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PREDICTIVE SIGNIFICANCE OF NITROGEN OXIDE IN COMMUNITY-ACQUIRED PNEUMONIA ASSOCIATED WITH TORH INFECTION IN CHILDREN

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Abstract
The aim of the study was to assess the prognostic significance of nitric oxide indicators in community-acquired pneumonia associated with mycoplasma, herpesvirus and chlamydial infections in children. The results of the study showed that community-acquired pneumonia associated with mixed infection occurs in 15.9% of the total number of children with bronchopulmonary pathology and develops against the background of unfavorable perinatal and intrapartum periods. The study of the oxide system showed that in children with community-acquired pneumonia in combination with mixed infection, there is an increase in the level of end products of nitric oxide metabolism and are characterized by changes in nitric oxide and its metabolites, increased oxidative stress, leading to the formation of peroxynitrates and to the separation of oxidative phosphorylation processes and concomitant a cycle of changes in the form of inflammation.
Keywords: community-acquired pneumonia, TORSH infection, nitric oxide, prognosis, children.

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该研究的目的是评估一氧化氮指标在与儿童支原体、疱疹病毒和衣原体感染相关的社区获得性肺炎中的预后意义。研究结果显示，社区获得性肺炎合并混合感染占支气管肺病理学患儿总数的15.9%，是在不利的围产期和产时的背景下发生的。氧化系统研究表明，社区获得性肺炎合并混合感染患儿，一氧化氮代谢终产物水平升高，特点是一氧化氮及其代谢产物发生变化，氧化应激增加。，导致过氧硝酸盐的形成和氧化磷酸化过程的分离，并伴随着炎症形式的变化循环。

关键词：社区获得性肺炎，TORSH 感染，一氧化氮，预后，儿童。

Introduction

Community-acquired pneumonia in children is an urgent problem in modern pediatrics. Despite the constant improvement of diagnostic methods, the availability of a wide range of highly effective antibacterial drugs and their active use, community-acquired pneumonia still occupies a leading place in the structure of morbidity and mortality from infectious diseases, including in socially developed countries [1, 2, 3, 4]. The variety of etiological agents, as well as the ways and factors of transmission of pathogens, determine their widespread prevalence among the population of the whole world. Of greatest interest is the identification of the role of intracellular infections capable of long-term persistence in the bronchial mucosa, which are the target organ in bronchopulmonary pathology, and, therefore, to long-term and constant maintenance and intensification of the inflammatory process of the bronchi. These include, first of all, mycoplasma, chlamydial and cytomegalovirus infections [5, 6, 7]. To date, significant progress has been made in the diagnosis, treatment and prevention of community-acquired pneumonia in children. But research continues, aimed at clarifying individual links of pathogenesis, improving programs for its diagnosis and therapy. The study of new aspects in the pathogenesis of infectious diseases, in particular, the study of mediators of intercellular interaction, which include nitric oxide and its metabolites, is of particular interest, especially in pediatrics.

Purpose of the study. To assess the prognostic significance of nitric oxide indicators in community-acquired pneumonia associated with mycoplasma, herpes-viral and chlamydial infections in children.

Materials And Methods

The study was conducted in 281 children with community-acquired pneumonia, aged 1 to 7 years, who were inpatient treatment in the department of pulmonology for the period 2015-2020. After determining the type of pathogen, all children were divided into 3 groups: Group I - patients with community-acquired pneumonia associated with mycoplasma and herpesvirus infection; Group II - patients with community-acquired pneumonia associated with mycoplasma and chlamydial infection; Group III - patients with community-acquired pneumonia associated with mycoplasma, chlamydial and herpesvirus infection. Of these, 115 (40.9%) patients with community-acquired pneumonia associated with mycoplasma and herpesvirus infection, 97 (34.5%) children with community-acquired pneumonia associated with mycoplasma and chlamydial infection, 69 (24.6%) children with community-acquired pneumonia associated with mycoplasma, chlamydial and herpesvirus infection. As a comparison group, 45 children with community-

acquired pneumonia were examined. The control group consisted of 24 apparently healthy children of the same age. The clinical examination included examination, anthropometry, examination of narrow specialists, laboratory and instrumental studies. Biochemical study: determination of the level of NO by the sum of metabolites of nitrates and nitrites (NO2 and NO3) according to the method described by P.P. Golikov et al. (2000). The absorption was measured at a wavelength of 546 nm on an SF-46 spectrophotometer (Russia). Sodium nitrite (NaNO2) was used as a standard.

Results

All observed patients were carefully analyzed anamnestic data. The analysis showed that patients with community-acquired pneumonia with mycoplasma and herpesvirus infection compared with community-acquired pneumonia 2.0 and 2.5 times more often were admitted to the hospital at the age of 1 to 3 years and from 3 to 7 years on the 15th or more day. from the onset of the disease. This can be explained by the serious condition of the child due to mixed infection.

