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Prognostic Value of Serum Amyloid A Protein in Egyptian Infants with Hypoxic Ischemic Encephalopathy (HIE), Two Centers Experience

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Abstract

Background: It is often difficult to predict which newborn with HIE will develop neurological sequlae so there is an urgent need for predictors for adverse neurological outcomes in these infants. **Aim of Study:** To evaluate the serum levels of serum amyloid A (SAA)protein in newborns with HIE during the first week of life and after 3 and 6 months of follow up to assess its correlation with degree of HIE neurological sequlee. **Patients and Methods;** This case-control study was conducted on 72 infants; group (1) included 36 full term neonates diagnosed as HIE and group (2)included 36 age and sex matched, infants as a control group, Serum amyloid A by ELIZA technique was measured at post natal age of 1 and 7 days, CT scan was done in justified cases .with follow up at age of 3 and 6 months for neurological sequlee. **Results:** SAA protein level was elevated in the asphyxiated group in comparison to the control group at day 1 and day 7, SAA level was significantly correlated to the Sarnat scoring system of HIE.SAA level significantly differ on follow up of developmental milestone at age of 3 and 6 months. ROC curve for validity of SAA for severity of HIE at cut off point > 25µg/ml at day 1 and at cut off point > 20 µg/ml at day 7 of HIE diagnosis reported sensitivity 100% and specificity 100% .**Conclusion:** SAA correlates with the severity of HIE and higher SAA expression is a prognostic marker for morbidity in these infants.

Keywords: Serum amyloid A; Hypoxic ischemic encephalopathy; Neurological sequlae.

1. Introduction

Asphyxia neonatorum before, during and after birth is one of the most important factors contributing to neonatal morbidty and mortality worldwide. Twenty five percent of neonates with hypoxic ischemic encephalopathy (HIE) develop severe and permanent neurological sequelae including mental retardation, cerebral palsy and epilepsy [1]. Hypoxic ischemic insult triggers a cascade of adverse events that leads to irreversible neuronal and white matter injury over a period of hours to days. Cellular loss occurs in the up new therapeutic modalities for HIE and the increasing knowledge about the pathogenesis of asphyxia-related disorders, it is often difficult to predict which newborn will develop neurological perinatal asphyxia lack specificity, implicating the need for other predictors for adverse neurological outcomes in infants with HIE [2].

Serum amyloid A (SAA) is an apolipoprotein that is found in the high-density lipoprotein fraction of serum and is involved in the chemotactic recruitment of inflammatory cells to the site of inflammation [3].

The response of SAA to stress, in general, and to tissue injury in particular has stimulated our interest to conduct this study in infants with asphyxia because of several reasons. First, SAA is an acute phase first class protein that increases in inflammation [4, 5]. Second, although SAA is released in acute inflammation in general, it is considered a more specific marker for ischemia-related inflammation, the condition that exactly pertains to HIE. For example, SAA has been shown to increase in patients with atherosclerosis and coronary artery disease [6].

Aim of the Work: To evaluate the serum levels of serum amyloid A (SAA)protein in newborns with HIE during the first week of life and after 3 and 6 months of follow up to assess its correlation with degree of HIE neurological sequlee.

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2. Subjects and Methods

This prospective case-control study was conducted on 72 neonates who were classified into two groups; group (1)included 36 full term neonates (Their gestational age ranged from 37-42 weeks)who were diagnosed as HIE and admitted to the Neonatal Intensive Care Unit (NICU) of Zagazig and Tanta Universites hospitals.

Infants were diagnosed with HIE if they had demonstrated at least two of the following:

APGAR score < 3 at 1 minute or < 6 at 5 minutes, arterial pH < 7.2 with base deficit > 10mmol/l, and the presence of post natal clinical complications attributed to birth asphyxia, such as seizures, abnormality in state, hypotension requiring inotropic support, severe apnea and oliguria.

Group (2) included 36 age and sex matched, apparently healthy neonates who were recruited as a control group.

2.1. Exclusion Criteria

Infants were excluded from the study if they met any of the following conditions:

-If increased SAA was attributed to inflammatory causes other than asphyxia such as sepsis or localized infection.

-If they were diagnosed with life threatening congenital anomalies, inborn errors of metabolism or preterm births.

