Serum Amyloid A an Early Diagnostic Marker for Neonatal Sepsis

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Abstract: 100 term neonates were included in the study. 50 neonates with clinically suspected sepsis, in which blood culture, SAA measurement, CRP, CBC, were done for all neonates when sepsis was first suspected (Reading A) and 48 hours post sepsis evaluation (Reading B). The other 50 matched neonates served as a control group and the same investigations were done once for all of them, during routine follow-up or bilirubin evaluation. **Patients and Methods:** Of 50 neonates with clinically suspected sepsis, 41 had positive blood culture (septic group) and 9 had negative blood culture (non-septic group). The SAA levels of septic group were significantly higher than those of the control and non-septic group ($p<0.001$) at Reading A. in comparison with CRP, SAA levels rose earlier and in a sharper manner, had the higher levels and returned faster to normal. **Results:** When sepsis was first suspected (Reading A), SAA had an overall diagnostic accuracy for early diagnosis of neonatal sepsis (97.6%), compared to CRP (36.6%). Statistical evaluation of SAA testing showed a sensitivity of 97.6%, specificity of 88.9%, positive predictive value of 97.6%, negative predictive value of 88.9%, and test efficiency of 96% in diagnosing of neonatal sepsis.
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1. Introduction

Neonatal sepsis is one of the leading causes of morbidity and mortality among the newborns. As many as 2% of fetuses are infected in utero and up to 10% of infants are infected during delivery or the first month of life **(Gonzalez et al., 2004).**

Serum Amyloid A (SAA) proteins comprise a family of apolipoproteins synthesized in response to cytokines released by activated monocytes, macrophages in a number of different inflammatory process **(Malle and DeBeer, 1996).**

Serum Amyloid A (SAA) was found to be increased in bacterial and fungal infections, invasive malignant disease, tissue injurie in the acute myocardial infarction and autoimmune diseases such as rheumatoid arthritis and vasculitis **(Jovanovic, 2004).**

The aim of the study was to evaluate the diagnostic value of serum Amyloid A as an early diagnostic marker for neonatal sepsis.

2. Subjects and Methods:

Subjects:

The study included 100 term neonates, 50 in the study group and 50 healthy neonates as control group. The study group (suspected group) included 50 neonates with maternal and neonatal criteria suggestive of sepsis. This study is a case control study conducted on a group of neonates admitted into NICU of El-Galaa Teaching Hospital in Cairo. The maternal criteria are intra partum fever, premature rupture of membrane (PROM) more than 18 hours and foul smelling amniotic fluid. The neonatal criteria are temperature instability (<36.5°C or >37.5°C), poor skin perfusion (capillary refill >3 seconds), poor activity and crying, poor suckling reflex, poor Moro's reflex, apnea or respiratory distress, pallor, lethargy or irritability, bradycardia and abdominal distention and vomiting. We excluded any case with traumatic tissue injury, congenital anomalies, metabolic liver disease and history of perinatal, natal and postnatal asphyxia.

According to blood culture results, the suspected group (50 neonates) was subdividual into two subgroups, septic subgroup (41 neonates) they are infants with clinical and biochemical evidence of infection and positive blood culture.

Non-septic subgroup (9 neonates) they are infants who suspected of having sepsis initially, but with negative blood culture and no evidence of localized infection such as pneumonia or NEC.

The control group includes 50 healthy neonates, age and sex-matched in whom serum Amyloid A (SAA) and C-reactive protein (CRP) were measured during routine blood sampling for biochemical or heamatological tests.

Methods:

All cases were subjected to the following:

- Careful history taking including, natal history.
- Full clinical examination for early detection of manifestations of neonatal sepsis.

- Assessment of gestational age by using new Ballard Score **(Ballard, 1991).**
- Anthropometric measurements including bodyweight, length and skull circumference.
- Laboratory investigations:

Two consecutive blood samples were collected from the suspected cases and one sample were taken from the control cases. The first sample (Reading A) when the sepsis was first suspected. The second sample (Reading B) after 48 hours from the first sample. The blood samples were investigated for complete blood picture (CBC), quantitative C-reactive protein (CRP), blood culture and serum Amyloid A (SAA) level measured by an immunoenzymometric assay using human SAA Elisa Kit **(Biosource Europe S.A., Belgium).**

Statistical Analysis:

Results are expressed as mean ± standard deviation (SD) or number (%). Comparison between the mean values of different variables in Reading A and Reading B in septic group was performed using paired student t-test. Comparison between the mean values of the different variables in the two groups was performed using unpaired student t-test SPSS computer program (version 12 windows) was used for data analysis.

