THE PREDICTIVE VALUE OF ALPHA 1 ACID GLYCOPROTEIN IN DIAGNOSIS OF NEONATAL SEPSIS

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ABSTRACT

Background: Neonatal sepsis is an important cause of morbidity and mortality despite the major advances in the management ***(Stoll, 2004).***

Objective: We aimed to evaluate the predictive value of alpha1-acid glycoprotein (alpha1AG) in the early diagnosis of neonatal sepsis.

DESIGN: This case control study was conducted among newborn admitted to neonatal intensive care unit (NICU) of Sayed Galal University Hospital.

Patient And Methods: A total of 90 newborn , 30 with confirmed sepsis by blood culture and laboratory investigation (Group I), 30 with clinically suspected sepsis (Group II), and 30 as a control group (Group III) were enrolled in the study. On admission to NICU, blood was taken for CRP, blood culture, and alpha1AG before starting antibiotic therapy.

Results: We found that serum level of Alpha-1acid glycoprotein was highly significant between clinically suspected septic(Group II) and control groups(Group III) (p=0.00) and highly significant between confirmed septic(Group I) and control groups(Group III) (p=0.00).In the present study the sensitivity, specificity, positive and negative predictive values of alpha 1 acid glycoprotein at cut of value 136ng/ml were found to be 93%, 91.3%, 93.1%, 66.4%, respectively.

Conclusion: Alpha-1-acid glycoprotein has high sensitivity and specificity in early diagnosis of neonatal sepsis.

Keywords: Alpha-1-acid glycoprotein, Neonatal sepsis.

INTRODUCTION

Sepsis is one of the most common infectious conditions in the neonatal period, and remains a major source of morbidity and mortality despite extraordinary progress in the field of neonatology in recent years ***(Campos, et al., 2010).*** According to the world health organization (WHO), neonatal deaths 2.6 million in 2016 ***(UN IGME, 2017).***

Neonatal sepsis may be categorized as early or late onset. 85% of newborns with early onset infection present within 24 hours, 5% present at 24-48 hours, and a smaller percentage of patients present within 48- 72 hours. Onset is most rapid in premature neonates. Early onset sepsis syndrome is associated with acquisition of microorganisms from the mother. Transplacental infection or ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary tract, with acquisition of the microbe by passage through a colonized birth canal at delivery ***(Klinger, et al 2009).***

Blood culture tests are still considered the gold standard for the diagnosis of sepsis although results are not available until at least 48 hour. There is a need for an effective and accurate biochemical marker to support or exclude the diagnosis of infection. Hematological indices, acute phase reactants, protein markers, and cytokines have been extensively examined as adjunctive tests for diagnosis of sepsis. None have shown sensitivity, specificity, positive predictive values (PPV), or negative predictive values (NPV) that can sufficiently guide clinical management ***(Bhandari, et al, 2008).***

A number of plasma proteins collectively termed acute phase proteins show a dramatic increase in concentration in response to infection or tissue injury. Acute phase proteins include α**1**-protease inhibitor, α**1**-acid glycoprotein, ceruloplasmin, C-reactive protein, fibrinogen and habtoglobin ***(Peter, et al. 2011).***

Alpha-1acid glycoprotein (α1AGP) is an acute –phase serum protein that is produced by the liver in response to inflammation and infection. It is a 183 amino acid protein with five N-linked glycans that comprise 45% of its 43 KDa mass. Alteration of N-glycosylation is associated with certain pathophysiological states. Alpha-1 acid glycoprotein belongs to the lipocalin family and binds numerous basic and neutral lipophilic drugs and steroid hormones ***(Colombo, et al.,2006).***

METHODS

This is case control study; it was carried out in the neonatal intensive care unit of Sayed Galal University Hospital, in the period from October 2016 to April 2017.The cases were selected by simple random method.

Patients:

Ninety neonates admitted to NICU were included in the study

and enlisted to one of 3 groups as following:

- **Group1 (confirmed septic group):** included 30 neonates admitted to neonatal intensive care unit (NICU) with sepsis proved with clinical & laboratory investigations (hematological sepsis score > 5 and positive blood culture).
- **Group2 (suspected septic group):** included 30 neonates admitted to NICU with clinical manifestation of sepsis (hematological sepsis score 2-5and negative blood culture).
- **Group3 (control group):** included 30 full healthy neonates enrolled from neonatal care clinic as a control group.

