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CLINICAL, IMMUNOLOGICAL, AND MICROBIOLOGICAL CHARACTERISTICS OF PROLONGED COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN AFTER COVID-19

Safura Nosirjonovna Zaynabitdinova
Andijan State Medical Institute,
Andijan, Uzbekistan

Furkat Mukhitdinovich Shamsiev
Republican Specialized Scientific and Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan,
Tashkent, Uzbekistan

Nilufar Irgasheva Karimova
Republican Specialized Scientific and Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan,
Tashkent, Uzbekistan

ABSTRACT
The aim of the study was to investigate the clinical, immunological, and microbiological characteristics of prolonged community-acquired pneumonia in children following COVID-19. The cytokine analysis results revealed elevated levels of IL-1β, IL-4, IL-8, and TNFα in children with prolonged community-acquired pneumonia after COVID-19. Bacteriological analysis of sputum samples showed the presence of Staphylococcus aureus in 32.1% of cases, Haemophilus influenzae in 21.4%, Mycoplasma pneumoniae in 14.3%, and Streptococcus pneumoniae in 14.3%. Staphylococcus aureus occupies a significant place in the etiological structure of prolonged community-acquired pneumonia in children and is difficult to treat with first-line antibiotics due to its high resistance, which is one of the main reasons for the prolonged course of community-acquired pneumonia following COVID-19.

KEYWORDS: community-acquired pneumonia, clinic, immunology, COVID-19, children

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most pressing issues in modern medicine due to its consistently high and growing incidence rates. According to the World Health Organization (WHO), in recent years, lower respiratory tract infections have become the third leading cause of death on Earth. Additionally, there has been an increase in the number of patients with a prolonged course of the disease (up to 40%) [1,5]. Prolongedcommunity-acquired pneumonia (PCAP)holds a significant position in contemporary internal medicine as there has been a notable tendency towards slow resolution of the inflammatory process in the lungs [10].

Despite treatment standardization, the regression rates of the inflammatory process in the lungs often do not meet expected results. The slow regression of the inflammatory process is referred to as "prolonged course" of pneumonia [2,3,6]. Globalization has led to the emergence and spread of new infectious diseases that do not respond to traditional treatments. A significant role in the development of a PCAP is played by previously contracted COVID-19 and the subsequent post-COVID conditions [8,11].

According to current understanding, COVID-19 represents a potentially severe acute respiratory infection caused by the SARS-CoV-2 coronavirus and manifests as a polymorphic clinical course in both children and adults. Therefore, it was important for us to establish the role of pro- and anti-inflammatory cytokines and respiratory tract microflora in the formation of PCAP in children after COVID-19. Insufficiency of cellular and humoral immune mechanisms and the cytokine imbalance in patients with a PCAP determine

the severity of the disease [4,7].

In recent years, studies on C-reactive protein (CRP) in blood serum have been conducted. Specifically, CRP levels are highest in patients with severe pneumococcal and legionella pneumonia, which has been proven to be an independent factor ineffective in antibiotic treatment [8]. Targeted therapy is conducted when microbiological diagnostic data indicate the key role of a specific microorganism in pneumonia development [14].

The research objective of this study is to meticulously examine and analyze the clinical, immunological, and microbiological characteristics associated with the extended duration of community-acquired pneumonia in children who have previously recuperated from COVID-19.

MATERIALS AND METHODS

Research involved the inclusion of 26 children with PCAPafter COVID-19, ranging in age from 1 year to 15 years (Group I), who were admitted for inpatient treatment at the Pulmonology Department of the Republican Scientific Center for Pediatric Medicine of the Ministry of Health of the Republic of Uzbekistan. A comparison group consisted of 30 children with community-acquired pneumonia (Group II) within the same age range. The diagnosis was established based on the classification of major clinical forms of bronchopulmonary diseases in children, approved at the special meeting of the 18th National Congress on Respiratory Diseases (2010). Prolonged duration of community-acquired pneumonia was diagnosed when there was a lack of reverse dynamics in the disease process within a period of 1.5 to 6 months. All children in Group I tested positive for IgG antibodies to COVID-19. The comprehensive clinical, biochemical, and immunological examination of the children involved the utilization of clinical, biochemical, and immunological research methods. The biochemical analysis included the determination of C-reactive protein (CRP) concentration in the blood serum. Immunological analysis involved the determination of cytokine concentrations - IL-1β, IL-4, IL-6, IL-8, TNF-α, and IFNγ were assessed using an enzyme-linked immunosorbent assay (ELISA) method with the use of Vector-Best test systems (Russia). Microbiological examination of sputum was conducted in accordance with modern clinical microbiology standards, where sputum samples were collected in the morning on an empty stomach and evaluated using the Gram stain bacterial smear method.