This study was approved by Research Ethical Commitee of Zagazig and Tanta University Hospitals and was conducted in accordance with the Universities' laws of human researches.

All subjects were subjected to the following:

A) Full history Taking: Focusing on age,sex,neurological symptoms such as seizures, perinatal history and APGAR scoring at 1 and 5 minutes,

B) Through clinical examination which included:

-*General examinations:*especially vital signs and urine output.

-*Neurological Examination:*

- Level of consciousness: Alert,lethargy or coma .

-Motor system: Power.

-MuscleTone and Reflexes:

C) HIE Staging system:

HIE was defined as mild, moderate or severe using the Sarnat and Sarnat staging system [7].The assessed elements included level of consciousness, muscle tone ,tendon and complex reflexes, seizures, autonomic function and electroencephalogram (EEG)description.

D)Laboratory testing:which were done for all subjects and included routine plus:

-*Arterial Blood gases(ABG):* PH, PO2, PCO2 and Base excess.

-*Serum amyloid A* assay :by ELIZA technique at a post natal age of 1 and 7 days,3mo &6 months.

E) Imaging Techniques:

-*CT scan* : which were done in justified cases.

F)Follow up: At age 3 and 6 months for developmental milestones.

2.3. Collection of Blood Samples

3 ml of venous blood was taken from all studied groups, samples were centrifuged at 4000 rpm for 10 min; serum samples were separated and stored -2 at -80 c until assay.

2.4. Principle

Serum Amyloid A (SAA)level :It was measured by Human Enzyme-Linked Immunosorbent Assay (ELISA) kit which is an in vitro test for the quantitative measurement of Human Serum Amyloid A in serum, plasma and cell culture supernatants. This assay employs an antibody specific for Human Serum Amyloid A coated on a 96 -well plate. Standards and samples are pipetted into the wells and Serum Amyloid A present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-Human Serum Amyloid A antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of Serum Amyloid A bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm**.** [8].

2.5. Assay Procedure

-Equilibrate all materials and prepared reagents to room temperature (18 - 25°C) prior to use.

-Add 100 µL of each standard and sample into appropriate wells.

-Cover well and incubate for 2.5 hours at room temperature or over night at 4°C with gentle shaking.

-Discard the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (300 µL) using a multi-channel Pipette or auto washer. Complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining Wash Buffer by aspirating or decanting. Invert the plate and blot it against clean paper towels.

-Add 100 µL of 1X Biotinylated Serum Amyloid A Detection Antibody to each well. Incubate for 1 hour at room temperature with gentle shaking.

-Discard the solution. Add 100 µL of 1X HRP-Streptavidin solution to each well. Incubate for 45 minutes at room temperature with gentle shaking.Discard the solution. Repeat the wash .

-Add 100 µL of TMB One-Step Substrate Reagent to each well. Incubate for 30 minutes at room temperature in the dark with gentle shaking.Add 50 µL of Stop Solution to each well.

Read at 450 nm immediately.

2.6. Calculations

Calculate the mean absorbance for each set of duplicate standards, controls and samples, and subtract the average zero standard optical density. Plot the standard curve on log-log graph paper, with standard concentration on the x-axis and absorbance on the y-axis. Draw the best-fit straight line through the standard points.

2.7. Statistical Analysis

All data were analyzed using (SPSS version 20.0) software for analysis. According to the type of data, the following tests were used to test differences for significance;. Differences between frequencies (qualitative variables) and percentages in groups were compared by Chi-square test. Differences between means (quantitative variables) IN two parametric group by t test. ROC curve for cut off, Kappa agreement to test the agreement. P value was set at <0.05 for significant results & <0.001 for high significant result.

3. Results

Table (1) showed that means of SAA levels were significantly increased in cases than in controls.

Table-1. Serum amyloid a protein level among studied groups

Variable (µg/ml)	Cases Mean±SD	Controls Mean±SD	t	P.value
SAA Day 1	78.3±33.2	6.3±3.7	9.1	0.001
SAA Day 7	48.2±13.4	7.6±3.7	9.6	0.001

Table-2. Comparison of SAA level in studied patient subgroups according to Sarnat staging

Variable (µg/ml)	Sarnat I n=16	Sarnat II n=12	Sarnat III n=8	P.value
SAA Day1	50.8±18.5	73.8±24.7	130.2±50.4	0.001
SAA Day7	32.8±25.7	56.3±48	80.3±35	0.001

Figure-1. Comparison of SAA level in studied patient subgroups according to Sarnat staging.

