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Determination of alpha-defensin levels in dynamics in newborns with sepsis

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Aim – to investigate some pathogenetic mechanisms of immune system changes during sepsis in premature and full-term infants by determining the levels of alpha-defensin.

Materials and methods. A total of 130 newborns were examined. Of these, 100 were infants undergoing inpatient treatment with a diagnosis of sepsis (early and late), and 30 were healthy newborns. The children participating in the study were divided into the following groups: Group I – full-term newborns diagnosed with sepsis, gestational age 38–41 weeks (n=35); Group II – premature newborns diagnosed with sepsis, gestational age 27–37 weeks (n=65); Control group: healthy newborns (n=30), of which 23 were born full-term and 7 were premature. The determination of alpha-defensin was carried out using a standard solid-phase(«sandwich « version) enzyme-linked immunosorbent assay. The statistical processing of the obtained data was carried out using the Wilkinson U-test.

Results. In full-term infants diagnosed with sepsis, α-defensin in the first days of the disease was 771.8±37.6 ng/ml and was significantly different from the results in the control group (p<0.001). Over time, this indicator decreased as a manifestation of the weakening of the inflammatory process and was 380.0±21.1 ng/ml. Similar dynamics of α-defensin (727.9±27.2 ng/ml and 363.2±14.5 ng/ml, respectively) were observed in premature infants. Statistically significant increase was observed in both early and late sepsis (716.7±53.3 ng/ml and 731.3±31.8 ng/ml, respectively). High values were the result of the manifestation of inflammation in both forms in the first days. With repeated measurements (re-check), this indicator decreased to a greater extent in children with early sepsis; this difference corresponded to the previous indicators (1.487±0.034 EU/ml and 0.987±0.110 EU/ml, respectively)

Conclusions. Based on the results of the study, it can be said that alpha-defensin in full-term and premature septic infants can be used as an additional criterion for characterizing the immune status and inflammatory process in sepsis, predicting outcomes, and assessing the degree of immunodeficiency.

Keywords: full-term infants, premature infants, sepsis, antimicrobial peptides, alpha-defensins.

Визначення рівня альфа-дефензину в динаміці у новонароджених із сепсисом

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Мета – дослідити деякі патогенетичні механізми змін імунної системи під час сепсису в недоношених та доношених дітей шляхом визначення рівня альфа-дефензину.

Матеріали та методи. Всього було обстежено 130 новонароджених. Із них 100 були немовлятами, які перебували на стаціонарному лікуванні з діагнозом сепсису (раннього та пізнього), та 30 – здоровими новонародженими. Дітей, які брали участь у дослідженні, було розділено на такі групи: I група – доношені новонароджені з діагнозом сепсису, гестаційний вік 38–41 тиждень (n=35); II група – недоношені новонароджені з діагнозом сепсису, гестаційний вік 27–37 тижнів (n=65); контрольна група: здорові новонароджені (n=30), з яких 23 народилися доношеними та 7 – недоношеними. Визначення альфа-дефензину проводили за допомогою стандартного твердофазного(«сендвіч»-версія) імуноферментного аналізу. Статистичну обробку отриманих даних проводили за допомогою U-тесту Вілкінсона.

Результати. У доношених дітей із діагнозом сепсису α-дефензин у перші дні захворювання становив 771,8±37,6 нг/мл і суттєво відрізнявся від результатів у контрольній групі. Із часом цей показник знижувався як прояв ослаблення запального процесу та становив 380,0±21,1 нг/мл). Подібна динаміка α-дефензину (727,9±27,2 нг/мл та 363,2±14,5 нг/мл відповідно) спостерігалася в недоношених дітей. Статистично значуще підвищення спостерігалося як при ранньому, так і при пізньому сепсисі (716,7±53,3 нг/мл та 731,3±31,8 нг/мл відповідно). Високі значення були результатом прояву запалення в обох формах у перші дні. Під час повторних вимірювань (повторній перевірці) цей показник знизився більшою мірою в дітей із раннім сепсисом; ця різниця відповідала попереднім показникам (1,487±0,034 ОД/мл та 0,987±0,110 ОД/мл відповідно).

Висновки. З огляду на результати дослідження, можна стверджувати, що альфа-дефензин у доношених та недоношених дітей із сепсисом може бути використаний як додатковий критерій для характеристики імунного статусу та запального процесу при сепсисі, прогнозування результатів та оцінки ступеня імунодефіциту.

Ключові слова: доношені діти, недоношені діти, сепсис, антимікробні пептиди, альфа-дефензини.