RESULTS AND DISCUSSION

The research findings revealed several unfavorable factors in the medical history of children with prolonged community-acquired pneumonia (PCAP) after COVID-19. Among the observed children, 46.2% (13) had documented complications during pregnancy and childbirth, including toxemia in the first and second trimesters in 42.8% (12) of cases, and threats of miscarriage in 85.7% (24) of cases, which was significantly higher compared to the children in the community-acquired pneumonia group (40.0%, 36.6%, and 76.6%, respectively). In the PCAP group, 53.6% (15) of the mothers had a history of abnormal delivery, while in the comparison group, this percentage was 40.0% (12). Additionally, 17.8% (5) of children in the PCAP group were born with asphyxia, and 10.7% (3) exhibited signs of prematurity. The main clinical manifestation of PCAP after COVID-19 was cough, predominantly productive in 89.2% (25) of the patients, cyanosis was observed in 75.0% (21) of patients, and shortness of breath was present in 92.8% (26) of patients. Wet rales were detected in 100% of the cases, while dry rales were present in 64.3% (18) of the patients (Figure 1).

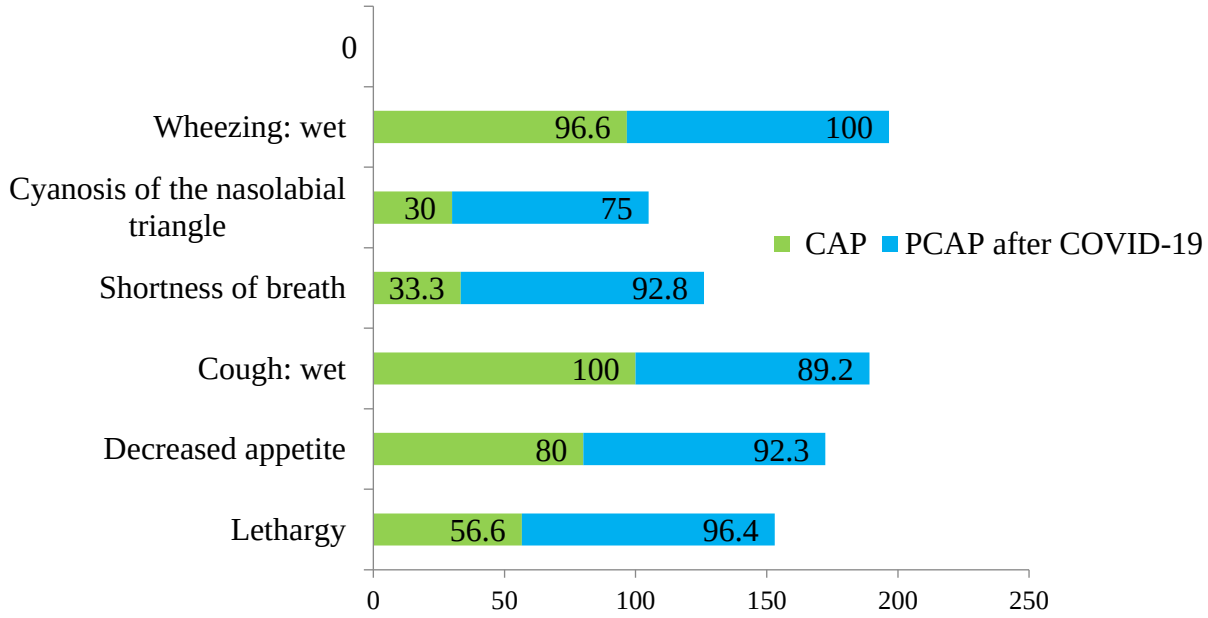

Figure 1. Frequency of clinical symptoms in the examined children, (%)

