острой

бронхолегочной патологии проводился с помощью ROC-анализа. Процедура классификации объектов осуществлялась с помощью иерархической кластеризации (Hierarchical Cluster Analysis) методом центроидной кластеризации.

Результаты. По результатам ROC-анализа было отобрано 15 потенциальных предикторов развития острых воспалительных заболеваний бронхолегочной системы у детей раннего возраста. Проведенный факторный анализ позволил выделить 6 основных компонентов, из которых наибольший вклад в развитие заболеваний с факторными нагрузками свыше 0,6 вносили «фактор анемии», «фактор воспаления», «материнский фактор», «фактор обеспеченности витамином Д», «иммунный фактор» и «фактор кальциевого обмена». Процедура иерархического кластерного анализа подтвердила инициальную роль аутоиммунных компонентов.

Выводы. Выделенные факторы позволили определить группу параметров, на которую необходимо воздействовать для достижения максимального эффекта при проведении профилактических и лечебных мероприятий. В первую очередь, необходимо воздействовать на «фактор анемии» и «фактор фосфорно-кальциевого обмена» «фактор обеспеченности витамином Д». Меры, направленные на предотвращение и лечение патологического течения состояний беременности, позволят стабилизировать в дальнейшем «материнский фактор».

The respiratory diseases are among the most important problems in pediatrics, because so far, they take the first place in the structure of infant morbidity [11]. Every year the number of children, who are hospitalized with acute bronchitis increases, which complicates the flow of acute respiratory disease every year [8]. Among the factors that raise the risk of heightened respiratory morbidity, are determined these: the mother age, abnormal pregnancy, prematurity, purulent-septic diseases in the neonatal period, prenatal CNS lesions [4]. In addition, the risk of infectious and inflammatory diseases of bronchopulmonary system among infants increases due to protein-vitamin deficiency and past diseases (rickets, anemia), environmental pollution, stress in the family, which lower the organism's resistance to respiratory pathogens [12].

Recent studies show the pathogenetic importance of endogenous antimicrobial peptides in the formation of the inflammatory process in various forms of pathology [2,5,14]. It is known that antimicrobial peptides act as a first line of defense when respiratory pathology is present [17]. The antimicrobial peptides, as a component of innate immunity, act as a natural defense against a wide spectrum of microbes. Considering the representation of antimicrobial peptides in many organs and systems of humans and their multidirectional action, it is certainly interesting to study their pathogenetic role in the development of acute bronchopulmonary disease in infants.

It is known that the production of antimicrobial peptides, including defensins and cathelicidin, is strengthened by the presence of vitamin D [15]. Currently, there is evidence that 1.25 (OH) 2D regulates the effectiveness of the immune response and has anti-inflammatory effect [3]. The connection between vitamin D deficiency and the incidence frequency of respiratory disease is detected [13,23]. In Wayne V. and all studies (2004), the increasing of serious lower respiratory tract infections risk among children with subclinical deficiency of vitamin D, was shown [22].

Considering the diversity of the mechanisms of infectious-inflammatory process in bronchopulmonary system formation, significant interest is the associative interaction between the individual sections of pathogenesis, determining the development of acute respiratory infections among infants. One of the possible and most effective ways to study complex systems is the use of factor analysis [10].

The purpose to study the factor structure and to establish the associative interaction of pathogenetic links of acute diseases development of the bronchopulmonary system in infants.

Materials and methods

The examination group consisted of 59 infants (average age 13.8 ± 1.4 months), of which 46 patients were diagnosed with acute bronchitis and 13 patients – community acquired pneumonia. The control group included 20 healthy children, resembling by age. Verification of the diagnosis was conducted in accordance with the criteria for the diagnosis of acute bronchitis (Order of the Ministry of Health of Ukraine № 18 dated December 31, 2005 "The protocol of treatment for children with acute bronchitis") and pneumonia among children (Ministry of Health of Ukraine № 18 dated December 31, 2005 "The protocol for treatment for children with pneumonia"). During the collection of the anamnesis, particular attention was paid to the peculiarities of the process of antenatal intranatal and neonatal periods, as well as the form of child feeding. A mandatory complex of examination included chest organs roentgenography, a general blood test examination, general urinalysis, blood chemistry test of glucose, total protein, total bilirubin, thymol test, ALT, AST, electrolytes (potassium, calcium, sodium, phosphorus). Also we tested the level of 25-hydroxyvitamin D (25(OH) D), vitamin D-binding protein, bactericidal protein that increases the permeability of cells (hBPI), cathelicidin LL-37, β 1-defensins, lactoferrin in blood serum with the help of immunoenzymometric analysis.