Inclusion criteria

● Term and preterm neonates with symptoms and signs of sepsis (confirmed and suspected sepsis).
● Signs of sepsis 3 or more of the following clinical manifestation:
- Temperature instability (<37ºC or >38.5ºC)
- Respiratory signs: increased oxygen requirement, apnea, cyanosis, intercostal retraction, tachypnea or grunting
- Circulatory signs: weak pulses, prolonged capillary refilling time >2 second, hypotension, tachycardia or shock.
- GIT signs: abdominal distention, diarrhea, bloody stool, feeding intolerance, hepatomegaly or jaundice.
- Neurological signs: irritability, hypotonia or lethargy.
- Hypoglycemia or hyperglycemia.
- Petechiae, bleeding (with thrombocytopenia) or DIC ***(Richard and Joan, 2008*)**.

Exclusion criteria

● Extreme low birth weight (ELBW).
● Age > 28 day.

All neonates were subjected to the following

Complete clinical history taking

Complete clinical examination:

Laboratory Investigations including:

1. Complete Blood Cell Count (CBC) with differential count by an automated cell counter (Abbott Cell-Dyn 1700, Abbott laboratories, USA).
2. Blood film.
3. Blood culture.
4. Plasma CRP concentration measured using an immuno-

turbidimetric method (Human, Diagnostic, Wiesbaden, Germany).

5. Alpha -1- acid glycoprotein measured by ELISA technique, manufactured by Bioneovan Co., Ltd., China.

Evaluation of sepsis: occur according to the scoring system for sepsis. ***(Khalada et al., 2010).***

Table (1): Sepsis score (*Hematologic scoring system*)

Points	Abnormality	Score
Total neutrophil count	< 1750 /cmm Or > 7500 to 8500 /cmm	1
Immature neutrophil count	>400 /cmm	1
(I/T) ratio	>0.16 at birth or 0.13 beyond 72 hours >0.2 as a maximal normal ratio	1
(I/M) ratio	> 0.3	1
Total WBC count	< 5000 /cmm Or > 25000 /cmm 12-24 hours Or > 21000 /cmm on day 2	1
Degenerative changes in neutrophils as toxic granulations or Dohle bodies	If present	1
Platelet count	< 100, 000/ mm3	1

Score less than 2: sepsis is very unlikely to occur**.**

Score from2- 4: sepsis is suspected to occur.

Score more than 5: sepsis is very likely to occur.

Ethical consideration:

- Approval of the ethical committee in the pediatrics department and university was obtained before the study.
- No conflict of interest either financial or commercial.
- Caregiver consent and approval for the study was obtained before the study

RESULTS

Table (2): Gender and mode of delivery among the studied groups.

Demographic data		suspected sepsis group (II) (No.=30)		Confirmed sepsis group (I) (No.=30)		Control group (III) (No.=30)	
		No.	%	No.	%	No.	%
Gender	Male	18	60.0	17	56.7	17	56.7
	Female	12	40.0	13	43.3	13	43.3
Mode of delivery	NVD	20	66.7	21	70.0	13	43.3
	CS	10	33.3	9	30.0	17	56.7

This table shows male predominance in the studied groups, in septic groups babies born by NVD more than CS and in control group babies born by CS more than NVD.

Table (3): Weight and gestational age among the studied groups.

Demographic data		Suspected sepsis group (II) (No.=30)	Confirmed sepsis group (I) (No.=30)	Control group (III) (No.=30)	F test	P. value	LSD
Weight(kg)	Range	1-4	2-4	3-4	23.163	0.000	P1=.665 P2=.000 P3=.000
	Mean±SD	2.51±0.667	2.58±0.574	3.36±0.301			
Gestational age (wks)	Range	32-39	33-40	37-39	2.701	0.042	P1=.905 P2=.024 P3=.030
	Mean±SD	36.90±2.006	36.83±2.27	37.80±0.714			

P1=between suspected sepsis group and confirmed sepsis group.
P2= between suspected sepsis group and control group.
P3=between confirmed sepsis group and control group.