During the prospective study involving 28 patients with PCAP after COVID-19, the serum concentration of CRP was found to be elevated. The conducted research revealed that the CRP levels in the serum of PCAP patients during the initial phase of the disease were significantly higher, reaching 30.2±2.1 mg/L, which was 6.7 times higher compared to the control group. In children with PCAP, the CRP levels were even more elevated, measuring 54.7±4.5 mg/L, which was 12.2 times higher than in the control group.

Further investigations during the admission period showed that the concentration of CRP in the serum of children with PCAP after COVID-19 was 1.8 times higher compared to the PCAP comparison group. When assessing the effectiveness of antibiotic therapy in both groups of patients, the dynamics of changes in CRP concentration should be taken into account (Figure 2). The dynamic analysis of CRP concentration in the serum of children with prolonged PCAP indicated a non-significant decrease by 1.1 times on the 10th day in the PCAP group, compared to the pre-treatment levels (P>0.05).

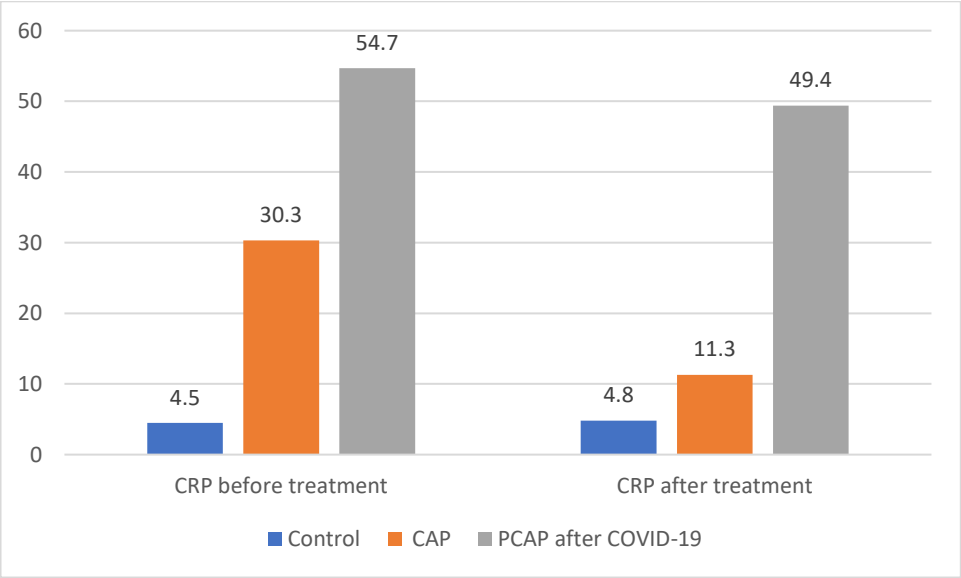

Figure 2. Dynamics of CRP indicators in children of the studied groups, (M ±m)

Moreover, a high level of CRP in the serum, which persisted during the 10-day course of the disease in children of the PCAP group, emerged as a predictor of ineffective antibiotic therapy among the examined patient groups.

The results of cytokine research presented in Figure 3 demonstrated elevated levels of IL-1β, IL-4, IL-8, and TNF-α in children with PCAP after COVID-19, which remained higher compared to children with PCAP. The production of IFN-γ in PCAP reached 19.5±1.7, whereas in the control group, it was 24.2±1.4 (P>0.05). In cases of PCAP, the level of IL-1β increased by 3.5 times compared to the control group, averaging at 103.2±6.7 pg/mL (P<0.01).

