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The role of adenosine monophosphate-activated protein kinase and serum amyloid A proteins in the early diagnosis of neonatal sepsis

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Neonatal sepsis is a leading cause of mortality among newborns globally, with an incidence of 1 per 1,000 live births. Current diagnostic markers such as C-reactive protein (CRP) and procalcitonin (PCT) lack specificity and sensitivity for early diagnosis, highlighting the need for more reliable biomarkers.

The **aim** of the study is to evaluate the role of adenosine monophosphate-activated protein kinase (AMPK) and serum amyloid A (SAA) proteins as potential biomarkers for the early diagnosis of sepsis in neonates suspected of having the condition.

Materials and methods. A cohort study was conducted involving 143 newborns suspected of sepsis, admitted to the intensive care units within the first 24 hours of life. Clinical evaluations included respiratory distress assessment, chest and abdominal imaging, and brain ultrasound. Blood samples were analyzed for CRP, PCT, AMPK, and SAA levels using enzyme-linked immunosorbent assay (ELISA) kits. Statistical analysis involved Mann–Whitney and independent samples t-tests, as well as receiver operating characteristic (ROC) analysis to determine diagnostic cutoff levels. The nonparametric Spearman rank correlation test (r — the Spearman rank-order correlation coefficient) was used. Differences at $p<0.05$ were considered reliable.

Results. Inflammatory markers CRP and PCT were used to confirm sepsis diagnosis in conjunction with clinical assessment. However, 12.8% of infants with PCT >2 ng/mL and 17.5% with CRP >5 mg/mL did not have confirmed sepsis. Conversely, sepsis was confirmed in 63.6% of infants with PCT <2 ng/mL and 53.7% with CRP <5 mg/mL. A significant correlation between AMPK and SAA was observed in 111 infants (r=0.192, p=0.044). The ROC analysis indicated that AMPK and SAA levels below specific thresholds were significant for excluding sepsis.

Conclusion. AMPK and AA levels are promising diagnostic markers for neonatal sepsis, warranting further investigation in larger studies. These biomarkers can improve early diagnosis and reduce unnecessary antibiotic usage, thus improving neonatal outcomes.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of a participating institution. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: neonatal sepsis, adenosine monophosphate-activated protein kinase, serum amyloid A, biomarkers, early diagnosis, C-reactive protein, procalcitonin.

Роль аденозинмонофосфат-активованої протеїнкінази та сироваткового амілоїду А в ранній діагностиці неонатального сепсису

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Неонатальний сепсис є основною причиною смертності серед новонароджених у всьому світі з частотою 1 випадок на 1000 живонароджених. Сучасні діагностичні маркери такі, як С-реактивний білок (СРБ) і прокальцитонін (ПКТ) недостатньо специфічні та чутливі для ранньої діагностики, що підкреслює потребу в більш надійних біомаркерах.

Метою дослідження є оцінка ролі аденозинмонофосфат-активованої протеїнкінази (AMPK) та сироваткового амілоїду А (САА) як потенційних біомаркерів для ранньої діагностики сепсису в новонароджених із підозрою на цей стан.

Матеріали і методи. Проведено когортне дослідження за участю 143 новонароджених із підозрою на сепсис, які надійшли до відділення інтенсивної терапії протягом перших 24 годин життя. Було проведено такі клінічні дослідження: оцінка респіраторного дистресу, візуалізація грудної клітки та черевної порожнини, а також ультразвукове дослідження головного мозку. Зразки крові було проаналізовано на рівні СРБ, ПКТ, AMPK і САА за допомогою наборів для імуноферментного аналізу (ІФА). Статистичний аналіз містив Манна–Уітні та t-критерії незалежних вибірок, а також аналіз робочих характеристик приймача (ROC) для визначення діагностичних рівнів відсікання. Було використано непараметричний тест рангової кореляції Спірмена (r — коефіцієнт рангової кореляції Спірмена). Достовірними вважалися відмінності при $p<0,05$.

Результати. Для підтвердження діагнозу сепсису було використано маркери запалення СРБ та ПКТ у поєднанні з клінічною оцінкою. Однак у 12,8% немовлят із показниками ПКТ >2 нг/мл і 17,5% СРБ >5 мг/мл сепсис не був підтверджений. Навпаки, сепсис був підтверджений у 63,6% немовлят із показниками ПКТ <2 нг/мл і 53,7% СРБ <5 мг/мл. У 111 немовлят спостерігався значний кореляційний зв'язок між AMPK і САА (r=0,192, p=0,044). ROC-аналіз показав, що рівні AMPK і САА нижче певних порогових значень були значущими для виключення сепсису.