This table shows statistically significant difference between septic group and control group regarding weight and gestational age, and no statistically significant difference between suspected sepsis group and confirmed sepsis group regarding weight and gestational age.

Table (4): percentage of clinical presentation of septic neonates.

Clinical presentation of septic neonates		
	Frequency	Percent (%)

R. distress	56	93.3
T instability	23	38.3
Poor reflex	52	86.7
Lethargy	44	73.3
Feeding intolerance	38	63.3
Poor perfusion	23	38.3
Pallor	22	36.7
Abd distention	23	38.3
Hypoglycemia	7	11.7
Convulsion	10	16.7
Mottling	22	36.7
Bleeding tendency	19	31.7
Apnea	20	33.3
Sclerema	4	6.7
Cyanosis	17	28.3
Jaundice	23	38.3

This table shows the most clinical presentation of septic neonate were RD and poor reflex, and the least clinical presentation hypoglycemia, convulsion and sclerema.

Table (5): Blood culture of the confirmed sepsis group

blood culture		
	Frequency	**Percent (%)**
E. coli	4	13.3
Klebsiella	10	33.3
Pseudomonas	4	13.3
Staph. Aureus	12	40.0
Total	30	100.0

This table shows that the most common organism was Staph. aureus (40.0%) followed by Klebsiella (33.3%) in the proved sepsis group.

Table (6): Comparison between suspected sepsis group, confirmed sepsis group and control group regarding labs parameters.

Labs parameters	**Suspected sepsis**	**Confirmed sepsis group**	**Control group** (III)	**F. test**	**P. value**	**LSD**

		group (II) **(No.=30)**	(I) **(No.=30)**	**(No.=30)**			
CRP(mg/ml)	**Range**	18-190	12-256	0-3	43.335	0.000	P1=0.000
	Mean±SD	43.80±33.44	101.33±64.69	.60±.894			P2=0.000 P3=0.000
HB (gm / dl)	**Range**	9-17	8-26	13-17	9.141	0.000	P1=0.441
	Mean±SD	11.92±2.58	12.59±3.96	14.91±1.33			P2=0.000 P3=0.004
TLC ($mm^3/x10^3$)	**Range**	3-47	3-38	6-9	16.055	0.000	P1=0.915
	Mean±SD	17.01±9.41	17.26±8.54	7.83±.850			P2=0.000 P3=0.000
PLT ($mm^3/x10^3$)	**Range**	6-647	10-693	156-450	3.207	0.045	P1=0.221
	Mean±SD	185.17±203.03	250.20±204.29	297.70±81.29			P2=0.007
	Mean±SD	5.18±1.07	4.59±1.06	4.70±.423			P3=0.242

This table shows statistically significant difference between suspected sepsis group, confirmed sepsis group and control group regarding CRP. Also show statistically significant difference between septic groups and control group regarding HB, TLC and PLT and no statistically significant difference between suspected sepsis group and Confirmed sepsis group regarding HB, TLC and PLT.

Table (7): Comparison between suspected sepsis group, confirmed sepsis group and control group regarding alpha -1-acid glycoprotein and sepsis scoring.

		Suspected sepsis group (II) **(No.=30)**	**Confirmed sepsis group** (I) **(No.=30)**	**Control group** (III) **(No.=30)**	**F. test**	**p. value**	**LSD**
Alpha 1acid glycoprotein (ng/ml)	**Range**	336-720	769-7548	33-230	22.314	0.000	P1=.000
	Mean±SD	533.77±128.23	1725.77±1665.64	123.33±60.29			P2=.000 P3=.000
Sepsis scoring	**Range**	2-5	4-7	0-1	326.456	0.000	P1=.000
	Mean±SD	3.63±.890	5.30±.952	0.20±0.407			P2=.000 P3=.000

This table shows statistically significant difference between suspected sepsis group, confirmed sepsis group and control group regarding Alpha -1-acid glycoprotein and sepsis score.

