RESEARCH BRIEF

Prognostic Value of Plasma Pro-Adrenomedullin and Antithrombin Levels in Neonatal Sepsis

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The aim of this study was to clarify the prognostic value of serum pro-Adrenomedullin level (pro-ADM) and Anti thrombin level in neonatal sepsis. 40 term neonates with sepsis were enrolled in this study including 20 cases with mild sepsis and 20 cases with severe sepsis. Twenty healthy matched neonates served as a control group. Serum levels of Pro ADM and Antithrombin were measured in all patients and the control group. Serum Pro ADM level was higher in neonates with sepsis than control group, higher in severe than mild sepsis, and was higher in non survivors. Antithrombin concentrations were lower in sepsis cases than control, lower in severe than mild sepsis, and lower in non-survivors.

Key words: *Antithrombin, Neonate, Pro-adrenomedullin, Prognosis, Sepsis.*

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Neonatal sepsis is a significant cause of morbidity and mortality in neonates [1]. Quantification of adrenomedullin (ADM) could be helpful in diagnosis, monitoring of sepsis and in the prognosis. Unfortunately, reliable measurement of ADM is almost impossible, as it is rapidly cleared from the circulation [2]. Recently, the more stable midregional fragment of pro-adrenomedullin, which directly reflects levels of the rapidly degraded active peptide ADM, has been detected in plasma of patients with septic shock [3]. Antithrombin is a potent inhibitor of thrombin-mediated vascular injury in the microcirculation during severe sepsis [4]. The aim of this study was to find out prognostic value of serum ADM and Antithrombin level in neonatal sepsis.

METHODS

Forty term neonates with sepsis were eligible for the study including 20 cases with manifestations of mild sepsis and 20 cases with severe sepsis. All were admitted to NICU, Tanta University Hospital. Twenty healthy neonates of matched gestational age and birthweight served as control group. This work was done with the approval of Research Committee, Tanta University Hospital. For all cases and controls, complete blood picture, C-reactive protein (EMIT; Merck Diagnostica, Zurich, Switzerland) and blood and urine cultures were obtained. CSF analysis and cultures, and plain *X*-ray chest were done in septic neonates only. *Serum pro-ADM concentration*: Blood samples were obtained before starting antibiotic therapy, separated into plasma and frozen to –70ºC. Measurements were done in a blinded manner as a batch analysis. Pro-ADM was detected in EDTA plasma of all patients using a new sandwich immunoassay (B.R.A.H.M.S. Sevadil LIA; B.R.A.H.M.S., AG, Hennigsdorf/Berlin, Germany), [5]. *Serum antithrombin concentration*: Determination was done by using a functional activity assay. The residual enzyme was measured by a clotting-based assay or by using chromogenic peptide substrates [6].

TABLE I DEMOGRAPHIC DATA OF STUDIED CASES

Patient information	Mild sepsis *n*= 20	Severe sepsis *n*= 20	Control *n*= 20	P value
Gestational age (wk)	38.85±0.88	38.75±0.97	38.9±0.64	0.84
Birth weight (kg)	3.175± 0.28	3.24± 0.25	3.26± 0.24	0.78
Total leucocyte count	9 ±3 ×10^3	10 ±4×10^3	8 ±2×10^3	0.14
ANC	2973±739	2835±822	3345±719	0.1
Immature/total ratio	0.35±0.1	0.4 ±0.1	0.15 ± 0.01	0.29
Platelet count[§]	140±20×10^3	110 ±20×10^3	290 ±20x10^3	0.0001
Serum Pro-ADM	0.086±0.96	3. 94 ±1.78	8.98±2.91	0.05*[$]
Serum Anti-thrombin	28.89±2.60	16.57±1.64	11.29±1.43	0.05*[$]

*[§]There were statistically significant differences in platelet count between septic neonates and control group (P<0.05); *mild cases versus control, [$]mild cases versus severe, [õ] severe cases versus control, ‡ P value < 0.05; ANC (absolute neutrophil count).*

RESULTS

The three study groups are compared for their demographic and clinical characteristics in Table I. Serum Pro ADM were significantly higher in neonates with mild and severe sepsis versus control (P<0.05). Serum ADM were significantly higher in neonates with severe versus mild sepsis (P<0.05). Serum antithrombin levels were significantly lower in neonates with mild, severe sepsis versus control (P<0.05) Also serum Antithrombin levels were significantly lower in neonates with severe versus mild sepsis (P<0.05). (***Table* I**). Serum pro-ADM levels were significantly higher in neonates who did not survive (P<0.05). Serum antithrombin levels were significantly lower in neonates who died. (***Table* II**). There was significant negative correlation between the plasma ADM levels and survival rate in sepsis cases [r = 0.67, P<0.05]. There was significant positive correlation between the plasma Antithrombin levels and survival in neonatal sepsis [r =1, P<0.01].

DISCUSSION

In this study we found a significant increase in pro-ADM in the plasma of septic patients as compared with controls. This was in agreement with previous studies [7,8], but in contrast to Christ-Crain, *et al.* [9] who found the circulating levels of ADM only modestly elevated and not significantly different between patients with SIRS and those with sepsis, prohibiting its use as a diagnostic tool. In contrast, they found that circulating levels of pro ADM vary to a much greater extent between health and disease with significantly higher levels in patients with sepsis who did not survive than in survivors and concluded that pro ADM can be used as predictor of outcome in sepsis.

In this study, initial Antithrombin levels were significantly lower in neonates with mild and severe sepsis versus control, significantly lower in neonates with severe versus mild sepsis and significantly lower in non survivor in contrast to survivor cases. These results were in agreement with [10] who found that newborns with lower AT levels initially, had a higher rate of developing DIC and death. Similar results were obtained by [11] in adult sepsis. Many previous adult studies have reported that initial AT levels of patients with sepsis who developed septic shock and DIC are an indicator of prognosis and cases with very low AT levels have a

TABLE II COMPARISON BETWEEN PRO ADM, ANTITHROMBIN AND CRP IN NEONATES WITH SEPSIS WHO SURVIVED AND WHO DID NOT SURVIVE

Parameters	Survived cases (*n*=32)	Non survived cases (*n*= 8)	*P*
Pro-ADM (nmol/L)	5.22 ± 2.24	11.40 ± 3.09	<0.05
CRP (mg/L)	73.09 ± 22.71	78.37 ± 15.23	>0.05
Antithrombin (mg/dL)	14.97 ± 2.46	9.75 ± 0.87	<0.05

WHAT THIS STUDY ADDS?

- Both Pro-ADM and AT levels can be useful markers in predicting clinical outcome in neonatal sepsis.

higher mortality rate; moreover, significantly lower initial AT levels in patients who did not survive compared to the survivors [12].

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