

ORIGINAL PAPER

DIAGNOSTIC VALUE OF IL-6 FOR COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN

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ABSTRACT

Introduction: Pneumonia in children of all age groups has a strong association with morbidity. This highlights the importance of studying the clinical and diagnostic aspects of community-acquired pneumonia. For those suffering from pneumonia, general biological patterns, in some cases, outstrip morphological changes in tissues and therefore biological changes can be considered as early signs of the development of the disease. Through this research, we looked at the possibility of using proinflammatory cytokines in the urine, by a non-invasive method, to assess the prognosis of community-acquired pneumonia in children.

Objective: To study the possibility of using IL-6 content in biological fluids in order to predict the severity of community-acquired pneumonia in children.

Methods: In a prospective cohort study, 110 children with community-acquired pneumonia aged between 5-10 years (who were undergoing treatment in the respiratory department of the Children's Hospital of Karaganda, Kazakhstan) were monitored. 43.64% were girls (CI 95% 31.51% -56 , 33%) and 56.36% boys (CI 95% 34.91% - 59.88%). Statistical processing of the

RÉSUMÉ

Valeur diagnostique de IL-6 pour la communauté d'enfants atteints de pneumonie

Introduction: La pneumonie chez les enfants de tous les groupes d'âges a une relation importante avec la morbidité. Cela renforce l'importance de l'étude sur les aspects cliniques et de diagnostic de la communauté atteinte de pneumonie. Pour ceux qui souffrent de symptômes biologiques généraux de pneumonie, dans certains cas, de changement morphologiques des tissus et donc les changements biologiques peuvent être considérés comme des signes avant le développement de cette maladie. Pendant cette recherche, nous avons évalué la possibilité d'utiliser des cytokines pro-inflammatoires dans l'urine, par une méthode non invasive afin d'évaluer le pronostic de la communauté enfantine atteinte de pneumonie.

Objectif: Etudier la possibilité d'utiliser IL-6 dans des fluides biologiques pour prédire la sévérité de la communauté enfantine atteinte de pneumonie.

Méthodes: Dans une étude de la cohorte prospective, 110 enfants de la communauté atteinte de pneumonie

research results was carried out with the determination of the mean value (M) and the standard error of the mean (m). A comparison of the series was carried out in cases of an abnormal distribution, by means of the nonparametric Mann-Whitney criterion. Differences were considered significant at $p < 0.05$.

Results: Elevated levels of IL-6 in serum were observed in all patient groups. In patients with grade II, the level of this marker was 2.5 times higher than in the control group ($p < 0.03$). At grade III of bacterial pneumonia, the level of IL-6 was 6.89 ± 0.53 pg/ml, 8-fold higher than in the control group ($p < 0.03$), 6-times higher compared with grade I ($p < 0.00$) and 3 times higher compared with the IInd degree ($p < 0.00$). When studying the level of IL-6 in urine, its increase is revealed as the severity of the disease worsens. In patients with grade II, the level of this marker was 3.5 times higher in comparison with the control group ($p < 0.002$) and 2 times compared with the Ist degree ($p < 0.015$). At grade III of bacterial pneumonia, the level of IL-6 was 5.21 ± 0.40 pg/ml, 5 times higher compared to the control group ($p < 0.002$), 3.5 times compared with grade I ($p < 0.002$) and 1.5 times in comparison with IInd degree ($p < 0.04$).

Conclusions: The results of our study indicate that as the severity of pneumonia increases, the titer of IL-6 in serum and urine in children with community-acquired pneumonia increases. During the study, based on the data obtained, as the severity of community-acquired pneumonia increased, titers of proinflammatory cytokines increased both in blood serum and in urine in sick children. This raises the possibility of using IL-6 as a non-invasive test for predicting the severity of community-acquired pneumonia in children.

Key words: pneumonia, children, diagnosis, IL-6.

INTRODUCTION

Pneumonia is an important acute or chronic respiratory disease. It is one of the main causes of hospitalization in the pulmonology department for children, and it can lead to the possible development of life-threatening complications and death^{1,2}. Pneumonia is one of the leading causes of death in developing countries³.

âgés de 5 à 10 ans (qui étaient soumis à un traitement dans le département respiratoire de l'hôpital des enfants de Karaganda) ont été suivis. Parmi groupe, 43.64% étaient des filles (CI 95% 31.51%-56.33%) et 56.36% des garçons (CI 95% 34.91% - 59.88%). Le procédé statistique d'obtention des résultats a été mené avec la moyenne (M) et l'erreur standard de la moyenne (m). Une comparaison entre les séries a été faite sur un cas de distribution anormale des moyennes des critères non paramétriques de Mann-Whitney. Les différences sont considérées comme importantes à $p > 0.05$.