Висновок. Рівні AMPK та АА є перспективними діагностичними маркерами неонатального сепсису, які вимагають подальшого вивчення у великих дослідженнях. Ці біомаркери здатні покращити ранню діагностику та скоротити непотрібне використання антибіотиків, таким чином покращуючи результати лікування новонароджених.

Дослідження виконано відповідно до принципів Гельсінської Декларації. Протокол дослідження ухвалений Локальним етичним комітетом установи, що брала участь у дослідженні. На проведення досліджень отримано інформована згоду пацієнта.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: неонатальний сепсис, аденозинмонофосфат-активована протеїнкіназа, сироватковий амілоїд А, біомаркери, рання діагностика, С-реактивний протеїн, прокальцитонін.

Introduction

Despite advancements in neonatal resuscitation, sepsis remains a leading cause of death among newborns worldwide. Neonatal sepsis is reported to occur in approximately 1 out of every 1,000 live births. However, due to the presence of risk factors that can lead to nosocomial sepsis in premature infants, the incidence of sepsis can range from 3% to 20% within the neonatal population. Mortality associated with neonatal sepsis is greatly dependent on the pathogen and the gestational age of the infants, with mortality rates rising to 20% in very early preterm neonates. Many of these deaths could be prevented through interventions such as early diagnosis, timely testing, appropriate antibiotic therapy, and continuous monitoring [22].

Early diagnosis is possible through the rapid recognition of clinical signs, symptoms, and syndromes [7]. The diagnosis of sepsis is based on clinical and laboratory indicators outlined in the American Academy of Pediatrics' protocol for managing neonatal sepsis. The primary markers considered in the diagnosis of sepsis, C-reactive protein (CRP) and procalcitonin (PCT), are highly sensitive but can easily change under the influence of various factors. Although numerous studies focused on the early diagnosis of sepsis, markers with high sensitivity and specificity for early diagnosis remain missing [5].

Late diagnosis of sepsis increases morbidity and mortality rates during the neonatal period, negatively impacting morbidity indicators at later developmental stages of surviving infants, as well as their psychoneurological and physical development, which can complicate the functions of social adaptation [14]. In this respect, neonatal sepsis is considered an urgent problem not only in neonatology but also in pediatrics and neurology. Timely detection and intervention can help prevent potential complications. Additionally, the identification of a highly sensitive and reliable marker can reduce the frequency of unnecessary use of antibiotics [3].

In recent years, the role of serum amyloid A (SAA) protein in the early diagnosis of neonatal sepsis has been explored. This protein, which belongs to the lipoprotein family, is produced by the liver in response to cytokines [21] Some studies suggest that SAA's synthesis during the early phase of inflammation and its diagnostic value may surpass that of CRP, though various cutoff levels have been noted [21,25]. However, the literature data on the role of SAA in monitoring neonatal sepsis remains contradictory [18,23].

From this perspective, it is intriguing to study the role of SAA protein in diagnosing sepsis compared to clinical signs, CRP, PCT, and other laboratory indicators. Moreover, understanding its role in the clinical course of sepsis depending on SAA levels is of interest.

In recent times, research has also focused on managing diseases by affecting various phases of metabolism. Sepsis can lead to sepsis-related dysfunctions and mitochondrial damage, disrupting cellular metabolism [20]. These disruptions occur across all organic substance metabolisms, with acute glycolysis, impaired transition of pyruvates into the Krebs cycle, and increased lactate levels observed. Disturbances in lipolysis result in elevated blood fatty acids and triglycerides. Disorders in the ketone body and amino acid metabolism are also noted during sepsis [28].

The study of metabolism during sepsis has become a major research focus. The central role of AMPK protein in metabolism is being explored in diabetes, obesity, sepsis, cardiometabolic and oncological diseases. Disruption of AMPK regulation in pathological processes has identified it as a pharmacological target during disease [1]. Although the role of AMPK in metabolism and its therapeutic target range has been extensively studied in vitro and in vivo, its role during the neonatal period, in particular during sepsis, has not been explored [10].