In the group of children with mixed infection during pregnancy, 31 (63.2%) mothers had acute respiratory infections and had a high degree of reliability (P <0.001) compared with community-acquired pneumonia. The number of mothers who received antibiotic therapy during pregnancy and after childbirth in the group of children with mixed infection was 26 (56%), this figure is 5.2 times higher than in children with community-acquired pneumonia.

Of the past diseases, acute respiratory diseases were noted - in children with mixed infection in 97.1% of cases and in 80.4% with community-acquired pneumonia with mycoplasma and chlamydial infection, in 63.5% of cases in the group of children with community-acquired pneumonia with mycoplasma and herpesvirus infections; pneumonia - in 92.7%, in 81.4% and in 51.3%, frequent acute bronchitis - 76.8%, 60.8% and 48.7%, respectively (P <0.001). Subsequently, these children began to get sick often, they had a prolonged cough (more than 2 weeks) with sputum separation.

The clinical picture was characterized by a complex of clinical manifestations against the background, a high degree of intoxication, fever, dry paroxysmal cough, skin rashes, lymphadenopathy, hepatomegaly, aggravated by premorbid background and concomitant diseases, the most significant changes prevail in the groups of patients with community-acquired pneumonia associated with mycoplasma associated infection.

In factor analysis, in the group with mixed infection, frequent acute respiratory diseases were significantly more frequent in 67 (97.1%) (RR = 11.43, OR = 50.25), pneumonia in 64 (92.7%) (RR = 5 , 21, OR = 21.1), acute obstructive bronchitis in 58 (84.0%), (RR = 2.8, OR = 9.6), recurrent bronchitis in 53 (76.8%) (RR = 2.32, OR = 7.33), conjunctivitis in 52 (75.4%) (RR = 2.30, OR = 7.52), hepatitis in 45 (65.2%) (RR = 2.23 , OR = 10.18), otitis media in 55 (79.7%) (RR = 3.07, OR = 15.71).

In recent years, the role of nitrosive stress in the pathogenesis of the respiratory system has been actively discussed, which manifests itself in impaired nitric oxide (NO) metabolism [8, 9, 10, 11]. Expression of inducible NO - synthase contributes to profound disturbances of microcirculation, maintenance of inflammation and chronicity of the course of the disease.

The study of the oxide system showed that in children with community-acquired pneumonia in combination with mixed infection, there is an increase in the level of end products of nitric oxide metabolism (Table 1). Their severity

depended on the type of pathogens. Thus, in children with community-acquired pneumonia, the level of end-products of nitric oxide significantly increased by 1.2 times relative to the values of practically healthy children. The combination of community-acquired pneumonia with viral infections further increased the content of these metabolites in the blood serum: in patients with community-acquired pneumonia with mycoplasma and herpesvirus infection, there was a significant increase in the content of NO2 (NO3) to 12.9 ± 0.4 μmol / L compared to community-acquired pneumonia without mixed - infections (P <0.05) and this indicator increased by 1.3 times in comparison with practically healthy children.

In patients with community-acquired pneumonia associated with mycoplasma and chlamydial infection, there was a significant increase in the content of NO2 (NO3) up to 13.8 ± 0.5 μmol / L compared with community-acquired infection without mixed infections (P <0.01) and this indicator increased 1.4 times compared to practically healthy children. In relation to community-acquired pneumonia with mycoplasma and herpesvirus infection, the indicator increased 1.1 times. In patients with community-acquired pneumonia with mycoplasma, chlamydial and herpesvirus infection, there was a more significant increase in the content of NO2 (NO3) to 16.1 ± 0.5 μmol / L compared with community-acquired pneumonia without mixed infections (P <0.001) and this indicator increased in 1.7 times compared to practically healthy children, in relation to community-acquired pneumonia with mycoplasma and herpesvirus infection, the indicator increased 1.2 times, in relation to community-acquired pneumonia with mycoplasma and chlamydial infection it increased 1.2 times, i.e. chlamydial infection, especially in combination with herpesvirus infection, significantly increased the production of nitric oxide.

Table 1. Indicators of the nitric oxide system in patients with community-acquired pneumonia associated with mixed infection, (M ± m)

Study groups	Products content		Enzyme activity	
	$NO_2(NO_3)$, μmol / l	$ONOO^-$, μmol / l	eNOS, μmol / min mg protein	HP, μmol / min mg protein
Community-acquired pneumonia with mycoplasma and herpesvirus infection, n = 85 (I)	12,9±0,4	0,13±0,009	12,4±0,4	0,27±0,01
P_{1-4}	<0,01	<0,01	<0,01	<0,01
P_{1-5}	<0,05	<0,05	<0,05	<0,05
Community-acquired pneumonia with mycoplasma and herpes-viral infection, n = 67 (II)	13,8±0,5	0,15±0,008	11,2±0,4	0,29±0,009
P_{2-4}	<0,001	<0,001	<0,001	<0,001
P_{2-5}	<0,01	<0,01	<0,01	<0,01