Selection of prognostically important pathogenetic factors was conducted using ROC-analysis of acute bronchopulmonary disease among infants. A zero degree of prediction of the indicator was established at an area under the ROC curve with 0.5 c. u. and less [6].

In order to determine the least possible number of hidden common factors, that affect the most the occurrence of acute diseases of the bronchopulmonary system in children and their factor loads, a factor analysis was conducted. The basis for modeling for the selection of factor complexes Spearman correlation matrix was chosen with the subsequent determination of the vector load of the indicators that were studied. Significant factors in the model were studied using the scree plot criterion and the Kaiser criterion [9]. For exponent sampling with a high factor load on the complex (more than 0,6), the method of orthogonal rotation VARIMAX was used. The factor analysis using VARIMAX rotation was performed along taking into account the results of the initial analysis and using it to describe the dispersion of the data array of the main components [9].

The procedure of classifying the objects was conducted using the Hierarchical Cluster Analysis by the method

of Centroid-based clustering. Hierarchical clustering was based on the unification of the most similar objects and was completed by the construction of the dendrogram. The measure of the distance between the formed clusters was Euclidean distances [9]. Received results were processed with using the statistic package of a licensed program Statistica® for Windows 6.1.RU”, serial number AXXR712D833214SAN5 and “SPSS 13.0” for Windows. The differences were considered meaningful, if $p < 0.05$ for all kinds of analysis.

Results of the research and discussion

Based on the results of the ROC-analysis, 15 potential predictors of the development of acute inflammatory diseases of the bronchopulmonary system, among infants, were selected, which included the age of the child, the course of the antenatal period, the nature of nutrition (natural or artificial), the parameters of the general blood test (the level of red blood cells, hemoglobin, leukocytes, ESR), serum levels of total protein and calcium, and vitamin D, vitamin D-binding protein, bactericidal protein that increases the permeability of cells (hBPI), cathelicidin LL-37, β 1-defensins, lactoferrin.

According to the analysis of the Spearman rank correlation matrix in the group of infants with acute diseases of the bronchopulmonary system, the presence of certain integrations between prenatal, metabolic and immune factors was indicated (Table 1). This way, the pathological flow of mother's pregnancy had an effect on the level of vitamin D-binding protein in the child's blood serum. Also, the associative interaction between cathelicidin and lactoferrin in serum levels and β 1-defensins was indicated.

In order to determine the factors, which that most affect the occurrence of acute diseases of the bronchopulmonary system in infants, as well as their factor loads, the correlation matrix exponents were analyzed with factor analysis. Conducted analysis of correlation integration of 15 indicators, that can influence the development and the flow of acute disease among infants, allowed to determine and rank “latent” factors (the main components) in terms of their effect on the pathological process in the bronchopulmonary system. After the initial analysis, the main components with proper numbers greater than 1.0 were distinguished (Table 2).

The proper number of the first 6 main components exceeded 1.0 and their summary contribution in the total variance was 66.9 %, with the first 4 main components accounting for almost half (48.9 %) of the total load. This indicated that these factors determine the major part of the pathogenetic factors of acute bronchopulmonary pathology in the examined patients. Then, a matrix of factor loads was determined using the principal component method (Table 3).

In accordance to the obtained data, the main factor was determined by the parameters of hemoglobin and erythrocytes (factor load, accordingly, 0.885 and 0.877) among infants with acute bronchopulmonary pathology. Conditionally, the first factor was designated as “the anemia factor”. The received data are logical, if we consider the fact that any anemia leads to a decrease in the respiratory function of the blood and the development of oxygen starvation of the tissues, which leads to a more severe and protracted flow of the disease.

In this case, in the clinical picture, the signs of respiratory insufficiency appear to the forefront. This factor explains 13.6 % of the total variance.

The integration of the second factor, which in the total dispersion was 13.0 %, characterized the ESR (factor load 0.812) and the level of leukocytes in the blood (factor load 0.719). This factor we can call “the factor of inflammation”.

In the structure of the third factor which was designated as the “the maternal factor” and accounted for 12 % of the total variance, the most load had the indicators of the child's age (0.795) and the antenatal period (0.617).