Studying AMPK protein in neonatal sepsis may provide new opportunities for diagnosing sepsis and managing the disease in the future.

The **aim** of the study is to determine the role of AMPK and SAA proteins in the early diagnosis of sepsis in newborns suspected of sepsis.

Materials and methods of the study

The present study utilized a cohort design, encompassing the examination results of 143 newborns suspected of sepsis. These newborns were admitted to the intensive care units (ICUs) of the Scientific Research Institute of Pediatrics named after K. Farajova and Perinatal Center from the first and second-level maternity homes within the first day of life. Signs of respiratory distress indicating suspicion of sepsis were noted in all infants. In addition to the initial clinical examination, chest and abdominal X-rays and ultrasound examinations were conducted on the first day,

if indicated. Routine ultrasound examinations of the brain were performed on the third day of life unless there were other indications. Upon admission, all children underwent complete blood count, including CRP and PCT determination. Furthermore, after centrifugation of blood taken for biochemical analysis, 40 microliters of blood plasma were separated and collected in ependymal tubes, then frozen at -20°C. The determination of AMPK and SAA proteins in blood plasma was performed using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Coon Koon Biotech Co., Ltd) based on the immunoassay method.

In the initial assessment of the children's condition, the diagnosis of sepsis was confirmed clinically and, in the laboratory, based on at least two clinical and two laboratory signs, as defined in the European Medicines Agency's guidelines for the management of sepsis.

As a result of the evaluation, the children were divided into two groups and the results of the analysis were examined in the sepsis and non-sepsis groups: the sepsis group included children with diagnosed sepsis (n=63) and non-sepsis group included children in whom the diagnosis of sepsis has not been confirmed (n=29). Since signs of sepsis were noted within the first 72 hours, it was evaluated as early-onset sepsis.

The analysis results were statistically processed using the SPSS statistical package on the Windows operating system, and the arithmetic mean ± standard deviation (mean ± SD) was assessed. The Mann–Whitney and independent samples t-test were utilized in data comparisons, and ROC analysis was conducted to determine the cutoff levels. In addition, the nonparametric Spearman rank correlation test (r — the Spearman rank-order correlation coefficient) was used. Differences at $p<0.05$ were considered reliable. Sensitivity and specificity indicators were processed in Excel spreadsheets, and the closest distance to the central line was chosen to determine the optimal diagnostic cutoff level.

Results of the study and discussion

In 143 children, the mean gestational age was 36.8±1.7 weeks (range: 34–42), weight was 2955±479.3 g (range: 2000–4200 g), and height was 49.2±2.69 cm (range: 41–56 cm). Based on the discharge summary data, the Apgar scores were rated at 6.6±1.2 (min — 2, max — 9) in the first minute and 7.3±0.9 (min — 5, max — 9) in the fifth minute. The number of children whose AMPK and SAA levels were determined is reflected in Table 1.

On the day of admission to the ICU, inflammation markers CRP and PCT proteins were used in blood plasma and the initial diagnosis based on the APA scoring table were used to confirm the diagnosis of sepsis. However, it should be noted that sepsis was not confirmed in 5 (12.8%) children with PCT >2 ng/mL and in 11 (17.5%) children with CRP >5 mg/mL on the first day. Sepsis was confirmed in 14 (63.6%) children with PCT <2 and in 29 (53.7%) children with CRP<5. A direct correlation was also noted between AMPK and SAA in 111 infants (r=0.192, p=0.044).

The AMPK, CRP, and SAA proteins under the ROC area were statistically significant. Specifically, the fact that the area under the ROC curves for the SAA and AMPK proteins was less than 0.5 was

Table 1

CRP, PCT, SAA, AMPK proteins level and gestational age, birth weight in the groups

Parameters	Sepsis group	Non-sepsis group	p, two-tailed significance
Gestational age, weeks, mean, (SD), CI	N=63 36.1(1.9) 36.3-37.3	N=29 37.8(1.9) 36.3-37.8	0.583
Birth weight, g mean, (SD), CI	N=70 2965 (521) 2841-3090	N=34 2896 (550) 2707-3085	0.529
PCT, nq/mL mean, (SD), CI	N=51 12.4 (17) 7.4-17.3	N=14 4.9 (6.3) 1.3-8.6	0.126
CRP, mq/L mean, (SD), CI	N=83 34 (51) 23-44	N=38 9 (15) 4-14	0.004
SAA, µq/ml mean, (SD), CI	N=76 3.5 (1.2) 3.2-3.7	N=35 4 (0.7) 3.8-4.3	0.002
AMPK, pq/ml mean, (SD), CI	N=80 1091 (353) 1012-1169	N=38 1355 (465) 1187-1492	0.003

Note: SD — standard deviation, CI — confidence interval, PCT — procalcitonin, CRP — C-reactive protein, SAA — serum amyloid A, AMPK — adenosine monophosphate-activated protein kinase.