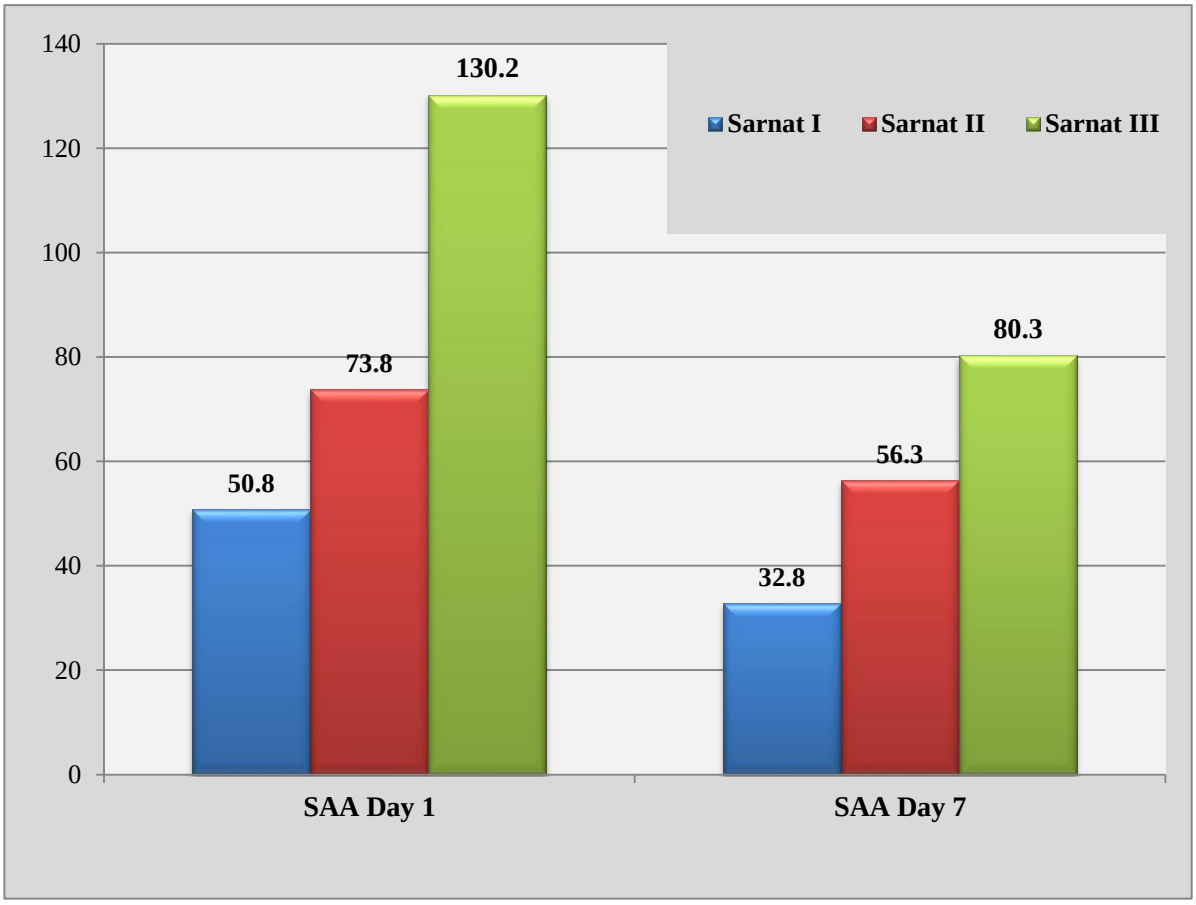

Table-3. Relation between serum amyloid A at day 1 and CT brain among studied cases.

CT brain	Serum amyloid At day 1 (µg/ml) Mean ±SD	t	p.value
Normal	67.5±30.8	4.993	0.025
Brain odema	92±18.4		
Sever ischemia	123.7±11		

Table (3) showed that there was statistically significant difference between serum amyloid A at day 1 and fingings of CT brain.