In the fourth factor, the integration is divided into two parts: negative (total protein: -0.712) and positive (vitamin D: 0.778). It is known that the activation of protein synthesis occurs with the participation of vitamin D, which in addition to participation in the mineral metabolism regulates the effectiveness of the immune response and has an anti-inflammatory effect [3,20]. The factor was defined as “the vitamin D supply factor”.

The fifth factor was “the immune factor” which was determined by two variables (the lactoferrin and β 1-defensins). These antimicrobial peptides are the main components of nonspecific protection of the respiratory tract and act as the main proteins of natural immunity [1,16]. When the expression of antimicrobial peptides is compromised, the risk of developing infectious diseases increases [7].

Table 1. The correlation matrix in the group with acute inflammatory diseases of the bronchopulmonary system in infants

№	The indicators	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	The calcium	-													
2	The total protein	-0.26													
3	The vitamin D	0.07	-0.28												
4	The vitamin D-binding protein	0.02	0.20	-0.20											
5	The lactoferrin	0.08	-0.06	0.06	0.19										
6	hBPI	0.05	-0.27	-0.02	0.09	-0.03									
7	The β 1-defensins	0.04	-0.09	0.02	-0.03	0.36	0.003								
8	The cathelicidin	0.11	-0.01	-0.003	-0.01	-0.07	-0.08	0.36							
9	The hemoglobin level	-0.01	0.09	0.08	0.17	-0.06	-0.09	-0.11	0.08						
10	The red blood cells	0.04	0.19	0.14	0.03	-0.03	-0.11	-0.05	0.09	0.72					
11	The leukocytes level	0.09	0.15	-0.06	0.18	0.02	-0.09	0.12	0.04	-0.32	-0.10				
12	ESR	-0.08	0.28	0.09	-0.32	0.20	-0.11	-0.02	0.02	-0.28	-0.13	0.53			
13	The pathology of pregnancy	0.19	-0.18	0.15	-0.29	0.01	-0.01	0.18	-0.02	0.08	0.06	0.38	0.05		
14	The age of the child	0.12	-0.10	-0.02	-0.26	-0.15	0.12	-0.01	-0.05	0.05	0.11	0.07	-0.01	0.23	
15	The nature of nutrition	0.19	0.01	-0.15	0.18	-0.07	0.06	0.03	-0.14	0.10	0.03	0.16	0.19	0.05	0.17

In the sixth factor, one variable is defined, precisely the level of calcium in the blood with a factor load of 0.840. The established factor was named as “the calcium exchange factor”. Calcium ions have an important place in immune processes. On the one hand, each population of immunocompetent cells has a calcium dependent activation mechanism [21]. On the other hand, excessive calcium saturation of cells closes the transmembrane channels and makes the cytocele impermeable [19]. Because of this, the deviation of calcium concentration in blood can negatively affect the vital activity and activity of immunocompetent cells and, as a consequence, reduce the resistance of the organism [18].

Thus, the development of acute diseases of the bronchopulmonary system among infants occurs in a dynamic interaction of a number of factors. On the basis of the factor analysis, a formation of a pathological process model was formed, which is associated with 6 different conditions. The data of factor analysis, confirmed a priority contribution to the development of acute bronchopulmonary pathology, the presence of anemia, immune disorders, the state of provision with vitamin D and calcium, and the course of the antenatal period.

Based on the obtained data of factor analysis, a cluster analysis of the main pathogenetic factors was performed. According to the results of hierarchical cluster analysis, 2 clusters were allocated in the sample of pathogenetic factors of development of acute bronchopulmonary pathology among infants (Fig. 1).

The conducted cluster analysis shows that at the initial stage an associative interaction between the indicators of red blood is formed with the subsequent addition of calcium level indices and the total protein of the blood. The level of these components is affected by the unfavorable course of the antenatal period (cluster 1).

Then, based on the results of the cluster grouping, an agglomeration was formed which was made up of lactoferrin, β 1-defensins, vitamin D, the index of ESR and the level of leukocytes in serum (cluster 2). The resulting structure is displayed in a hierarchical tree of different branches and a certain cluster emphasized the initial role of immuno-inflammatory components in the development of respiratory diseases among infants. The received line interactions were completed by indicator of child's age, which formed a common agglomerate with these parameters. With all this, the components of the formed clusters not only logically complemented each other, but also indicated their pathogenetic role in the development of the broncho-pulmonary system among infants.