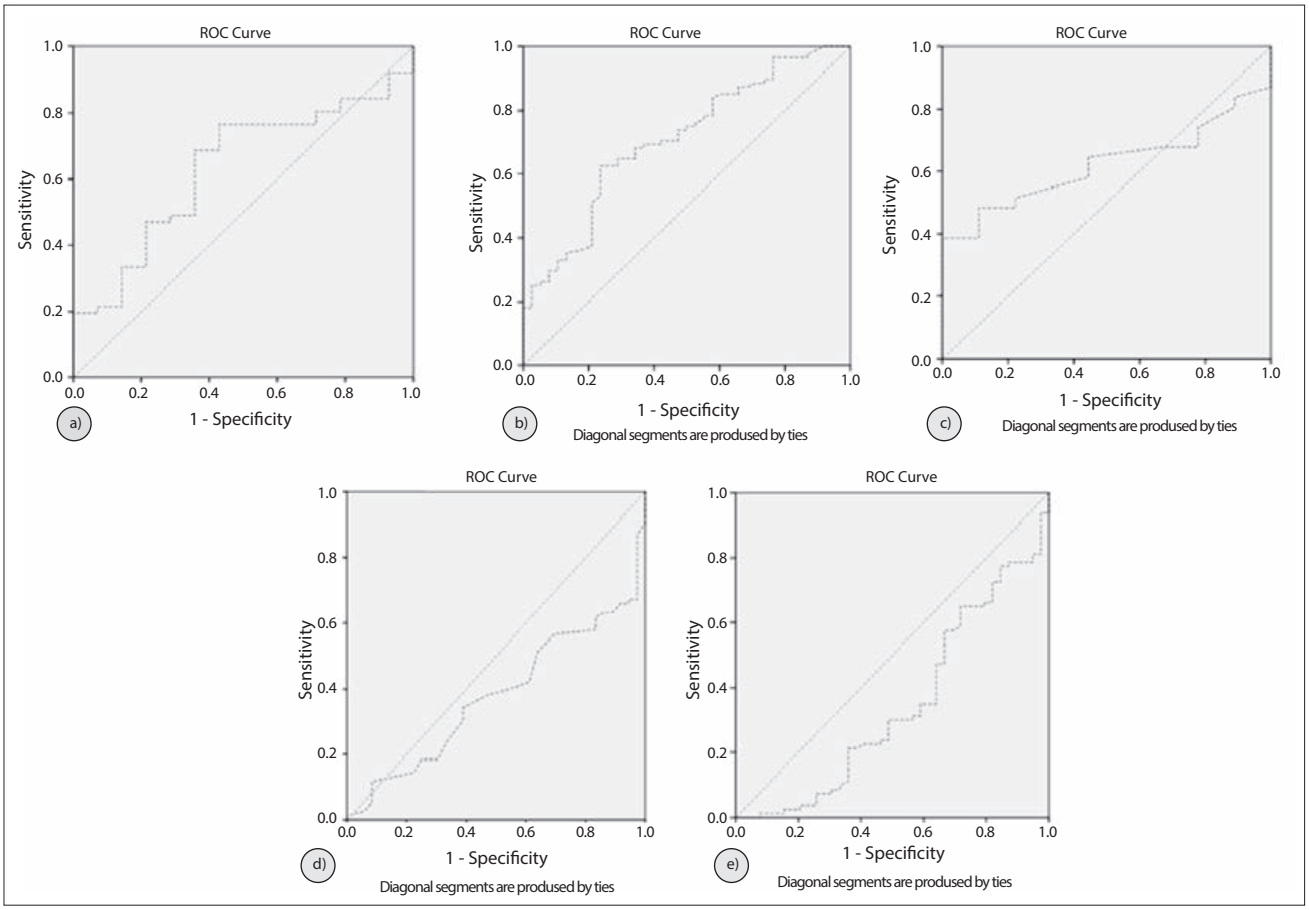

Fig. 1. ROC analysis for sepsis: a — PCT, b — CRP, c — AlaT, d — SAA, e — AMPK

Table 2

ROC parameters of CRP, PCT, ALaT, AMPK and SAA for sepsis

Proteins	Area under ROC	SE	P value	CI lower band	CI upper band	Cutoff level	Sensitivity	Spesificity
CRP	0.708	0.049	0.001	0.612	0.805	6.65	63%	76%
PCT	0.633	0.078	0.130	0.480	0.786	2.87	69%	64%
ALaT	0.622	0.086	0.271	0.453	0.79	18.5	45%	89%
AMPK	0.343	0.055	0.006	0.236	0.451	971.6	57,5%	33%
sAA	0.379	0.053	0.039	0.275	0.483	4.25	34%	61%

Note: SE — standard error, CI — confidence interval, PCT — procalcitonin, CRP — C-reactive protein, SAA — serum amyloid A, AMPK — adenosine monophosphate-activated protein kinase, ALaT — alanine aminotransferase.

significant for ruling out the diagnosis of sepsis (Figure). Therefore, SAA levels above 4.25 and AMPK levels above 971.6 ruled out the diagnosis of sepsis. A CRP level over 6.65 confirmed the diagnosis of sepsis with 63% sensitivity and 76% specificity (see Table 2).

During infection, an increase in PCT and CRP is noted. However, these markers do not provide precise diagnostic information in the diagnosis of sepsis. In our study, SAA and AMPK levels were lower in children who developed sepsis compared to other children. Considering that all children had signs of suspected sepsis, the low level of AMPK in children who developed sepsis indicates weak immune defense. The function and activation of AMPK during infections further substantiate this. Adequate AMPK increases in other children may also prevent generalized infection [26].

AMPK is involved in regulating the innate immune response. For example, the innate immune stimulator toll-like receptor (TLR) 9 inhibits energy substrates (intracellular ATP levels) and activates AMPK, enhancing stress tolerance in cardiomyocytes and neurons, while stimulation by the TLR9 ligand induces inflammation [17]. The AMPK activator AICAR suppresses lung inflammation induced by lipoteichoic acid, a major component of the Gram-positive bacteria cell wall [8]. AMPK activators enhance neutrophil chemotaxis, phagocytosis, and bacterial killing to protect against peritonitis-induced sepsis [15].

