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Studying the efficacy of resistin as a diagnostic biomarker of neonatal sepsis

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Abstract

Sepsis is an important cause of neonatal death and perinatal brain damage, particularly in preterm infants. It is thought that activation of the inflammatory cascade triggered by cytokine may play a role in the pathogenesis of sepsis. Recent evidence supports a role for resistin in inflammation. There are no data in the literature on resistin levels in neonates with sepsis, which can also cause an inflammatory response. The objective of this study was to evaluate the role of resistin as an indicator in neonatal sepsis. Forty neonates considered to have sepsis were included in the study. Forty gestational and postnatal age- and sex-matched neonates without prolonged premature rupture of membrane or sepsis had served as controls. The mean resistin level of the neonates with sepsis was 115 ng/mL and was higher than those of the control group (41.1 ng/mL). There was statistically significant direct correlations between serum resistin and both TLC and CRP. The sensitivity, specificity, positive, and negative predictive values for resistin were 100%, 93%, 96%, and 100%, respectively. Resistin levels were higher in newborns with sepsis and correlated with TLC and CRP levels, which are indicators of neonatal sepsis. This suggests that resistin may also be used in the diagnosis of neonatal sepsis.

Keywords: C-reactive protein, resistin, neonatal, sepsis, biomarker

Introduction

Sepsis a major cause of mortality and co-morbidity in preterm babies and it accounts for forty five percent of deaths in the neonatal intensive care units (NICUs) [1]. Early diagnosis and management of sepsis is a big difficulty facing neonatologists. Clinical diagnosis is difficult due to non-specific symptoms and signs while laboratory diagnosis is time consuming [2]. Blood culture is the main traditional method of diagnosis of neonatal sepsis. However, technical problems as insufficient blood sample or maternal use of antibiotics can be an obstacle in isolating the responsible pathogens. Recently, there is a vast concern about studying new indicators of infection such as interleukin-6 (IL-6), IL-8, and procalcitonin (PCT) and their role in the early diagnosis of neonatal sepsis [2,3]. Resistin is a newly discovered hormone secreted by the adipocytes and found to be responsible for the development of type 2 diabetes in obese patients [4]. In rats, resistin is secreted only by adipocytes, whereas in humans, other cells can secrete it as muscle cells, and macrophages [5]. Studies in adult patients with sepsis established that resistin is secreted by the macrophages and neutrophils in response to acute bacterial infection [6,7,8]. In addition, it has been reported that resistin levels is correlated with the severity and duration of the disease

in patients with sepsis and septic shock [8]. The objective of this work was to study the role of resistin as an indicator of neonatal sepsis.

Material and Method

We obtained informed consents from the parents of the neonates enrolled in the study. Forty neonates (18 male and 22 female) considered to have sepsis were included in the study; forty age and sex matched neonates without premature rupture of membranes (PROM) or sepsis served as controls. The diagnosis of sepsis was established according to the presence clinical findings, laboratory data including the positive blood culture. The clinical findings of sepsis included apnea, vomiting, diarrhea, severe hypoxia or ventilatory support, hypotonia, poor neonatal reflexes and hypotension. The components of the laboratory investigation are hematological counts and ratios such as white blood cells count, absolute neutrophilic count, platelets count, staff-to-total neutrophils ratio, and serum or plasma concentrations CRP. All included cases were proved to have sepsis by positive blood cultures.

Samples collection

Venous blood samples were obtained to measure whole blood count, CRP, and resistin level on the 1st day of sepsis. The CRP levels were quantitatively estimated using latex agglutination assay using the AVITEX CRP commercial kit. The resistin level

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(LINCO Research, St. Charles, MO, USA) was determined using enzyme-linked immunosorbent assay kit.

Statistics

Statistical analysis was done using statistical package for social sciences (SPSS), computer software (version 22), IBM software, USA. Data were described in the form of mean $\pm$ standard deviation for quantitative data, and frequency and proportions for qualitative data. A p value <0.05 was considered statistically significant. Differences were analyzed between the groups by Student t test as regards normally distributed data; otherwise, Mann–Whitney U test was used. Correlations were analyzed by Spearman correlation coefficient test. The receiver operating characteristics (ROC) curve analysis was performed to identify the optimal cutoff value for resistin distinguishing between the cases with sepsis and the controls

Results

The two groups of cases and controls included in the study were matching for gestational age, body weight and age in days. Forty neonates with sepsis were included in the study and a pathogen could be isolated in 90% of them. The isolated microorganisms were as follows: Staphylococcus aureus in three cases, Enterobacter in eight cases, Klebsiella species in eight cases, Escherichia coli in six cases, Pseudomonas aeruginosa in three cases, Acinetobacter in eight cases.

