

COMPARATIVE ANALYSIS OF INFLAMMATORY BIOMARKERS IN THE DEVELOPMENT OF THE SEVERITY OF COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN

ARDAK AKHAYEVA¹, IVAN SCOSAREV³, DANA GUPENOVA¹, TATTIGUL KENGETAEVA¹, DAN MORARU², SORINA ANAMARIA PESTRE A³, ANTONELLA CHESCA^{2,4}, SEBASTIAN IONUT TOMA⁴

¹Karaganda State Medical University, Kazakhstan, ⁴Faculty of Medicine, Transilvania University of Braşov, Romania - ²Clinical Hospital of Pneumophthisiology Brasov, Romania - ³Clinical Hospital of Psychiatry and Neurology Brasov, Romania

ABSTRACT

Objective: Conduct a comparative analysis of inflammatory biomarkers in the development of severity in community-acquired pneumonia

Material and method: In a prospective cohort study under the supervision of 110 children at the age of 5 to 14 years, of them 90 children with community-acquired pneumonia and 20 children from the control group, 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 57.27% (95% CI 34.91% - 59.88%). The diagnosis of pneumonia was verified on the basis of standards ICD -10 (10th revision of the International Statistical Classification of Diseases) for diagnosis and treatment of pneumonia in children. General clinical examination was carried out in accordance with the protocols of examination of children with this pathology approved in the Republic of Kazakhstan, with the inclusion of: a bacteriological method of investigation, studies of TNF- α , IL-6 and PCT in serum by enzyme immunoassay.

Statistical processing of the obtained results of the difference in quantitative traits marker concentrations was carried out using a nonparametric Mann-Whitney's U test

Conclusion: The results of our study indicate that as the severity of pneumonia increases, the titers of pro-inflammatory cytokines and procalcitonin in the blood serum of patients increase. The results of the study in patients with bacterial and viral pneumonia, proinflammatory cytokines (TNF- α , IL-6) and procalcitonin can be used as predictors to predict the severity of pneumonia.

Keywords: Inflammatory biomarkers, community-acquired pneumonia, children, IL-6, TNF- α , PCT.

DOI: 10.19193/0393-6384_2017_2s_189

Received December 30, 2016; Accepted June 20, 2017

Introduction

Community-acquired pneumonia in children is one of the most relevant infectious diseases, due to the high prevalence among the children's population⁽⁵⁾. In recent years, significantly increasing the number of patients with severe and complicated course of community-acquired pneumonia⁽⁶⁾.

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, but in these studies analyze

data trends cytokine profile reflected pneumonia insufficient depending on the form and severity of the disease. In this regard, the 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.

The main focus in the assessment of pneumonia is a complex approach assessment of the severity of the patient's condition for the prediction of the disease, especially in the early stages of its develop-

ment. At the present stage, many authors have studied procalcitonin as one of the markers for the differential diagnosis of bacterial and viral infection^(1,2). At the same time, the information available in the scientific literature characterizing the role of inflammatory markers in community-acquired pneumonia can not be considered exhaustive. The patterns of the distribution of markers of inflammation of the activity of the inflammatory process are not sufficiently defined depending on the degree of severity, course and outcome of community-acquired pneumonia in children. There is practically no comparative analysis of the diagnostic significance of PCT, cytokines in children with community-acquired pneumonia.

Objective

Conduct a comparative analysis of inflammatory biomarkers in the development of severity in community-acquired pneumonia.

Material and method

In a prospective cohort study, under the supervision of 110 children, 90 children with community-acquired pneumonia at the age of 5 to 14 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 control group consisted of 20 healthy children. 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 5-14 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: failure of parents of children participating in the study, previously held antimicrobial therapy, 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).

Depending on the severity of the 90 patients were divided into three groups (I,II,III). In each group of 30 children with community-acquired pneumonia. The control group consisted of 20 healthy children.

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

Interleukin 6 (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). Tumor necrosis factor (TNF- α) 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).

Statistical processing of the obtained results of the difference in quantitative traits marker concentrations was carried out using a nonparametric Mann-Whitney's U test.

Results

When carrying out a bacteriological examination, it was revealed that most often in children was sown *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* (figure 1).