3. Results:

The septic subgroup, the frequency of clinical manifestations were increased gradually with progress of illness from Reading A (when the sepsis was first suspected) to Reading B (after 48 hours from Reading A). There was a significant increase of the frequency of manifestation as regard poor Moro, poor suckling, lethargy, respiratory distress, and feeding intolerance as shown in table (1).

Table (1): Comparison between clinical findings among septic subgroup when the sepsis was first suspected (Reading A) and after 48 hours (Reading B).

Characteristics	Reading A	Reading B	P.value	Sig.
Poor Moro	20 (48.8%)	39 (95.1%)	0.000	HS
Poor sucking	22 (53.7%)	37 (90.2%)	0.000	HS
Hypotonia	7 (17.1%)	11 (26.8%)	0.286	NS
Lethargy	14 (34.1%)	35 (85.4%)	0.000	HS
Convulsions	1 (2.4%)	3 (7.3%)	0.305	NS
Apnea	9 (22%)	9 (22%)	1.0	NS
Respiratory distress	17 (41.5%)	30 (73.2%)	0.004	S
Bradycardia	7 (17.1%)	7 (17.1%)	1.0	NS
Hypothermia	9 (22%)	8 (19.5%)	0.785	NS
Poor skin perfusion	12 (29.3%)	14 (34.1%)	0.635	NS
Jaundice	6 (14.6%)	6 (14.6%)	1.0	NS
Pallor	4 (9.8%)	3 (7.3%)	0.693	NS
Abdominal distension	12 (29.3%)	13 (31.7%)	0.810	NS
Feeding intolerance	13 (31.7%)	23 (56.1%)	0.26	S

Value are expressed as number

NS = Non-significant HS = Highly significant S = Significant

Blood culture was done for all cases of the suspected group. According to the blood culture results, they were subdivided to non-septic group with negative blood cultures (9 cases) and septic group (41 cases) with positive cultures.

Gram negative organisms were predominant in 28 cases (68.3%), they were klebsiella 16 cases (39%), pseudomonas 5 cases (12.2%), Escherichia coli 4 cases (9.8%) and enterobacter 3 cases (7.3%). On the other hand gram positive organism were cultured in 13 cases (31.7%) of the septic group, mainly staphylococcus aureus 6 cases (14.6%), stephalococcus coagulase negative 5 cases (12.2%), and streptococcus pneumoniae 2 cases (4.9%), as shown in table (2).

Table (2): Distribution of the blood cultured organisms among the septic group (n=41).

Organism	No. of cases	%
• **Gram negative organism:**	28	68.3%
- *Klebisella*	16	39%
- *Pseudomonas*	5	12.2%
- *E.coli*	4	9.8%
- *Enterobacter*	3	7.3%
• **Gram positive organism:**	13	31.7%
- *Staph. aureis*	6	14.6%
- *Staph. coagulase negative*	5	12.2%
- *Srept. pneumonie*	2	4.9%

Different laboratory parameters were studied in the three groups, when sepsis was first suspected (Reading A), as shown in table (3).

Table (3): Laboratory data of the studied groups (when sepsis was first suspected = Reading A).