Table 1 shows CRP and resistin levels in both the study and the control groups. Both resistin and CRP levels substantially decreased on the 7th day of sepsis and positive correlations were observed between them (Figure 1,2).

Table 1. TLC, C reactive protein and plasma resistin levels in babies with sepsis compared with control

	Study group (n = 40)	Control group (n = 40)	p
TLC($\times 10^3$ cell/mm ³)	15.23 $\pm$ 0.62	5.51 $\pm$ 0.36	<0.001
CRP (ng /mL)	38.8 $\pm$ 5.54	2.32 $\pm$ 0.2	<0.001
Resistin (ng/mL)	115 $\pm$ 2.29	41.1 $\pm$ 1.01	0.001

Data are presented as mean $\pm$ standard deviation
TLC=total leukocytes count
CRP = C-reactive protein

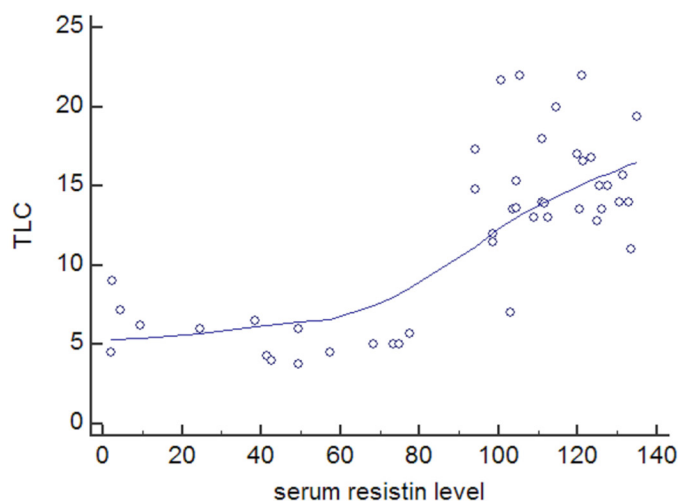


Figure 1. Correlations between plasma resistin and TLC levels in the patients with sepsis ($r = 0.73$, $p = 0.000$)

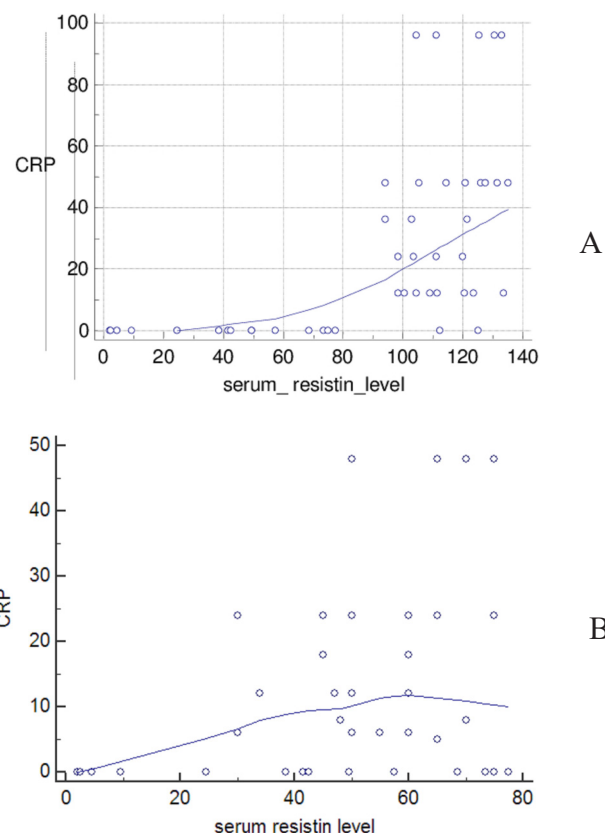
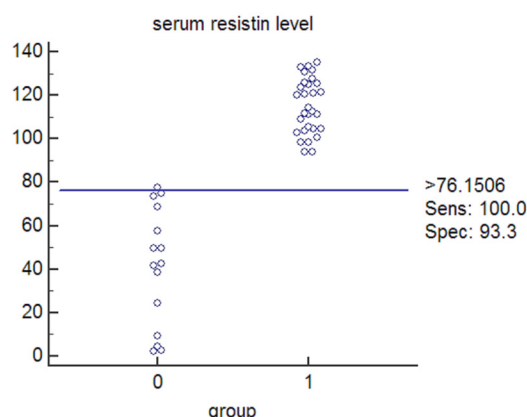