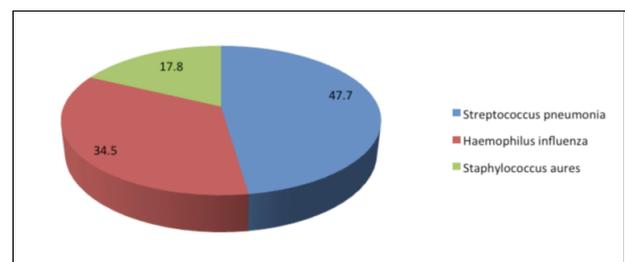


Fig. 1: Results of bacteriological study in children with community-acquired pneumonia.

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

The analysis of the obtained data of one of the main cytokines IL - 6 showed quite significant differences in its content in the blood serum, depending on the severity of community-acquired pneumonia in children (table 1).

Significant differences were obtained when the level of IL-6 was compared in the groups of

sick children, and in particular, depending on the severity of the groups in the I and III severity of community-acquired pneumonia ($p < 0,05$). At the same time, a significant level of significance of differences was obtained when comparing the data of the II and III groups of children's observation ($p < 0,05$).

Severity of pneumonia	Control group (n=20) Me (Q25Q75)	I (n=30) Me (Q25Q75)	p-level	II (n=30) Me(Q25Q75)	p-level	III (n=30) Me (Q25Q75)	p-level		
community-acquired pneumonia	0,17	1,80	$P_{C-I} < 0,05^*$	2,37	$P_{C-II} < 0,05^*$	6,16	$P_{C-III} < 0,05^*$		
	0,11	1,38		3,95		$P_{I-II} < 0,05^*$		5,14	$P_{I-III} < 0,05^*$
	0,81	2,36		3,22				6,90	$P_{II-III} < 0,05^*$

Table 1: Content of IL-6 in serum depending on the severity of community-acquired pneumonia in children (pg/ml).

Severity of pneumonia	Control group (n=20) Me (Q25Q75)	I (n=30) Me (Q25Q75)	p-level	II (n=30) Me (Q25Q75)	p-level	III (n=30) Me (Q25Q75)	p-level		
community-acquired pneumonia	0,97	1,23	$P_{C-I} > 0,05$	1,44	$P_{C-II} < 0,05^*$	5,43	$P_{C-III} < 0,05^*$		
	(0,40	(0,52		(2,20		$P_{I-II} < 0,05^*$		(3,69	$P_{I-III} < 0,05^*$
	1,25)	1,82)		1,69)				6,62)	$P_{II-III} < 0,05^*$

Table 2: Content of TNF- α in serum depending on the severity of community-acquired pneumonia in children (pg / ml).

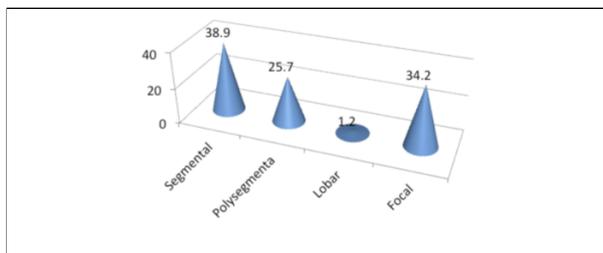


Fig. 2: Data from an X-ray examination of children with community-acquired pneumonia.

Severity of pneumonia	Control group (n=20) Me (Q25Q75)	I (n=30) Me (Q25Q75)	p-level	II (n=30) Me (Q25Q75)	p-level	III (n=30) Me (Q25Q75)	p-level
community-acquired pneumonia	0,04	0,03	$P_{C-I} > 0,05$	0,19	$P_{C-II} < 0,05^*$ $P_{I-II} < 0,05^*$	0,39	$P_{C-III} < 0,05^*$
	(0,00	(0,01		(0,42		$P_{I-III} < 0,05^*$	
	004)	0,17)		0,19)		1,54)	$P_{II-III} > 0,05$

Table 3: Content of PCT in serum depending on the severity of community-acquired pneumonia in children (ng/ml).

The analysis of serum TNF- α values in children with community-acquired pneumonia (table 2) showed the presence of significant differences when comparing children in groups, depending on the severity of community-acquired pneumonia in

children. Thus, TNF- α in children of the 1st group was 1.23 pg / ml, and in the third group this index was 4.5 and higher at 5.43 pg / ml with the children in the control group 0.97 ($p < 0, 05$). The values obtained in children of 1,2 and 3 groups of children with community-acquired pneumonia had significant differences, depending on the severity of the course of community-acquired pneumonia.