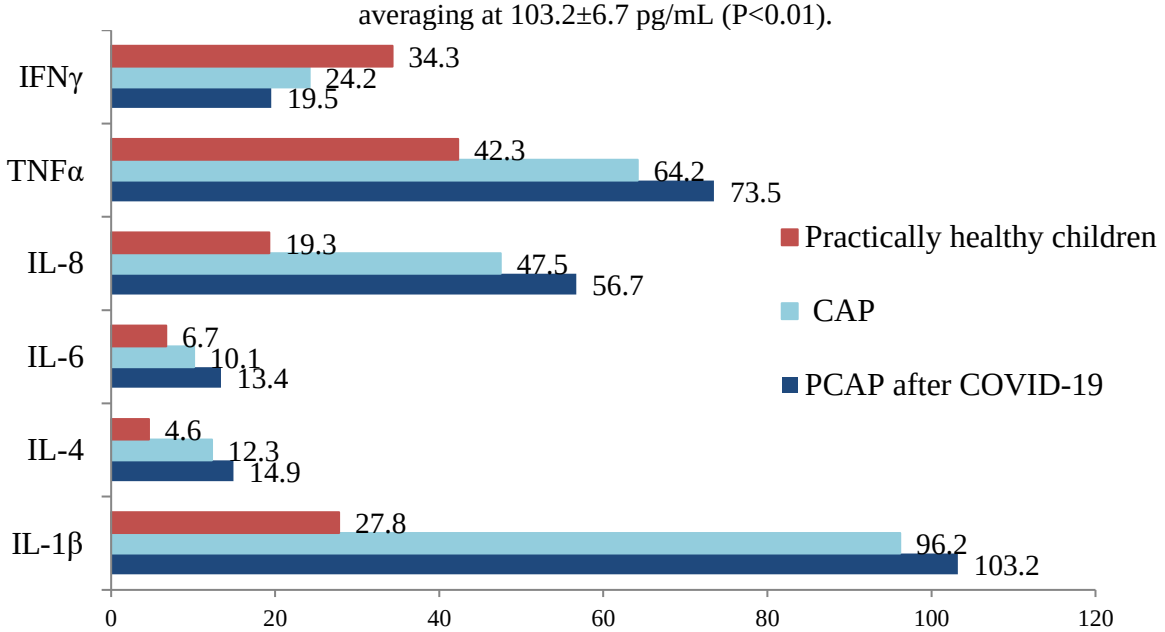

Figure 3. Cytokine indices in children with CAP and PCAP after COVID-19, (M±m)

It is noteworthy that the level of IL-6, one of the most informative markers of inflammation, in children with PCAP reached 13.4±0.3 pg/mL, which was 2 times higher than in the control group (P<0.05). The level of IL-4 in children with PCAP was 2.2 times higher than in the control group. In cases of PCAP, the level of IL-4 increased by 3.2 times to 14.9±0.9 pg/mL (P<0.01) compared to the control group. IL-8 plays an important role as an inflammatory mediator in the lungs. In PCAP, the average level of IL-8 was 47.5±4.3 pg/mL, which was 2.5 times higher, and in the PCAP group, it was 2.9 times higher than the levels in the control group (P<0.01). Analysis of TNF-α levels in PCAP patients showed an increase to 64.2±3.2 pg/mL compared to the control group (P<0.01) and a 1.5-fold increase (42.3±2.1 pg/mL, P<0.05). In children with PCAP, this indicator reached 73.5±6.1 pg/mL, which was 1.7 times higher than in the control group. Our research on the level of IFN-γ in PCAP patients revealed a significant deficiency. In children with PCAP, the serum level of IFN-γ was on average 24.6±1.4, which was 1.3 times lower than in the control group (34.3±2.7 pg/mL) (P<0.01).

Bacteriological examination of sputum was performed on the examined patients, and the comparative analysis data are presented in Table 1. The results showed that in more than half of the cases, bacteria of the Streptococcus genus, predominantly Streptococcus mitis, were detected in sputum cultures. No statistically significant differences were observed in the frequency of detection of different microorganisms between the groups.