Variable		Control (n=50)	Suspected group (n=50)		P. value	Sig.
			Septic subgroup (n=41)	Non-septic subgroup (n=9)		
Hb (gm/dL)	Range Mean ± SD	11.5 – 20.7 15.8±1.99	8.2 – 17.8 13.49±2.42	12.8 – 18.6 16.04±1.86	0.000	HS
Platelets ($x10^3$/cm)	Range Mean ± SD	112 – 268 192.74±28.4	38 – 237 155.94±44.92	168 – 213 191.33±14.72	0.000	HS
TLC ($x10^3$/cm)	Range Mean ± SD	8.9 – 18.3 13.20±2.23	5.3 – 22 14.25±04.72	11.7– 19.2 15.27±2.42	0.000	NS
Immature neutroph. ($x10^3$/cm)	Range Mean ± SD	1 – 7 2.9±1.47	3 – 20 8.37±03.94	3 – 9 5.89±2.03	0.000	HS
Total neutroph. ($x10^3$/cm)	Range Mean ± SD	24– 45 34.56±5.65	32 – 69 42.56±9.25	29 – 40 34.44±4.1	0.000	HS
I/T ratio	Range Mean ± SD	0.3 – 0.18 0.08±0.03	0.08 – 0.31 0.19±0.06	0.1 – 0.23 1.17±0.04	0.000	HS
I/M ratio	Range Mean ± SD	0.3 – 0.22 0.09±0.04	0.08 – 0.45 0.24±0.09	0.11 – 0.29 0.2±0.06	0.000	HS
Degenerative changes	No. (%)	0	3(7.3%)	0	0.000	NS
HSS	Range Mean ± SD	0 – 2 0.42±0.58	0 – 5 2.46±1.36	0 – 3 1.22±0.83	0.000	HS
CRP (mg/L)	Range Mean ± SD	0 – 6 0.12±0.85	0 – 48 7.17±10.58	0 – 6 2.67±3.16	0.000	HS
SAA (µg/m)	Range Mean ± SD	0 – 9 3.16±2.97	8-245 – 6 116.8±54.04	4 – 17 7.78±03.77	0.000	HS

HS = Highly significant NS = Non significant

- **The CRP level** ranged from 0-6 mg/L with a mean of 0.12±0.85 in control group, increased in septic group and ranged from 0-48 mg/L with a mean of 7.17±10.58, and finally it ranged from 0-6 mg/L in non-septic group with a mean of 2.67±3.16 (table 3).

When comparing the CRP level between septic and control group, there was a highly significant difference (p=0.000), but no significant difference between septic and non-septic groups (p=0.079), and between control and non-septic groups (p=0.309) (table 3)

- As regard **Hematological scoring system of sepsis (HSS)**, there was statistically significant difference between septic and control group, and septic and non-septic group (p=0.000) (table 3).
- Newborns of the septic group had a higher levels of **Serum Amyloid A (SAA)** ranged from 8-245 µg/ml. with a mean of 116.8±54/04, while in the control group, it ranged from 0-9 µg/ml, with a mean of 3.16±2.97. In the non-septic group, it ranged from 4-17 µg/ml, with a mean of 7.78±3.77 (table 3).

As regard SAA levels, there was a highly significant statistical difference between septic group and both non-septic and control groups (p=0.000), while there was no statistically significant difference between control and non-septic groups (p=0.715) (table 3).

A comparative study was done in between the mean values of different hematological parameters among the septic neonates with progress of illness.

Table (4): Comparison of the laboratory data of the septic group when sepsis was first suspected (Reading A) and after 48 hours (Reading B).

Variable		Suspected group (n=41)		P. value	Sig.
		Reading A	Reading B		
Hb (gm/dL)	Range Mean ± SD	8.2 – 17.8 13.49±2.42	8 – 16 12.5±2.08	0.001	HS
Platelets (x10^3/cm)	Range Mean ± SD	38 – 237 155.94±44.92	48 – 211 138.24±41.73	0.001	HS
TLC (x10^3/cm)	Range Mean ± SD	5.3 – 22 14.25±04.72	4.2– 23 15.45±5.33	0.001	HS
Immature neutroph. (x10^3/cm)	Range Mean ± SD	3 – 20 8.37±03.94	7 – 23 11.88±3.97	0.001	HS
Total neutroph. (x10^3/cm)	Range Mean ± SD	32 – 69 42.56±9.25	29 – 72 45.17±8.56	0.001	HS
I/T ratio	Range Mean ± SD	0.08 – 0.31 0.19±0.06	0.17 – 0.40 0.26±0.06	0.001	HS
I/M ratio	Range Mean ± SD	0.08 – 0.45 0.24±0.09	0.2 – 0.67 0.36±0.11	0.001	HS
Degenerative changes	No. (%)	3(7.3%)	12(29.3%)	0.001	S
HSS	Range Mean ± SD	0 – 5 2.46±1.36	2 – 6 4.07±0.99	0.10	HS
CRP (mg/l)	Range Mean ± SD	0 – 48 7.17±10.58	12 – 192 47.41±44.98	0.001	HS
SAA (µg/m)	Range Mean ± SD	8-245 116.8±54.04	0 – 73 20.39±17.40	0.001	HS

HS = Highly significant S = Significant

From table (4), there was a highly statistically significant different (p<0.001) in all hematological parameters if we compare the results of Reading A and Reading B.

