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DETERMINATION OF BIOMARKERS FOR PREDICTING THE SEVERITY OF THE PROCESS OF COMMUNITY AQUIRED PNEUMONIA ON CHILDREN

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Summary

Introduction: The most important factor is the determination of biomarkers inflammation for predicting the severity of the process of community-acquired pneumonia in children. In this context, the purpose of the present study is to study the possibility of using quantitative content of proinflammatory cytokines and serum procalcitonin to predict the severity of the process of community-acquired pneumonia in children

Materials and methods: In a prospective cohort study under the supervision of 110 children with community-acquired pneumonia at the age of 5 to 10 years, undergoing treatment in the respiratory department of Children's Hospital of Karaganda, in which 43.64% were girls (95% CI 31.51% - 56 , 33%) and boys 47.27% (95% CI 34.91% - 59.88%). The content of IL-6, TNFα and PCT in the blood serum of 48 children with community-acquired pneumonia of varying severity. Group I included 24 patients whose smears in bacteriological method were cultured in bacterial microflora. Streptococcus pneumoniae was found in 18 patients, which accounted for 75.00% (95% CI, 46.96% -93.08%) and 7 patients has Streptococcus haemolyticus group A, which accounted to 29.17% (95% CI, 9.30% -57.32%). In the II[nd] group of 24 patients they have a viral etiology of the disease.

Results: A significant increase in the levels of IL-6, TNFα and PCT 5-6 times with CAP compared with the control group performance and recorded a tendency to increase the content of these cytokines, depending on the severity of the disease. Depending on the level of TNFα in the etiology of bacterial pneumonia higher than with viral pneumonia. The most significant differences were observed when comparing with the III[rd] degree of bacterial and viral pneumonia ($p < 0.032$). At the same time, the content of the proinflammatory cytokine IL-6 was significantly higher in the serum of patients with bacterial pneumonia than in patients with pneumonia III severity ($p < 0.03$).

Résumé

Détermination des biomarqueurs pour prédire la gravité du processus de pneumonie communautaire chez les enfants

Introduction: Le plus important facteur est la détermination des biomarqueurs de l'inflammation pour prédire la gravité du processus de pneumonie communautaire chez les enfants. Dans ce contexte, l'objectif de la présente étude est d'étudier la possibilité d'utiliser la quantité des cytokines pro-inflammatoires et de procalcitonine sérique pour prédire la gravité du processus de pneumonie communautaire chez les enfants.

Matériels et méthodes: Dans une étude d'un groupe représentatif de 110 enfants atteints de pneumonie à l'âge de 5 à 10 ans, en cours de traîtement dans le département respiratoire de l'Hôpital pour enfants de Karaganda, où 43,64% étaient des filles (95% CI 31,51% - 56, 33%) et les garçons 47,27% (IC à 95% 34,91% - 59,88%). La quantité de l'IL-6, TNFα et PCT dans le sérum de sang de 48 enfants atteints de pneumonie communautaire est variable. Le groupe I a inclus 24 patients dont les frottis suivant la méthode bactériologique ont été cultivés dans la microflore bactérienne. Le streptococcus pneumoniae a été constaté chez 18 patients, qui représentaient 75,00% (IC à 95%, 46,96% -93,08%) et 7 patients ont un groupe Streptococcus haemolyticus A, qui représentait 29,17% (IC 95%, 9,30% -57,32%). Dans le groupe II, 24 patients ont une étiologie virale de la maladie.

Résultats: Une augmentation significative du taux d'IL-6, TNFα et PCT 5 à 6 fois avec CAP comparé à la performance du groupe témoin, a confirmé une tendance croissante de la teneur de ces cytokines, en fonction de la gravité de la maladie. Le niveau de TNFα dans l'étiologie de la pneumonie bactérienne est supérieure à celle d'une pneumonie virale. Les différences les plus importantes ont été observées lorsque l'on compare le degré de la pneumonie bactérienne et virale ($p < 0,032$) III. Dans le même temps,

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Conclusion: The results of our study suggest the worsening of the severity of pneumonia increased level of anti-inflammatory cytokines in the blood serum procalcitonin patients. The results obtained from studies of patients with bacterial and viral pneumonia proinflammatory cytokines (TNFα, IL- 6) and procalcitonin predictors can be used to predict the severity of pneumonia.
Key words: community-acquired pneumonia, children, bacterial pneumonia, viral pneumonia, IL-6, TNFα, PCT.

la teneur de la cytokine pro-inflammatoire IL-6 est significativement plus élevée dans le sérum des patients atteints de pneumonie bactérienne que chez les patients présentant une pneumonie virale de gravité III (p <0,03).
Conclusion: Les résultats de notre étude suggèrent que la gravité de la pneumonie a fait augmenter le niveau de cytokines anti-inflammatoires ainsi que la procalcitonine dans le sérum sanguin des patients. Les résultats d'étude des patients avec des cytokines bactériennes et virales de pneumonie montrent que la teneur des cytokine pro-inflammatoires (TNFα, IL-6) et de la procalcitonine peuvent être utilisés pour prévoir la gravité de la pneumonie.
Mots clés: pneumonie communautaire, enfants, pneumonie bactérienne, pneumonie virale, IL-6, TNFα, PCT

INTRODUCTION

Pneumonia has traditionally had a high percentage as a cause of morbidity in children of all age groups [5, 6]. In recent years, there has been a significant increase of the number of patients with severe and complicated course of community-acquired pneumonia [4-14]. The main focus in the assessment of pneumonia requires a complex assessment of the severity of the patient's condition for the prediction of the disease, especially in the early stages of its development [2-11].