Table 1.
Results of bacteriological examination of sputum of patients with CAP of the studied groups, %

Groups of patients / Type of microorganism	PCAP (n=26)	CAP (n=30)	P

	abs.	%	abs.	%	
Streptococcus pneumoniae	4	14,3	3	10,0	>0,01
Streptococcus mitis	1	3,6	11	36,6	>0,01
Streptococcus salivarius	1	3,6	4	13,3	>0,01
Streptococcus parauberius	1	3,6	5	16,6	>0,01
Staphylococcus aureus	9	32,1	2	6,6	>0,001
Haemophilus influenzae	6	21,4	1	3,3	>0,001
Micoplasma pneumoniae	4	14,3	1	3,3	>0,01
Neisseria subqlava	0	0	3	10,0	>0,01
Micoplasma pneumoniae	4	14,3	1	3,3	>0,01
Neisseriasubqlava	0	0	3	10,0	>0,01

Note: n - the number of observations; P - the significance of differences between groups.

The analysis of the bacteriological examination of sputum in children with PCAP revealed that in 32.1% of cases, Staphylococcus aureus was detected, followed by Haemophilus influenzae in 21.4%, Mycoplasma pneumoniae in 14.3%, and Streptococcus pneumoniae in 14.3%. In the comparison group, the predominant growth was observed for Streptococcus mitis (36.6%), followed by Streptococcus salivarius (13.3%), Streptococcus parauberius (16.6%), and Streptococcus pneumoniae (10.0%). The prolonged course of PCAP is associated with the growth of Staphylococcus aureus, Haemophilus influenzae, Mycoplasma pneumoniae, and Streptococcus pneumoniae, which should be taken into account when prescribing antibiotic therapy for pneumonia. Assessing the etiological significance of the detected infectious agents such as S. mitis, S. salivarius, S. parauberius, and N. subqlava is challenging, as they are not typically associated with inflammation in lung tissue. The presence of these microorganisms in sputum may indicate contamination of bronchial secretions with oropharyngeal flora.

Thus, the data indicate that Staphylococcus aureus predominates among the major pathogens of PCAP. There is ample evidence of the significance of Staphylococcus aureus in the development of severe and antibiotic-resistant CAP in children, which are often difficult to treat with first-line antibiotics due to the high resistance of most strains. Therefore, we believe that a revision of existing treatment protocols is necessary for more effective management of PCAP.

CONCLUSIONS

1. Consequently, PCAP (viral pneumonia of unclear etiology) in children after recovering from COVID-19 predominantly developed in an unfavorable pre-existing condition. Complications during pregnancy and childbirth were observed in 46.2% of the mothers of the observed children. The disease was accompanied by fever, shortness of breath, cyanosis, and symptoms of intoxication such as weakness and loss of appetite. Additionally, the intensity of the temperature response was more pronounced.
2. The evaluation of the inflammation biomarker CRP (C-reactive protein) serves as an informative indicator in diagnosing PCAP in children after recovering from COVID-19. Its elevation confirms the bacterial nature of the pathological process and can be utilized in selecting appropriate differentiated therapy.
3. PCAP in children after recovering from COVID-19 was characterized by an imbalance in the cytokine status, manifested by elevated levels of IL-1β, IL-4, IL-6, IL-8, TNFα, and decreased levels of IFNγ, depending on the progression of the inflammatory process. This contributes to a delayed recovery and serves as an additional prognostic criterion in the diagnosis and treatment of PCAP following COVID-19.
4. Microbiological investigations have demonstrated that Staphylococcus aureus plays a significant role in the etiological structure of PCAP in children. Its resistance to first-line antibacterial agents poses a major challenge in treatment, which is one of the primary reasons for the PCAP after recovering from COVID-19.

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CURRENT POSITIONS OF AUTHORS:

1. Zaynabitdinova Safura Nosirjonovna
Assistant of the Department of "Hospital Pediatrics" of Andijan State Medical Institute, Tashkent, Uzbekistan
(ORCID ID: 0000-0003-2506-2649)
2. Shamsiev Furkat Mukhitdinovich
MD, Professor, Head of the Department of Pulmonology of the Republican Specialized Scientific and Practical Medical Center of Pediatrics, Uzbekistan, Tashkent
3. Karimova Nilufar Irgashevna
PhD, doctoral student of the Department of Pulmonology of the Republican Specialized Scientific and Practical Medical Center of Pediatrics, Uzbekistan, Tashkent
(ORCID ID: 0000-0002-3687-4995)

Corresponding author, E-mail:
Zaynabitdinova Safura Nosirjonovna