Among the septic neonates (n-41), a comparative study was done between the sensitivity of the results of SAA, CRP, and HSS (using cross tab) in diagnosing neonatal sepsis.

Table (5): Comparison between laboratory results of SAA, CRP and HSS for early diagnosis of neonatal sepsis.

	Reading A	Reading B
CRP (mg/L)	15/41 (36/6%)	41/41 (100%)
SAA (µg/ml)	40/41 (97.6%)	25/41 (61%)
Heamtological sepsis scoring	11/41 (26.8%)	32/41 (78%)

Statistical evaluation of SAA testing as an early diagnostic parameter of neonatal sepsis showed a sensitivity of 97.6%, specificity of 88.9%, positive predictive value (PPV) of 97.6%, negative predictive value (NPV) of 99.9%, and test accuracy of 96%.

Table (6): Accuracy of SAA in diagnosis of neonatal sepsis in suspected group (after using blood cultures as standard test).

	Blood culture +ve	Blood culture -ve
SAA +ve	40 TP	1 FP
SAA –ve	1 FN	8 TN

4. Discussion

In this study, analysis of maternal and obstetrical data revealed that the most important risk factors for sepsis was premature rupture of membrane (PROM) and maternal fever. Maternal fever was found in 14.6% of septic subgroup and PROM was found in 12.2% of them. This agrees with **Ahmed et al (2002)** who found PROM in 11.9% of cases' and maternal fever in 6.8% cases. In a study done by **Veskari et al. (2000),** PROM was found in 19% of cases.

On clinical evaluation of the septic group, poor suckling, poor Moro, respiratory distress, and lethargy were the commonest clinical presentations at early suspicion of sepsis (Reading A) (54%, 49%, 42%, and 34% respectively), **Fathy et al. (2009)** found RD, poor Moro and suckling, and lethargy in 65%, 60%, and 550/0 respectively, that is slightly higher than our results.

Respiratory symptoms in this study was RD in 41.5% and apnea in 22% of cases. **Gotoll (2000),** stated that, RD in the form of apnea, mild tachypnea, increase in oxygen requirement, and severe RD requiring mechanical ventilation (MV) occurs in 90% of infants with sepsis.

In the present study; gastrointestinal manifestations of sepsis, mainly in the form of abdominal distension were found in 29.3% of cases, while feeding intolerance and jaundice occurred in 31.7% and 14.6% of cases, respectively. **Cloherty et al. (2004),** found abdominal distension in 45% of cases of neonatal sepsis. It might be due to NEC or toxic ileus which was reported to be frequently associated with sepsis **(Roberton, 2002).**

It was also found that the clinical manifestations of neonatal sepsis were increased gradually with progress of illness. In reading A, poor suckling, poor Mora, RD, and lethargy were found in 54%, 41%, 42%, and 34% of cases respectively. While in reading B (after 48 hours) the same manifestations were found in 90%, 95%, 73%, and 85% respectively. This agrees with **Weisman et al. (1992)** who stated that the early symptoms and signs of neonatal sepsis are usually delayed and non-specific.

Blood culture is the gold standard method for isolation of the organisms, and it should be obtained before the initiation of antibiotics. There is no laboratory test having 100% sensitivity and specificity for diagnosis of neonatal sepsis with the exception of blood culture **(Buttery, 2002)**

In the present study, Klebseilla was the dominant organism isolated from the blood of infected group (39%), followed by Staph. aureus (14.6%), Pseudomonas (12.2%), Coagulase-negative Staph. (12.2%), E.coli (9.8%), Enterobacter (7.3%), and Strept: pneumoniae (4.9%).