Community-acquired pneumonia is accompanied by a systemic response of the organism of inflammation in the lung tissue. In recent years, much attention is given to study biological biomarkers of infection; however, these studies, that analyze data trends of the cytokine profile to reflect pneumonia, can be insufficient depending on the form and severity of the disease [11-20]. In this regard, alternative study of the possibility of using the quantitative determination of complex biomarkers of inflammation, such as pro-inflammatory cytokines and procalcitonin, is of great practical importance for the assessment of prognosis of community-acquired pneumonia in children.

OBJECTIVE

To study the possibility of using quantitative content of proinflammatory cytokines and serum procalcitonin to predict the severity of the process of community-acquired pneumonia in children.

MATERIAL AND METHODS

In a prospective cohort study, 110 children with community-acquired pneumonia at the age of 5 to 10 years, who were undergoing treatment in the respiratory department of Children's Hospital of Karaganda, were reviewed. The subjects were divided between 43.64% girls (95% CI 31.51% - 56, 33%) and 47.27% (95% CI 34.91% - 59.88%) boys. Patients and healthy children were included in the study on the basis of informed consent. The criteria for inclusion in the group of subjects were: children from 5-10 years with verified diagnosis of community-acquired pneumonia, the voluntary participation of parents of children with registration of informed consent, to eliminate the risk of harm, damage (physical, psychological, social and economic).

Exclusion criteria were:

1. parents not allowing children to participate in the study;
2. those who had previously the antimicrobial therapy;
3. the presence of comorbidity: another chronic inflammatory disease, congenital heart disease, active tuberculosis, the presence of cancer, neurological and endocrine diseases.

Verification of the diagnosis of pneumonia was carried out based on standards of diagnosis and treatment of pneumonia in children (ICD 10, J15.8). During examination children were divided into two groups based on etiology of the disease:

- Ist group, which included 24 patients, whose smears bacteriological method cultured in bacterial microflora.
- IInd group consisted of 24 patients with negative results of bacteriological research, which was regarded as a viral etiology.

Depending on the severity of the patients, subjects were divided into three groups (I,II,III). Criteria severity pneumonic process developed by V.G. Maydannik [14]. The control group consisted of 25 healthy children.

On admission to hospital in patients was determined the content of pro-inflammatory cytokines (IL-6, TNFα) and procalcitonin in serum.

IL-6 was determined by ELISA using reagents for immunoassay for determining the concentration of IL-6 in serum (Interleukin-6 - ELISA BEST) (0-250 pg/ml). TNFα was determined by IFA using a kit of reagents for immunoenzyme determination of the concentration of tumor necrosis factor alpha in serum (TNF-alpha ELISA- BEST) (0-300 pg/ml). PCT was determined by ELISA using a kit of reagents for immunoenzyme determination of procalcitonin concentrations in serum (0-12,8 ng/ml) (Procalcitonin ELISA-BEST).

RESULTS

The study of children with community-acquired pneumonia showed that Streptococcus pneumoniae was detected in 18 patients, accounting for 75.00% (95% CI, 46.96 % -93.08 %) and in 7 patients, Streptococcus beta-

haem. group A, which accounted to 29.17 % (95% CI, 9.30% -57.32 %), was detected.

Analysis of quantitative evaluation results of characteristics of proinflammatory cytokines (TNFα, IL- 6) and procalcitonin are presented in tables 1,2,3.

As can be seen from table 1 the high content of TNFα was observed in all groups of patients. In patients with bacterial pneumonia TNFα levels increased in tandem with the increase in severity of the disease. In the control group the level of TNF - α was 1.15 ± 0,76pg / ml. In patients with bacterial pneumonia II severity TNFα levels 4 times higher compared with the control group (p < 0.015). TNFα levels in patients with bacterial pneumonia II degree, in comparison with I degree, had higher level than with the 2-group (p< 0.047).

In patients with viral pneumonia TNFα levels also increased with the increase in the severity of the disease, as well as in patients with bacterial pneumonia. Patients with pneumonia virus I and II degree TNFα levels compared with the control group tend to increase, but no significant difference was observed. In patients with grade III viral pneumonia TNFα level was 3,50 ± 0,44pg / ml, 3 times higher compared to the control group (p < 0.03).

Depending on the level of TNFα in the etiology of bacterial pneumonia, levels are generally higher than with viral pneumonia. The most significant differences were observed when comparing the III degree of bacterial and viral pneumonia (p< 0.032).

At level IL-6 study revealed this increase as worsening disease severity (table 2). In patients with bacterial pneumonia I severity IL-6 level is greater than this cytokine in the control group. In patients with grade II level of this marker, levels were 2.5 times higher compared with the control group (p< 0.00).