Introduction

Infectious diseases are a leading cause of neonatal mortality. Neonatal sepsis is an invasive infection, predominantly bacterial, that develops during the neonatal period. Symptoms of sepsis are varied and nonspecific and include decreased spontaneous activity, poor sucking, apnea, bradycardia, fluctuations in body temperature, respiratory distress, vomiting, diarrhea, abdominal distension, increased nervous irritability, seizures, and jaundice. Neonatal sepsis, a bloodstream infection in the first 28 days of life, is a leading cause of morbidity and mortality among infants in both developing and developed countries. Furthermore, neonatal sepsis has unique pathophysiological and clinical features associated with its development in the immature immune system of newborns [2,3,5].

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In sepsis, the liver, as one of the main organs affected, provides information about the severity of the disease and also causes certain changes in the levels of other blood markers due to its loss of ability to adequately perform its functions [4,6].

Determining antimicrobial peptides (AMPs) in neonates with various forms of neonatal sepsis is important for improving early diagnosis and selecting treatment strategies. AMPs and cytokines interact with clinical and biochemical parameters in neonates with sepsis, which determine the varying course of the disease and the risk of complications [8].

Very low birth weight infants are at higher risk of developing sepsis. This is due to their immature immune system, prolonged stay in the intensive care unit on mechanical ventilation, and the use of endotracheal tubes, catheters, and other invasive procedures [2,5].

Antimicrobial peptides (alpha-defensins, beta-defensins, etc.) are the innate nonspecific humoral factors of the immune system. AMPs protect the body from a number of pathogens (viruses, bacteria, fungi, etc.) [6,7,9]. The primary localization of these peptides is the lysosomes of neutrophils. AMPs, which possess a broad spectrum of biological activity, ensure chemotaxis of dendritic cells, micro- and macrophages during inflammatory processes and stimulate degranulation of barrier cells [4,7].

The aim of the study was to investigate the pathogenetic mechanisms of immune system changes during sepsis in premature and full-term infants by determining the information content of alpha-defensin (α-defensin).

Materials and methods of the study

The study was conducted at the Scientific Research Institute of Pediatrics named after K.Yu. Faradzheva and Maternity Hospital No. 7 in Baku. Examinations were conducted in the neonatal pathology, anesthesiology, and intensive care departments, and the research laboratory of the Scientific Research Institute of Pediatrics named after K.Yu. Faradzheva. A total of 130 newborns were examined. Of these, 100 were children undergoing inpatient treatment with a diagnosis of neonatal sepsis (NS), and 30 were healthy newborns. The children participating in the study were divided into the following groups:

Group I – newborn baby diagnosed with NS, gestational age 38–41 weeks (n=35);

Group II – newborn baby diagnosed with NS, gestational age 27–37 weeks (n=65); this group was divided into 2 semigroups according to time of onset: early NS – onset within the first 72 hours after birth (n=15), and late NS – onset of disease after 72 hours (n=50);

Control group: healthy newborns (n=30), of which 23 were born full-term and 7 were premature.

In accordance with the aims and objectives of our study, we determined the dynamics of α-defensin in children with neonatal sepsis. The determination was carried out by a standard method of solid-phase («sandwich» version) enzyme immunoassay ELISA on an automatic analyzer «Elisys Uno» made in Germany. The obtained data from statistical processing were carried out by the program – Wilcoxon U-criterion (Mann–Whitney). The informativeness of the biomarker was established by determining sensitivity and specificity (in cases of necrotizing enterocolitis, pneumonia, septic shock, ventriculitis, enterocolitis, which are clinical manifestations of the general septic process, as well as neonatal mortality) based on ROC analysis.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of the mentioned institution. The informed consent was obtained from all participants.

Results of the study and discussion

In full-term infants diagnosed with sepsis, α-defensin in the first days of the disease was 771.8±37.6 ng/ml and was significantly different from the results in the control group ($p<0.001$). Over time, this indicator decreased as a manifestation of the weakening of the inflammatory process and was 380.0±21.1 ng/ml. (Table 1)

Table 1

α-defensin levels in full-term infants with sepsis

Indicators	Control group (n=23)	Group I (n=35)		P1	P2
		First check	Re-check		
α-defensin, nq/ml	48.4±1.3 (31.2–58.4)	771.8±37.6 (323.9–1098.0)	380.0±21.1 (113.4–625.7)	<0.001	<0.001

Note: p – coefficient of statistical significance: P1 – with the control group; P2 – between the first check and re-check.