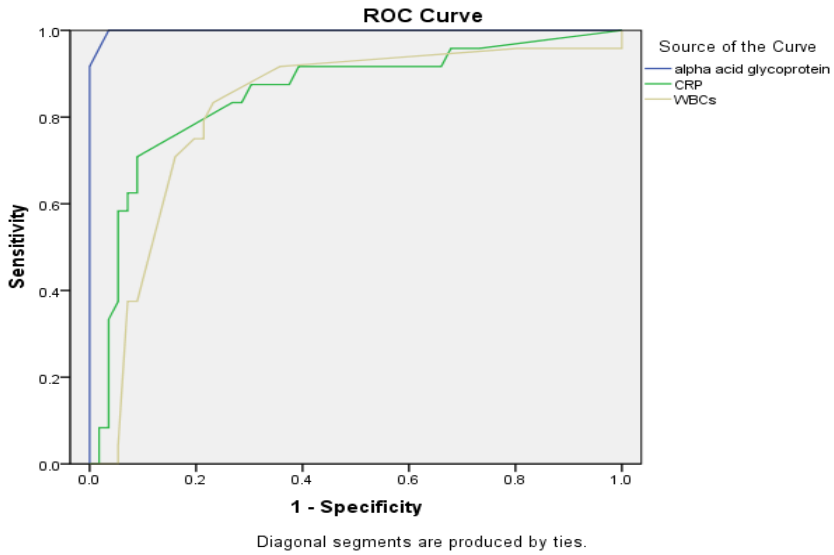

Figure (1): ROC curves for alpha acid glycoprotein CRP, and WBCs

Table (8): Sensitivity, specificity, PPV, NPV, Accuracy and Cut off of α-1-acid glycoprotein between septic group and control group.

Marker	Cut off value	AUC	Sensitivity %	Specificity %	PPV%	NPV%
α-1-acid glycoprotein(ng/ml)	136	0.99	93%	91.3%	93.1%	68.4%
CRP (mg/ml)	6	0.85	87.8%	84.8%	81.1%	67.7%
WBCs($mm^3/x10^3$)	11.5	0.81	83.3%	75.3%	81.1%	63.9%

Roc curve Figure (1) and **table (8)** shows cut off value of serum **α**-1- acid glycoprotein to detect sepsis136 ng/ml with sensitivity 93% and specificity 91.3%, also show cut off value of CRP to detect sepsis 6 mg/ml with sensitivity 87.8% and specificity 84.8% and cut off value of WBCs to detect sepsis11.5 with sensitivity 83.3% and specificity 75.3%.

DISCUSSION

In this study a male predominance was found in the studied groups as males represents 60% of the suspected septic group and 56.7% of confirmed septic group. This male predominance is apparent in almost all studies of

neonatal sepsis as in a study done by **Gerges, (2009**) who found that males represented 64% of septicemic group in his study and **Abdelfatah, (2005)** who found that males represented 57.7% of his cases.

Also **Abdul Salam (2011)** who found the males represented 55%, **ElGohary (2014)** who found males represent 51, 4%, and **El Bashir (2010)** who found males represent 55%. This may be due to gene located on the X chromosome which is involved with the function of the Thymus or with synthesis of immunoglobulins ***(Klein and Remington, 2001)***.

In this study, regarding the mode of delivery babies born by NVD are more than babies born by CS in both septic groups **(**NVD 20 (66.7%) in clinically suspected sepsis group and 21 (70.0%) in confirmed sepsis group**.** CS 10 (33.3%) in clinically suspected sepsis group and 9 (30.0%) in confirmed sepsis group**)**.

This agrees with **Stoll et al (2008)** who observed that babies born by NVD were more likely to have sepsis than those delivered by CS and **Wageah (2015)** who observed that babies born by NVD are more 66% in clinically suspected septic groups and 74% in confirmed septic groups. This may be due to the infant is colonized with the pathogen from birth canal ***(Gomella, 2013).***

The most common clinical finding among patients was respiratory distress (93.3%) followed by poor reflex (86.7%)، lethargy (73.3%), feeding intolerance (63.3%). **El-Kerdani et al., (2001)** found that weak reflexes followed by lethargy and respiratory distress were the most common clinical signs among neonates with sepsis as it was detected in 65% and 60% of their patients respectively.