Analyzing the data IL-6 in patients with viral pneumonia it was observed that patients with indicators and I degree

Table 1 - Content of TNFα in serum depending on the severity and etiology of community-acquired pneumonia in children

	I (n-8)		II (n-8)		III (n-8)		C (n-25)
Bacterial pneumonia	2,13±1,27	pc-1>0,05	4,38±0,65	pc-II<0,015* pI-II<0,047*	5,66±0,69	pc-III<0,01* pI-III<0,025* pII-III>0,05	1,15±0,76
Virus pneumonia	1,97±0,51	pc-1>0,05	3,72±0,84	pc-II>0,05 pI-II>0,05	3,50±0,44	pk-III<0,03* pI-III>0,05 pII-III>0,05	1,15±0,76
Bacterial pneumonia/ Virus pneumonia		pIb-v>0,05		pIIb-v>0,05		pIIIb-v<0,02*	

Table 2 - Content of IL-6 in serum depending on the severity and etiology of community-acquired pneumonia in children

	I (n-8)		II (n-8)		III (n-8)		C (n-25)
Bacterial pneumonia	1,96±0,76	pc-1>0,05	2,17±0,28	pc-II<0,003* pI-II>0,05	6,89±0,53	pc-III<0,03* pI-III<0,00* pII-III<0,00*	0,84±0,27
Virus pneumonia	3,05±1,57	pc-1>0,05	3,83±1,90	pc-II<0,03* pI-II>0,05	4,24±0,65	pc-III<0,00* pI-III<0,005* pII-III>0,05	0,84±0,27
Bacterial pneumonia/ Virus pneumonia		pIb-v>0,05		pIIb-v>0,05		pIIIb-v<0,03*	

Table 3 - Content of PCT in serum depending on the severity and etiology of community-acquired pneumonia in children

	I (n-8)		II (n-8)		III (n-8)		C (n-25)
Bacterial pneumonia	0,26±0,12	pc-1>0,05	0,44±0,15	pc-II<0,015 pI-II>0,05	1,76±0,24	pc-III<0,00* pI-III<0,00* pII-II<0,012*	0,04±0,01
Virus pneumonia	0,13±0,06	pc-1>0,05	0,31±0,14	pc-II<0,00* pI-II>0,05	1,58±1,31	pc-II<0,032* pI-III>0,05 pII-III>0,05	0,04±0,01
Bacterial pneumonia/ Virus pneumonia		pIb-v>0,05		pIIb-v>0,05		pIIIb-v<0,03*	

were not significantly different from the weight from II degree, thus significant differences were observed in patients with severity II compared to the control group ($p < 0.03$). At III level of IL-6 levels in the group were significantly higher compared with the control group ($p < 0.00$) and compared with patients whose disease proceeded with the II degree of severity ($p < 0.005$).

At the same time, the content of the proinflammatory cytokine IL- 6 was significantly higher in the serum of patients with bacterial pneumonia than with patients with viral pneumonia III severity ($p < 0.03$).

The level of procalcitonin in the control group was 0.04 ± 0,01pg / ml (table 3). When analyzing the indicators, it was revealed that in patients with bacterial pneumonia PCT levels increased with the increase in severity of the disease. In patients with bacterial pneumonia II degree, PCT levels were 9 times higher compared with the control group ($p < 0.015$).

As shown in table 3 in patients with viral pneumonia PCT levels also increased with the increase in severity of the disease. Patients with moderate viral pneumonia PCT levels compared with the control group exceeded 6-fold ($p < 0.00$). In patients with grade III viral pneumonia PCT level was 1.58 ± 1,31pg/ml, 5 times higher compared to the control group ($p < 0.032$).

When bacterial pneumonia PCT levels of I and II severity were higher than in viral pneumonia, but we have seen significant differences when comparing the severity of severe bacterial and viral pneumonia ($p < 0.032$).

Discussion

Literature data on the level of proinflammatory cytokines and procalcitonin in children with community-acquired pneumonia are rare and contradictory. Research conducted Gendrel and al (1999) and Moulin and al (2001) shows that the PCT is more important for the differentiation of bacterial and viral infections, in contrast to IL- 6 [8,17].

At the same time research by Toikka and al (2000) shows that measurement of serum and PCT IL- 6 is of little importance in differentiating bacterial and viral pneumonia in children [21]. However, patients with high levels of PCT and IL-6, bacterial pneumonia are more likely to be detected [22]. The results of our studies show that a high level of PCT, IL-6 and TNFα in blood serum was observed in children with a severe degree of the disease, which can be a predictor of disease severity.

Determination of PCT serum can reduce the unnecessary use of antibiotic therapy in patients with community-acquired pneumonia and reduce the duration of antibiotic therapy. This is confirmed in a number of researches noting the high level of procalcitonin [12,19].

Conclusion

The results of our study suggest the worsening of the severity of pneumonia increased titers of anti-inflammatory cytokines in the blood serum of procalcitonin patients. The results of research in patients with bacterial and viral pneumonia proinflammatory cytokines (TNFα, IL- 6) and procalcitonin predictors can be used to predict the severity of pneumonia.

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