So, the results of conducted factor and cluster analysis were of interest for determination the main indicators when predicting the possibility of developing of acute inflammatory diseases of the bronchopulmonary system in infants.

Conclusions

1. The highlighted factors allowed to define a group of parameters, that must be influenced to achieve a maximum effect in carrying out preventive and therapeutic measures.

2. When developing therapeutic measures, that are aimed at preventing the occurrence of acute inflammatory diseases of the bronchopulmonary system in infants, first of all, it is necessary to influence the “the anemia factor”

Table 2. The factor analysis of indicators that affect the development of acute inflammatory diseases of the bronchopulmonary system among infants

The components	The initial analysis		VARIMAX rotation	
	Own number (A)	The total part in the total variance (%)	Own number (A)	The total part in the total variance (%)
The main component-1	2.208	15.772	1.901	13.582
The main component-2	1.859	29.054	1.823	26.603
The main component-3	1.628	40.679	1.681	38.612
The main component-4	1.336	50.224	1.441	48.906
The main component-5	1.233	59.031	1.334	58.433
The main component-6	1.101	66.894	1.184	66.894
The main component-7	0.921	73.472		
The main component-8	0.849	79.537		
The main component-9	0.753	84.917		
The main component-10	0.587	89.112		
The main component-11	0.517	92.807		
The main component-12	0.460	96.092		
The main component-13	0.316	98.349		
The main component-14	0.231	100		

Table 3. The calculation of factor loads on indicators that were studied among infants with acute bronchopulmonary pathology

The indicators	The Factor loadings					
	1	2	3	4	5	6
The age of the child			0.795			
The leukocytes level		0.719				
The calcium						0.840
The total protein				-0.712		
The vitamin D				0.778		
The lactoferrin					0.601	
The β 1-defensins					0.731	
The hemoglobin level	0.858					
The red blood cells	0.877					
The pathology of the antenatal period			0.617			
ESR		0.812				

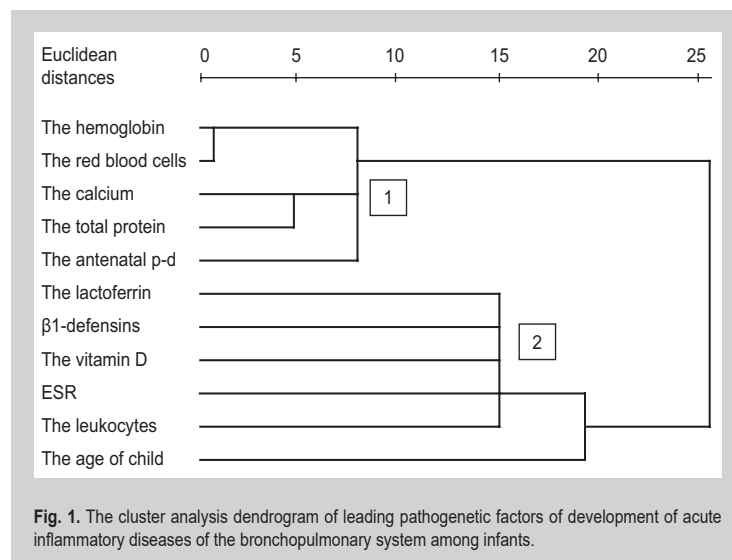


Fig. 1. The cluster analysis dendrogram of leading pathogenetic factors of development of acute inflammatory diseases of the bronchopulmonary system among infants.

and “the calcium exchange factor” as well as “the vitamin D supply factor”, meaning to correct vitamin D deficiency and carry out measures aimed to prevent the development of anemia.

3. Taking into account the fact that the unfavorable course of the antenatal period is one of the risk factors for the development of acute bronchopulmonary diseases in infants, then those activities, aimed at the prevention and treatment of the pathological course of pregnancy will help stabilize the “the maternal factor” in the future.

The prospects. In the future we plan to analyze the peculiarities of the flow of acute bronchopulmonary diseases among infants, taking into account highlighted pathogenetic factors with the justification of preventive measures aimed at preventing their occurrence.

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Конфлікт інтересів: відсутній.

Conflicts of interest: authors have no conflict of interest to declare.

Надійшло до редакції / Received: 24.05.2017
Після доопрацювання / Revised: 01.06.2017
Прийнято до друку / Accepted: 07.06.2017