Résultats: Des niveaux élevés de IL-6 dans le sérum ont été observés dans tous les groupes de patients. Pour les patients de II^e degré, le niveau de ce marqueur était 2.5 fois plus élevé que dans le groupe de contrôle ($p < 0.03$). À un degré III de pneumonie bactérienne, le niveau de IL-6 était de 6.89 ± 0.53 pg/ml, 8 fois plus haut que dans le groupe de contrôle ($p < 0.03$), 6 fois par rapport au groupe de I^{er} degré ($p < 0.00$) et 3 fois en comparaison avec le groupe de II^e degré ($p < 0.00$). En analysant le niveau d'IL-6 dans l'urine, son augmentation est liée à la sévérité de la maladie. Chez les patients de II^e degré, le niveau de ce marqueur est 3,5 fois supérieur par rapport au groupe de contrôle ($p < 0.002$) et 2 fois en comparaison avec ceux du I^{er} degré ($p < 0.015$). Dans les cas de pneumonie bactérienne de III^e degré, le niveau de IL-6 était 5.21 ± 0.40 pg/mL, 5 fois plus important en comparaison avec le groupe de contrôle ($p < 0.002$), 3.5 fois en comparaison avec celles de I^{er} degré ($p < 0.002$) et 1.5 fois en comparaison avec celles de II^e degré ($p < 0.04$).

Conclusions: Les résultats de notre étude indiquent que le taux de IL-6 dans le sang et l'urine augmente par rapport à la sévérité de la pneumonie chez la communauté enfantine atteinte de cette maladie. Pendant l'étude, basé sur les résultats obtenus, le taux des cytokines pré-inflammatoires augmente aussi bien dans le sang que dans l'urine par rapport à l'augmentation de la sévérité de la pneumonie chez les enfants malades. Cela augmente la possibilité d'utiliser IL-6 comme test non invasif pour prédire la sévérité de la pneumonie dans la communauté enfantine atteinte de cette maladie.

Mots-clés: pneumonie, enfants, diagnostic, IL-6.

The increase of the specific gravity in the structure of morbidity in children of all age groups determines the urgency of studying the clinical and diagnostic aspects of community-acquired pneumonia. Finding an approach to optimize the complex of measures for diagnosis of community-acquired pneumonia in childhood remains an important area.

One concern is that diagnoses are often wrong. The high level of diagnostic errors in community-

acquired pneumonia is due to the often poor clinical and radiological picture of the disease. This dictates the need to search for new effective and affordable methods for early diagnosis, as well as to evaluate the effectiveness of starting antibacterial therapy for this disease. In accordance with general biological patterns, in some cases, these outstrip the morphological changes in tissues and therefore can be considered as early signs of the development of the disease and can provide reliable criteria for the resolution of the pathological process⁴. In accordance with this, the identification of markers for early diagnosis in children with community-acquired pneumonia, is of great importance. Interleukin 6 (IL-6) provides a potential measure.

However, the diagnostic role of the pro-inflammatory cytokine IL-6 in assessing the dynamics of the inflammatory process in community-acquired pneumonia remains insufficiently investigated. The definition of cytokines is associated with blood collection, which in itself is an invasive method, and therefore the study of the possibility of using proinflammatory cytokines in the urine by a non-invasive method is an alternative diagnosis method of great practical importance for assessing the prognosis of community-acquired pneumonia in children. Of the cytokines and chemokines that can be measured in the bloodstream for acute inflammation, IL-6 can be the most valuable as a prognostic indicator.

METHODS

In a prospective cohort study, 110 children with community-acquired pneumonia, aged 5 to 10 years, who were treated in the respiratory department of the Children's Hospital of Karaganda, Kazakhstan, were monitored, of which 43.64% were girls (95% 31.51% – 56.33%) and 56.36% boys (CI

95% 34.91%– 59.88%). Patients and healthy children were included in the study on the basis of informed consent. The criteria for inclusion in the group of study were:

- 1) A group of bacterial pneumonia was formed by patients with bacteriological confirmation of *Streptococcus pneumoniae* as an etiological agent.
- 2) Children between 5-10 years old.
- 3) Voluntary participation of parents of children with signed informed consent.
- 4) Elimination of the risk of harm (physical, psychological, social and economic).

The exclusion criteria were:

- 1) Refusal of parents of children to participate in the study.
- 2) Previously antimicrobial therapy.
- 3) The presence of concomitant pathology: another chronic inflammatory disease, congenital heart disease, active tuberculosis, the presence of cancer, neurological and endocrine pathology.