These results were in agreement with other several studies done by **Fathy et al., (2009); Badrawi et al., (2005); Abou Hussein et al., (2005 and Hashim et al. (2004),** who reported that Klebseilla is the commonest isolated organism in septic newborns, with a ratio ranging from 35-56% of all isolated organisms.

In our study, the findings of total leucocytic count (TLC) were not informative for the diagnosis of neonatal sepsis. There was non-significant difference in TLC between septic and control groups. This was in concordance with **Thurlbeck and Meintoch (2002),** who stated that, TLC is the least useful index for sepsis because the normal range is so wide, varies with gestational and postnatal age.

In the present study, HSS was positive (score above 3) in only 26.85% of septic neonates when sepsis was first suspected, and became positive in 78% of them after 48 hours, not to be considered as an early marker for sepsis diagnosis.

This was in agreement with **Awad et al. (2002),** who found a positive HSS in 13.3% of septic neonates when the sepsis was suspected~ and 73.3 % of the same cases after 48 hours.

In our study, there was a highly significant increase of CRP level between septic and control groups, and this agrees with the results of **Fathy et al. (2009), Abou Hussien et al., (2005).**

CRP was positive (>6 mg/L) in 36.6% of septic neonates in reading A and 100% in reading B. This was in concordance with **Awad et al., (2002),** who found positive CRP in 26.7% in early readings and became 100% after 48hours.

In **2007, Arnon et al.** found that SAA, is an early and accurate marker of neonatal early-onset sepsis (EOS).

In the present study, we tested the diagnostic accuracy and the dynamics of SAA during neonatal sepsis in term neonates.

The findings of our study revealed that serum concentrations of SAA were significantly elevated in septic group, compared to non-septic and control groups.

The mean value of SAA in septic group was (116.8±54 μg/ml), compared to control group (3.16±2.97 μg/ml), and this was proved highly statistically significant ($p<0.001$). This was in agreement with **Arnon et al. (2002)** who found the mean value of SAA among septic group (187.6±78.3 μg/ml) compared to (10.2±8.3 μg/ml) of the non-septic group. Also, **Arnon et al. (2005)** found that the median value of SAA among septic group was 122 μg/ml which was significantly higher than the level of the control group 6 μg/ml.

If we are comparing the results of SAA among the septic group when the sepsis was suspected (Reading A) and after 48 hours (Reading B), there was a highly statistical significant difference in between both readings. The mean value of SAA in reading A was 116.8±54 μg/ml, while the mean value of SAA in reading B was 20.4±17 μg/ml. This was in agreement with **Litmanovitz et al. (2007),** who stated that SAA is more sensitive at onset of sepsis, rose earlier and in a sharper manner, had higher levels and returned faster to normal values in infants who recovered. Same results were found by, **Arnon et al., (2005),** who found that the medians of SAA at sepsis onset was 122 (79-185 μg/ml) compared to 16 (4-29 μg/ml) 48 hours after sepsis onset.

Compared with CRP, SAA was positive (≥10 μg/ml) in 97.6% of septic group in reading A and 61 % of cases in reading B, while CRP was positive (>6 mg/l) in only 36.6% of septic group in reading A and 100% of cases in reading B.

This results was in agreement with the findings of **Litmanovitz et al. (2007),** who stated that SAA was more sensitive than CRP at onset of sepsis. In a study done by **Arnon et al. (2007),** SAA was sensitive in 96% of septic group at onset of sepsis, compared to 30% sensitivity of CRP at the same time.

In our study, at a cut-off value of SAA ≥10 μg/ml, the sensitivity of measuring SAA level was 97.6%, specificity was 88.9%, positive predictive value (PPV) was 97.6%, negative predicative (NPV) was 88.9%, and test accuracy was 96% in diagnosis of neonatal infection when the sepsis was suspected.

On the same cut-off value of SAA, **Arnon et al., (2007)** found a sensitivity 96%, specificity 95%, PPV 85%, and NPV 99% at onset of sepsis.

From the results, we can concluded that SAA seems to be an early, highly sensitive and specific marker for the diagnosis of neonatal sepsis at the first suspicion of infection, especially if compared to diagnostic accuracy of CRP and HSS at this time. The Quick and reliable use of SAA in early diagnosis of neonatal sepsis can be useful in; early initiation of antibiotic treatment, duration, response, and outcome after therapy.

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