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Table 2

α-defensin levels in premature infants with sepsis

Indicators	Control group (n=7)	Group II (n=65)				P1	P2
		early NS (n=15)		late NS (n=50)			
		First check	Re-check	First check	Re-check		
α-defensin (ng/ml)	41.9±4.2 (25.8–58.4)	716.7±53.3 (448.7–1033)	336.7±31.6 (155.5–521.5)	731.3±31.8 (397.2–1076)	371.2±16.2 (189.4–655.8)	<0.001	<0.001

Note: p – is the statistical integrity coefficient: P1 – with the control group; P2 – among patients with neonatal sepsis and the control group.

A statistically significant increase was observed in both early and late sepsis (716.7±53.3 ng/ml and 731.3±31.8 ng/ml, respectively). High values are due to the obvious manifestation of inflammation in both forms in the first days. With repeated measurements (re-check), this indicator decreased to a greater extent in children with early sepsis.

Similar dynamics of α-defensin (727.9±27.2 ng/ml and 363.2±14.5 ng/ml, respectively; $p<0.001$) were observed in premature infants (Table 2).

According to the results, the level of α-defensin in newborns with sepsis differed from those with sepsis. In full-term infants diagnosed with sepsis, α-defensin levels from the first days of illness were 15.9 times higher than those in the control group ($p<0.001$). A statistically significant increase in α-defensin levels was observed in both early and late sepsis.

In children with neonatal sepsis, the following pathologies (as a clinical manifestation of sepsis) were observed: enterocolitis (14%), ventriculitis (15%), osteomyelitis (8%), pneumonia (56%), necrotizing enterocolitis (14%), and scleroderma (10%). During the course of the disease, septic shock developed in 12% of patients.

Determination of the sensitivity and specificity of α-defensin in relation to these pathologies based on ROC analysis showed that high sensitivity of alpha-defensin in neonatal sepsis is associated with necrotizing enterocolitis (92.9%), pneumonia (85.7%), septic shock (91.7%) and neonatal mortality (92.3%), and high specificity is associated with ventriculitis (77.6%) and enterocolitis (74.4%).

The protective function of AMPs against early-life infections – including chorioamnionitis, neonatal sepsis, and necrotizing enterocolitis – relies predominantly on the innate immune system, where AMPs serve as key effectors. Numerous investigations have underscored the critical involvement of α- and β-defensins, cathelicidin LL-37, and antiproteases such as elafin, secretory leukocyte protease inhibitor (SLPI), and hepcidin in maintaining fetal and neonatal immune defense [5,6].

Although studies examining AMP expression and concentration in fetuses and newborns remain limited, the available evidence supports their contribution to the pathogenesis of chorioamnionitis and neonatal sepsis, particularly in cases complicated by necrotizing enterocolitis, and highlights their correlation with disease severity. In a study by E. Agakidou et al. (2022), AMPs were proposed as potential diagnostic, preventive, prognostic, and therapeutic biomarkers for sepsis and necrotizing enterocolitis. The authors emphasized emerging data suggesting that AMPs may serve as diagnostic or prognostic indicators and as alternative or adjunct therapeutic agents to antibiotics, which is of particular relevance in light of growing antibiotic resistance within neonatal intensive care units [1]. These observations are largely consistent with our findings, which indicate that α-defensin possesses substantial predictive value as a biomarker for necrotizing enterocolitis and other septic manifestations in neonates.

J. Wiesner et al. (2010) noted that the onset of action of most AMPs is extremely rapid compared to traditional antibiotics, and the bactericidal effect is observed at concentrations very close to the minimum inhibitory concentrations. Furthermore, some AMPs have an unusually broad spectrum of activity and are capable of destroying multidrug-resistant pathogens [9]. It is precisely this mechanism that the authors use to explain the dynamic changes in α-defensin, as one of the representatives of antimicrobial peptides, during sepsis.

Conclusion

Thus, α-defensins, as active participants in every inflammatory process, are indicators that manifest as important changes in the course of generalized inflammatory pathology, sepsis. Overall, neonates with neonatal sepsis exhibit multifaceted, multidirectional, complex relationships between clinical manifestations and biochemical parameters. These interactions confirm the importance of thorough, accurate, and detailed analysis of biochemical tests, which we

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consider routine, having both diagnostic and prognostic value.

Based on the results of our study, it can be said that α-defensins in full-term and premature septic infants can be used as an additional criterion for characterizing the immune status and inflammatory process in sepsis, predicting outcomes, and assessing the degree of immunodeficiency.

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