Figure 2. Correlations between plasma resistin and CRP levels in the patients with sepsis. A. in the first day of sepsis ($r = 0.58$, $p = 0.000$). B. in the 7th day of sepsis ($r = 0.032$, $p = 0.02$)

The cutoff value for resistin that can be used to distinguish the babies with sepsis from healthy ones was found to be 76 ng/mL. The area under the curve value for resistin was 1.00 (95% confidence interval = 0.92–1.00; $p < 0.001$). The sensitivity, specificity, positive and negative predictive values for this cutoff value were 100%, 93%, 96%, and 100% respectively (figure 3).



Discussion

Figure 3. ROC curve for serum resistin level

Our study has shown that the mean resistin levels in the neonates with sepsis were significantly higher than in neonates without sepsis. Serum resistin levels significantly directly correlated with both CRP and TLC levels in neonates with sepsis. It has been thought that activation of the inflammatory surge triggered by cytokines may have a role in the pathogenesis of sepsis [9,10].

The first step of the inflammatory response is largely characterized by the influx of neutrophils [11] and the release of IL6 [12]. IL-6 is a well-known biomarker of inflammation that alters the expression of other inflammatory proteins [13]. Besides its direct proinflammatory effects, IL-6 also increases the CRP production by the liver and the expression of resistin on peripheral blood mononuclear cells [14]. As mentioned before, resistin has emerged as a powerful proinflammatory mediator and its role in both acute and chronic inflammatory processes has been described [7,15]. In adult patients with sepsis, resistin was implicated as an effective biomarker of sepsis severity and as a predictor of mortality of critically ill adult patients. Also, Serum resistin levels were elevated in patients with inflammatory bowel disease and it was correlated with CRP, TLC levels and with the disease activity [16]. In a study done by Adrych et al., they reported that serum-resistin levels were elevated in patients with chronic pancreatitis and they suggested its role in the development of pancreatic fibrosis [17]. There are limited data on resistin levels in neonatal sepsis. Recently, Cekmez et al [18] studied resistin as an indicator of neonatal sepsis and they showed that resistin can be used as a biomarker of neonatal sepsis with the same efficacy as other markers such as CRP, IL-6, and procalcitonin. Furthermore, Gursay et al [19] showed that resistin levels were higher in neonates with PPRM than in those without PPRM. In addition, they observed that the mothers who administered antenatal steroids, their babies had lower resistin levels than those whom their mothers did not receive steroids. Therefore, they suggested that elevated resistin levels in babies with PPRM is due to the effect of fetal inflammation on resistin while the suppressed levels in babies whose mothers received antenatal steroids is due to the anti-inflammatory effect of steroids. In another study done by Gokmen et al [20] to evaluate the diagnostic value of resistin in neonatal sepsis in premature infants, they reported that the basal serum resistin levels were significantly lower than the pretreatment and follow up levels in both EOS and LOS groups and was significantly correlated with CRP levels. The diagnosis of neonatal sepsis is hard due to vague clinical symptoms and signs. Therefore, reliable biomarkers of sepsis can be helpful in the accurate diagnosis, resulting in a decrease in the unnecessary use of antibiotics and improvement in the outcome of neonates with sepsis. In this study, we investigated the use of resistin in the diagnosis of neonatal sepsis and compared it with CRP as a known marker of sepsis. The cutoff value for resistin that can be used to discriminate the babies with sepsis from healthy babies was found to be 76 ng/mL. The sensitivity, specificity, positive, and negative predictive values for this cutoff value were found to be 100%, 93%, 76%, and 100%, respectively. The area under the curve was 1.00 for resistin.

Conclusion

In conclusion, plasma-resistin levels were significantly increased in neonates with sepsis. Increased levels of resistin and correlations found with the CRP and TLC levels suggest that resistin may be used as an indicator of neonatal sepsis.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

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