Community-acquired pneumonia with mixed infection, n = 49 (III)	16,1±0,5	0,23±0,02	9,3±0,5	0,43±0,02
P_{3-4}	<0,001	<0,001	<0,001	<0,001
P_{3-5}	<0,001	<0,001	<0,001	<0,001
Pr. healthy children, n = 24 (IV)	9,67±0,4	0,08±0,003	16,88±0,9	0,22±0,005
Community-acquired pneumonia, n = 45 (V)	11,4±0,6	0,10±0,008	14,5±0,6	0,24±0,007
P_{5-4}	<0,05	<0,05	<0,05	<0,05

Note: P1-4 - reliability of differences between indicators of 1 and 4 groups of patients; P1-5 - reliability of differences between indicators of 1 and 5 groups of patients; P2-4 - reliability of differences between indicators of 2 and 4 groups of patients; P2-5 - reliability of differences between indicators of 2 and 5 groups of patients; P3-4 - reliability of differences between indicators of 3 and 4 groups of patients; P3-5 - reliability of differences between indicators of 3 and 5 groups of patients. P5-4 - reliability of differences between indicators of 5 and 4 groups of patients;

It should be said, despite the observed increased production of NO., There was an inhibition of eNOS in 1.2; 1.4; 1.5 and 1.8 times in blood serum in children of all groups, respectively, compared to practically healthy children. Moreover, to a greater extent this was observed with mixed infection in patients with community-acquired pneumonia with mycoplasma and chlamydial infection, where there was a significant decrease in eNOS to 11.2 ± 0.4 μmol / min * mg protein compared to community-acquired pneumonia without mixed infections (P <0.01). In patients with community-acquired pneumonia with mixed infection, there was a more significant decrease in eNOS to 9.3 ± 0.5 μmol / min * mg protein compared to community-acquired pneumonia without mixed infection (P <0.001).

The activity of HP in the blood of patients with community-acquired pneumonia increased 1.1 times, in patients with community-acquired pneumonia with mycoplasma and herpesvirus infection - 1.2 times, in patients with community-acquired pneumonia with mycoplasma and chlamydial infection - 1.3 times compared with practically healthy children. Especially in patients (by a factor of 2.0, P <0.001), a more significant increase in NR in the blood was observed in patients with mixed infection up to 0.43 ± 0.02 μmol / min * mg of protein, i.e. 1.8 (P <0.001) times higher than the values of children with community-acquired pneumonia without mixed infections. If there is a violation in the enzymatic generation of NO., Then disorders arise, which are primarily due to the ability of all NOS isoforms to produce superoxide radical along with nitric oxide. The subsequent reaction of these producers leads to the formation of a toxic agent due to the high oxidative activity - ONOO-. When nitric oxide and superoxide are generated by the same system, the probability of such an interaction increases, so that these enzymes can make a significant contribution to the formation of ONOO- in cells and tissues, often causing cell death.

To clarify this, we determined the content of ONOO-in the blood of sick children with community-acquired pneumonia associated with mixed infection. Studies carried out in this regard

have shown an increase in its content by 1.3 times in the group of children with community-acquired pneumonia, 1.6 times in patients with community-acquired pneumonia with mycoplasma and herpesvirus infection. We observed an even greater increase in children with a combination of community-acquired pneumonia with mycoplasma and chlamydial infections, its level significantly increased by 1.9 times. We noted a sharp surge of this compound in patients with community-acquired pneumonia with mixed symptoms, while there was an increase in ONOO- in the blood to 0.23 ± 0.002 μmol / L, i.e. 2.3 ($P < 0.001$) times higher than the values of children with community-acquired pneumonia without mixed infections, and this indicator increased 2.9 times compared with practically healthy children.

As can be seen from the data presented, a more pronounced production of nitric oxide is characteristic of patients with community-acquired pneumonia with mycoplasma and chlamydial infection and community-acquired pneumonia with mixed infection, which is most likely due to the toxic effect of viruses, since they affect blood cells, epithelial cells, and move freely on the vascular endothelium, causing hemorrhages in various tissues, especially in combination with mixed infection. Thus, on the basis of the data obtained, we can say that children with community-acquired pneumonia associated with mixed infection have overproduction of nitric oxide associated with the activation of the inducible form of nitric oxide synthesis. This is more pronounced in patients of groups II and III.

Conclusion

Community-acquired pneumonia associated with mixed infection occurs in 15.9% of the total number of children with bronchopulmonary pathology and develops against the background of unfavorable peri - and intrapartum periods. Investigation of the pathogenetic mechanisms of the development of community-acquired pneumonia associated with mycoplasma, herpesviral and chlamydial infections makes it possible to develop informative prognosis criteria for effective treatment of these diseases. The results are characterized by changes in nitric oxide and its metabolites, increased oxidative stress leading to the formation of peroxynitrates and uncoupling of oxidative phosphorylation processes and a concomitant cycle of changes in the form of inflammation. Both the inflammatory response and oxidative stress will have a destructive effect both on the detoxification system, in particular, on the digestive system, and on all the main systems of the body, which, possibly, will make it possible to formulate criteria for the severity of the disease and the prognosis of its course, to optimize therapy by enhancing antioxidant impact.

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