The diagnosis of pneumonia was verified on the basis of standards for the diagnosis and treatment of pneumonia in children (ICD 10, J 15.8). Depending on the degree of severity, 24 patients were divided into three subgroups (I, II, III). Criteria for the degree of severity of the pneumonic process were developed by V.G. Maidannik⁵. The control group consisted of 25 healthy children.

IL-6 was determined by ELISA, using a set of reagents for the enzyme-linked immunosorbent assay of interleukin-6 in serum and urine (Interleukin 6-IFA-BEST) (0-250 pg/mL). Statistical processing of the obtained research results was carried out with the determination of the mean value (M) and the standard error of the mean (m). A comparison of the series was carried out in cases of an abnormal distribution by means of the nonparametric Mann-Whitney criterion. Differences were considered significant at $p < 0.05$.

Table 1. IL-6 serum content, depending on the severity of community-acquired pneumonia in children.

Severity of pneumonia	I (n=8)	Level significance	II (n=8)	Level significance	III (n=8)	Level significance	K (n=25)
Bacterial pneumococcal pneumonia	1.96±0.76	$p_{K-I} > 0.05$	2.17±0.28	$p_{K-II} < 0.003^*$ $p_{I-II} > 0.05$	6.89±0.53	$p_{K-III} < 0.03^*$ $p_{I-III} < 0.00^*$ $p_{II-III} < 0.00^*$	0.84±0.27

Note: p_i is the significance level, where i is the comparison group

* – differences in the compared groups ($p < 0.05$)

Table 2. IL-6 content in urine, depending on the severity of community-acquired pneumonia in children

Severity of pneumonia	I (n=8)	Level significance	II (n=8)	Level significance	III (n=8)	Level significance	K (n=25)
Bacterial pneumococcal pneumonia	1.47±0.47	$p_{K-I} > 0.05$	3.64±0.61	$p_{K-II} < 0.002^*$ $p_{I-II} < 0.015^*$	5.21±0.40	$p_{K-III} < 0.002^*$ $p_{I-III} < 0.004^*$ $p_{II-III} < 0.04^*$	0.96±0.17

RESULTS

An analysis of the results of the evaluation of the quantitative characteristics of IL-6 is presented in Tables 1 and 2.

As it can be seen from Table 2, elevated levels of IL-6 in serum were observed in all patient groups. In patients with community-acquired pneumonia of the 1st degree, the level of TNF α in comparison with the control group tends to increase, but no significant differences were observed. In patients with grade II, the level of this marker was 2.5 times higher than in the control group ($p < 0.03$). At grade III of bacterial pneumonia, the level of IL-6 was 6.89 ± 0.53 pg/mL, 8 times higher than in the control group ($p < 0.03$), 6 times compared with grade I ($p < 0.00$) and 3 times compared with the IInd degree ($p < 0.00$).

When studying the level of IL-6 in urine, its increase was revealed as the severity of the disease worsened (Table 2). In patients with bacterial pneumonia of the 1st degree, the level of IL-6 exceeded the value of this cytokine in the control group. In patients with grade II, the level of this marker was 3.5 times higher in comparison with the control group ($p < 0.002$) and 2 times compared with the 1st degree ($p < 0.015$). At grade III of bacterial pneumonia, the level of IL-6 was 5.21 ± 0.40 pg/mL, 5 times higher compared to the control group ($p < 0.002$), 3.5 times compared with grade I ($p < 0.002$) and 1.5 times in comparison with IInd degree ($p < 0.04$).

DISCUSSION

Data on the level of proinflammatory cytokines in children with community-acquired pneumonia are scarce and contradictory. A number of studies indicate that the increase in the level of cytokines occurs before the clinical manifestations of the inflammatory process, as well as before the change in laboratory parameters^{4,6,7}. Interleukin-6 is a multifunctional cytokine with well-defined pro- and anti-inflammatory properties^{8,9}. Some studies conducted by P. Toikka et al showed that the measurement of serum PCT and IL-6 also has little significance in differentiating bacterial and viral pneumonia in children¹⁰. However, in patients with high levels of PCT and IL-6, bacterial pneumonia is more likely^{10,11}.

The literature data on the level of proinflammatory cytokines in urine in children with community-acquired pneumonia are scarce and the studies were mainly conducted for the pathology of the urinary tract¹². Hence the need for the present study.

The results of our study indicate that as the severity of pneumonia increases, the titer of IL-6 in serum and urine in children with community-acquired pneumonia increases. The results of our study in patients with bacterial pneumonia highlight that proinflammatory cytokines can be used as predictors for the severity of pneumonia. In the course of the study, based on the findings, as the severity of community-acquired pneumonia increases, titers of pro-inflammatory cytokines in both serum and urine of sick children increase. Therefore, the possibility of using IL-6 as a non-invasive test for prognostic assessment of the severity of community-acquired pneumonia in children is justified.

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