Indeed, AMPK activators, including metformin, inhibit injurious inflammatory responses, including neutrophil pro-inflammatory responses and injury to multiple organs such as the lung, liver, and kidney [2,4,29].

Pharmacologic activation of AMPK by metformin, berberine, or AICAR dampens excessive TLR4/NF-κB signaling, M2-type macrophage polarization, and the production of pro-inflammatory mediators in vitro and in sepsis models [6,9,16,19,24,30]. The anti-inflammatory effect of metformin in mice with lipopolysaccharide (LPS)-induced septic shock and in ob/ob mice is mediated at least partly by AMPK activation [11]. In septic mice, AMPK activation by AICAR or metformin reduces the severity of sepsis-induced lung injury, enhances AMPK phosphorylation in the brain, and attenuates the inflammatory response [12,13]. AMPK activation not only modulates the acute inflammatory response but also promotes neutrophil-dependent bacterial uptake and killing [15].

A meta-analysis indicated that SAA showed moderate accuracy and longer diagnostic cycle in diagnosing neonatal sepsis. Furthermore, the SAA test demonstrated better accuracy than the CRP test for diagnosing neonatal sepsis at the first suspicion of sepsis. It not only has higher accuracy at the first suspicion, but also maintains its usefulness 8–96 hours after the first suspicion [27]. However, scientific data comparing SAA and AMPK levels in children with pneumonia and local infections who develop sepsis are limited. Therefore, we believe that combining SAA and AMPK with CRP and PCT will improve the diagnosis of sepsis.

Conclusion

The present study suggests that AMPK and SAA levels on the first day may be significant diagnostic markers for the development of sepsis in newborns suspected of sepsis, paving the way for more extensive studies in this area.

No conflict of interests was declared by the authors.

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