However **Nabih et al., (2001)** found that 24% had respiratory distress, 88% were lethargic, 22% had apnea, 48% had hepatosplenomegally, 42% had abdominal distension, 12% had seizures and 56% had sclerema. **Ottolini et al (2003)** found that the most frequent sepsis signs and symptoms were tachypnea 58%, cyanosis 25% then lethargy 20%. **Kaseb et al (2004)** found 56.6% of cases had respiratory distress, 33.3% were lethargic, 16.6% apnea, 16.6% had abdominal distension, and 33.3% had convulsions of cases.

These differences may be explained by the difference in the causative organisms and the course of sepsis or due to non-specific symptoms and signs of neonatal sepsis.

In our study, TLC was significantly higher in confirmed septic group than in control group (P value <0.05) this comes in agreement with **Ahmed et al (2002), Elwan et al (2004), and Abou-Hussein et al (2005)** who mentioned in their studies that, TLC showed statistically significant difference between septic group and control group. However,**Hashim et al (2004), Ali (2006) and Fergany (2006)** found that TLC did not show any significant difference in patients with confirmed sepsis versus patients with no infection.

As regarding hemoglobin concentration, confirmed septic group tended to have lower concentration than control. This difference was statistically significant regarding Hb concentration (P value <0.05), this agrees with **El-Kerdani et al (2001)** who found significant anemia in neonates with proven sepsis.

As regards the type of bacteria isolated from blood cultures in the present study, Staph was found to be the main organism of the cultures growth. Staphylococci (40%), Klebsiella (33.3%), E-coli (13.3%) and pseudomonas (13.3%).

This agree with **Abdul Salam (2011)** who found that causative organism in 37% of the cases caused by staph, 27%caused by klebsiella, 17% by E Coli, and 12% by pseudomonas.

Furthermore **El Bashir (2010)** found that blood culture result in septic neonates the cause in 40% of the cases is staph, 25% klebsiella 15% streptococcus, and 15%caused by pseudomonas.

Moreover **El Gohary (2014)** found that blood culture of the study group showed that 25.7% were caused by staph, 17.1% caused by E Coli, 14% caused by streptococcus, 11.4% caused by klebsiella, and 8.6% pseudomonas.

Also **Ipek et al (2010)** found that themost common isolated microorganism was staphylococcus aureus, and **Kaseb et al., (2004)** found that gram-positive bacteria accounts for the majority of the culture growth, staph was isolated in 40%, on the other hand Klebsiella was found in 36.7%, and E.coli in 6.7%.

The predominance of gram-positive bacteria in this study was against some previous study done in Egypt by ***Ahmed et al., (2002)*** who found that gram-negative bacteria accounts for the majority of the culture growths (55.9% *enterbacteria*, 20.3% *pseudomonas* and 15.3% *Klebsiella*). These findings prove that every neonatal unit has its own pattern of

microorganisms, which change from time to time, and antimicrobial combinations should be altered according to culture results.

In our current study it was found that CRP was significantly higher in septic group than control group (p=0.00). This was in agreement with **Linda (2006)** who found that CRP was significantly higher in case group than control group. Similarly, **Ipek et al (2010)** carried out a study on 105 neonates and found that there were significant differences between groups for CRP level.

In the present study the sensitivity, specificity, positive and negative predictive values of α-1acid glycoprotein at cut off value 136 ng/ml were found tobe 93%, 91.3%, 93.1%, 66.4%, respectively.

Which agree with other previous studies:

Ipek et al (2010) found that sensitivity 56.25% then increased to 81.25% in the second test after 3 days, specificity 93.62%, PPV 75% then 81.25% and NPV 86.27% then93.62%.

El Bashir (2010) found that sensitivity 75%, the specificity 90%, PPV 64.3% and NPV 93.7%.

Abdul Salam (2011) found that sensitivity91%, specificity 100%, PPV 00% and NPV 80%.

El Gohary (2014) found that sensitivity 80% in first test then 91%in the second test, specificity 95%, PPV 96.5% then96.9% and NPV73% then 86%.

Ipek et al., (2011) found that in their study sensitivity, specificity, positive and negative predictive value47.05%, 93.62%, 84.25% and 70.96% respectively.