Given that most researchers studying PCT determine that it is a specific marker of infection, our analysis of the findings in children with community-acquired pneumonia, depending on the degree of severity, showed (Table 3), the presence of significant differences when comparing children in groups I and II and of the control group, respectively, the values were determined in the range of 0.03 pg / ml; 0.19 pg / ml and 0.39 pg / ml. There were no significant differences when comparing the indices of the II and III groups ($p > 0,05$).

The analysis of the X-ray study data showed the predominance of the segmental variant of prevalence in children with unilateral lesion (71.5 + 5.21).

Quite often, the examined children with community-acquired pneumonia had a focal variant of recording the pathological focus, it was most often found in the middle and lower parts of the right lung (figure 2).

Discussion

A large number of researchers in different countries have studied the role of procalcitonin as a marker of severe infection, as well as a mediator of systemic inflammation. Also procalcitonin is mentioned as a reliable prognostic factor of vesicoureteral reflux and that the level of PCT is markedly elevated in children with bacterial rather than viral meningitis, useful in order to establish a proper differential diagnostics^(2, 4). Literary data on the level of proinflammatory cytokines and procalcitonin in children with community-acquired pneumonia are rare. From this point of view, one study shows the use of biomarkers of inflammation in differentiating between acute pneumonia and bronchitis in children⁽³⁾.

In this case, the role of procalcitonin in the pathophysiology of community-acquired pneumonia and its association with other cytokines in severe bacterial infections has not been sufficiently studied to date. In most studies, each marker is studied separately, there is practically no data on the complex of markers that determine several components of the inflammatory response, and in particular the PCT; IL-6; TNF- α .

The results of our studies show that a high level of PCT, IL-6 and TNF α 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.

Comparative analysis of our study suggest that as the severity of pneumonia increases, the titres of proinflammatory cytokines and procalcitonin in the blood serum of patients increase. The results of the study in patients with community-acquired pneumonia, proinflammatory cytokines (TNF- α , IL-6) and procalcitonin can be used as predictors for the diagnosis of the severity of community-acquired pneumonia in children. The data of the complex study of markers of inflammation (TNF- α , IL-6, PCT), depending on the severity of community-acquired pneumonia in children, certainly determines the possibility of their use in diagnosis.

References

- 1) Don M, Valent F, Korppi M, Canciani M. Differentiation of bacterial and viral community-acquired pneumonia in children. *Pediatr Int.* 2009 Feb;51(1):91-6. doi: 10.1111/j.1442-200X.2008.02678.x.
- 2) Dubos F., Korczowski B., Aygun D, Martinot A, Prat C, Galetto-Lacour A, Casado-Flores J, Leclerc F, Rodrigo C, Gervaix A, Breart G, Gendrel D, Chalumeau M. Serum procalcitonin and other biologic markers to distinguish between bacterial and aseptic meningitis in children: a european multicenter case cohort study. *Arch Pediatr Adolesc Med.* 2008; 162: 1157-63.
- 3) Hoshina T., Nanishi E., Kanno S., Nishio Hi., Kusuhara K., Hara T. The utility of biomarkers in differentiating bacterial from non-bacterial lower respiratory tract infection in hospitalized children: Difference of the diagnostic performance between acute pneumonia and bronchitis. *Journal of Infection and Chemotherapy*, Volume 20, Issue 10, October 2014, pp. 616-620
- 4) Leroy S., Romanello C., Smolkin V. Galetto-Lacour A, Korczowski B, Tuerlinckx D, Rorigo C, Gajdos V, Moulin F, Pecile P, Halevy F, Gervaix A, Duhl B, Vander Borgh T, Prat C, Foix-L'Hlias L, Altman DG, Brart G, Gendrel D, Chalumeau M. Prediction of high-grade vesico-ureteral reflux after a first urinary tract infection in children: construction and internal validation of a clinical decision rule. The European society for Paediatrics infectious Disease (esPID) 28th Annual Meeting, nice (May, 2010).
- 5) Liu L., Oza S., Hogan D., Perin J., Rudan I., Lawn J.E., et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet*, 385 (2015), pp. 430-440. Moulin F., Raymond J., Lorrot M., Marc E., Coste J., Iniguez J., et al. Procalcitonin in children admitted to the hospital with community acquired pneumonia. *Arch Dis Child*, 84 (2001), pp. 332-336
- 6) Qin Q., Shen K.L.. Community-acquired Pneumonia and its Complications. *Indian J Pediatr.* 2015 Aug; 82(8): 745-51.

Corresponding author
CHESCA ANTONELLA
(Romania)