Wageeh(2015) found that sensitivity, specificity, positive and negative predictive value of alpha -1-acide glycoprotein 78%, 86.3%, 91.1%, 65.4%, respectively between control and clinically suspected sepsis group and 87%, 91%, 93%, 68%, respectively between control & confirmed sepsis group.

ROC curve for serum alpha-1-acid glycoprotein level in septic group showing an area under the curve (AUC) 0.99.it showed that serum α-1-acid glycoprotein was reliable to detect sepsis ($p<0.01$) and the cutoff value of serum alpha-1-acid glycoprotein to detect sepsis was> 136 ng /dl with sensitivity 93%and specificity 91.3%.

This comes in agreement with study done by ***(Ipek et al., 2011***) which show similar results as ROC

curve for serum α- 1-acid glycoprotein level was constructed showing an area under the curve (AUC) 0.922 and cut off value to detect sepsis was> 134 ng/dl, yielded sensitivity of 89%, specificity of 91%.

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القيمة التنبؤيه لحمض الفا -1- جليكوبروتين في تشخيص التسمم الدموي لدى الاطفال حديثي الولادة

مازالا التسمم الدموي مشكله كبيره في الاطفال حديثي الولادة مع ارتفاع معدلات الإصابة والوفيات على الرغم من التقدم في الرعاية المركزة لحديثي الولادة.

أن تشخيص التسمم الدموي يبدأ بالشك السريري والتحدي الذى يواجه طبيب الأطفال حديثي الولادة هو تقرير أي الأطفال بحاجه إلى علاج بالمضادات الحيوية التجريبية ولكن هذا يسبب الإفراط بالمضادات الحيوية وعدوى المستشفيات بسبب حجز الحالات في المستشفى بدون داعى وللأسف لا يوجد اختبار تشخيصي واحد يمكن الوثوق به لتشخيص التسمم الدموي في الأطفال حديثي الولادة لذا تستخدم العديد من الاختبارات التشخيصية لتشخيص او تأكيد التسمم الدموي .

وقد أجريت هذه الدراسة بهدف تقييم القيمة التشخيصية لحمض الفا -1- اسيد جليكوبروتين في التشخيص المبكر للتسمم الدموي في حديثي الولادة.

وقد أجريت هذه الدراسة على 90 من حديثي الولادة بوحدة العناية المركزة لحديثي الولادة بمستشفى السيد جلال الجامعي .

الأطفال حديثي الولادة في هذه الدراسة تم تقسيمهم إلى 3 مجموعات على النحو التالي :

- المجموعة الأولى :تشمل 30من حديثي الولادة تظهر عليهم العلامات السريرية للتسمم الدموي الذى تم إثباته بالتحليلات المختبرية ومزرعة الدم.
- المجموعة الثانية :تشمل 30من حديثي الولادة تظهر عليهم العلامات السريرية للتسمم الدموي ومزرعة الدم سالبه.
- المجموعة الثالثة :تشمل 30 من حديثي الولادة أصحاء كمجموعه تحكم.

وقد تم إخضاع جميع الذين شملتهم الدراسة إلى ما يلى :-

1- اخذ التاريخ الطبي .
2- استكمال الفحص الإكلينيكي .
3- عمل الفحوص المختبرية .القياس الكمي لمستوى بروتين سي التفاعلي في بلازما الدم
4- القياس الكمي لنسبه حمض الفا -1- جليكوبروتين في الدم.

وقد أظهرت الدراسة ارتفاع مستوى الفا -1- جليكوبروتين في الدم ارتفاعا عاليا في الأطفال حديثي الولادة المصابين بالتسمم الدموي مقارنه بالأطفال الأصحاء في هذه الدراسة سجل قياس نسبه ألفا -1- جليكوبروتين في الدم درجه من الحساسية والتخصصية وقيمه تنبؤ ايجابيه وسلبيه كما يلى :-

- 93%،91.3%،93.1%،68.4% وذلك عندما كانت قيمته اعلى من 136نانو جرام/ المليلتر بالمقارنة بمجموعه التحكم.
- ويظهر تحليل منحنى الروك حمض الفا -1- جليكوبروتين كعلامة تشخيصيه مبكرة في حديثي الولادة مع خاصية الحساسية والخصوصية.