Table-4. Relation between serum amyloid A at day 7 and CT brain among studied cases.

CT brain	Serum amyloid At day 7 (µg/ml) Mean ±SD	t	p.value
Normal	15.4±43.8	5.011	0.024
Brain odema	50.5±0.7		
Sever ischemia	73±10.8		

Table (4) showed that there was statistically significant difference among serum amyloid A at day 7 and findings of CT brain.

Table-5. Follow up of developmental milestone of cases at age 3 months.

		NO.	%
Gross motor development	Able to lift head.	28	77.8
	Unable to lift head.	8	22.2
Vision and fine motor	Follows slowly moving object with his eyes.	24	66.7
	Unable to follows moving object.	12	33.3
Hearing, speech and language	Vocalises alone say (aa,aa).	24	66.7
	Unable to vocalises alone.	12	33.3
Social,emotional and behavioral development	Smiles responsively.	24	66.7
	Unable to smiles responsively.	12	33.3

Table-6. Follow up of developmental milestone of cases at age 6 months.

		NO.	%
Gross motor development	Sits with support.	28	77.8
	Unable to sits with support.	8	22.2
Vision and fine motor	Follows rapidly moving object with his eyes. Unable to follows moving object.	24	66.7
		12	33.3
Hearing,speech and language	Turn to soft sounds.	24	66.7
	Unable to turns to soft sounds.	12	33.3
Social,emotional and behavioral development	Puts food in mouth.	24	66.7
	Unable to put food in mouth.	12	33.3

Table-7. Relationship between SAA at day1 and gross motor development of cases at age 3, 6 months

	Gross motor development	No	Mean ± SD	P.value
SAA Day1 (µg/ml)	3 months	14	71 ±33	0.03
		4	105±18	
	6 months	14	70.7±33.1	0.025
		4	104.7±18.2	

Table (7) showed that means of SAA at day1 levels were significantly different in gross motor development milestone of cases at age 3 and 6 months.

Table-8. Relationship between SAA at day 1 and fine motor milestones of cases at age 3, 6 months .

	Vision and fine motor	N	Mean±SD	P.value
SAA Day7 (µg/ml)	3months	12	58.7±13.4	0.00**
		6	117.5±24.6	
	6months	12	58.7±13.4	0.00**
		6	117.5±24.6	

Table (8) showed that means of SAA at day1 level were significantly different in vision and fine motor milestone of cases at age 3, 6 months.

Table-9. Relationship between SAA at day1 and language milestones of cases at age 3, 6 months

	Hearing,speech and language	N	Mean±SD	P.value
SAA Day1 (µg/ml)	3 months	12	58.7±13.4	0.00**
		6	117.5±24.6	
	6 months	12	58.7±13.4	0.00**
		6	117.5±24.6	

Table (9) showed that means of SAA at day1 level were significantly different in hearing,speech and language milestone of cases at age 3 ,6 months.

Table-10. Relationship between SAA at day1 and social,emotional and behavioral development of cases at age 3, 6 months

	Social,emotional and behavioral development	No	Mean±SD	P.value
SAA Day1 (µg/ml)	3 months	12	58.7±13.4	0.00**
		6	117.5±24.6	
	6 months	12	58.7±13.4	0.00**
		6	117.5±24.6	

Table (10) showed that means of SAA at day1 level were significantly different in Social, emotional and behavioral developmental milestone of cases at age 3 ,6 months. Table (10) showed that means of SAA at day1 level were significantly different in Social, emotional and behavioral developmental milestone of cases at age 3 ,6 months.

Table-11. Validity of SAA for predicting severity of HIE in the studied patients group.

	Cut-off value	Sensitivity %	Severity of HIE Specificity %	+ve PV %	-ve PV %
Serum amyloid 1st day (µg/ml)	>25	100%	100%	100%	100%
Serum amyloid 7th day(µg/ml)	>20	100%	100%	100%	100%

Figure-2. Receiver operating characteristics (ROC) graph discriminate the sensitivity and specificity of SAA at day 1 in diagnosis of perinatal asphyxiated infants.

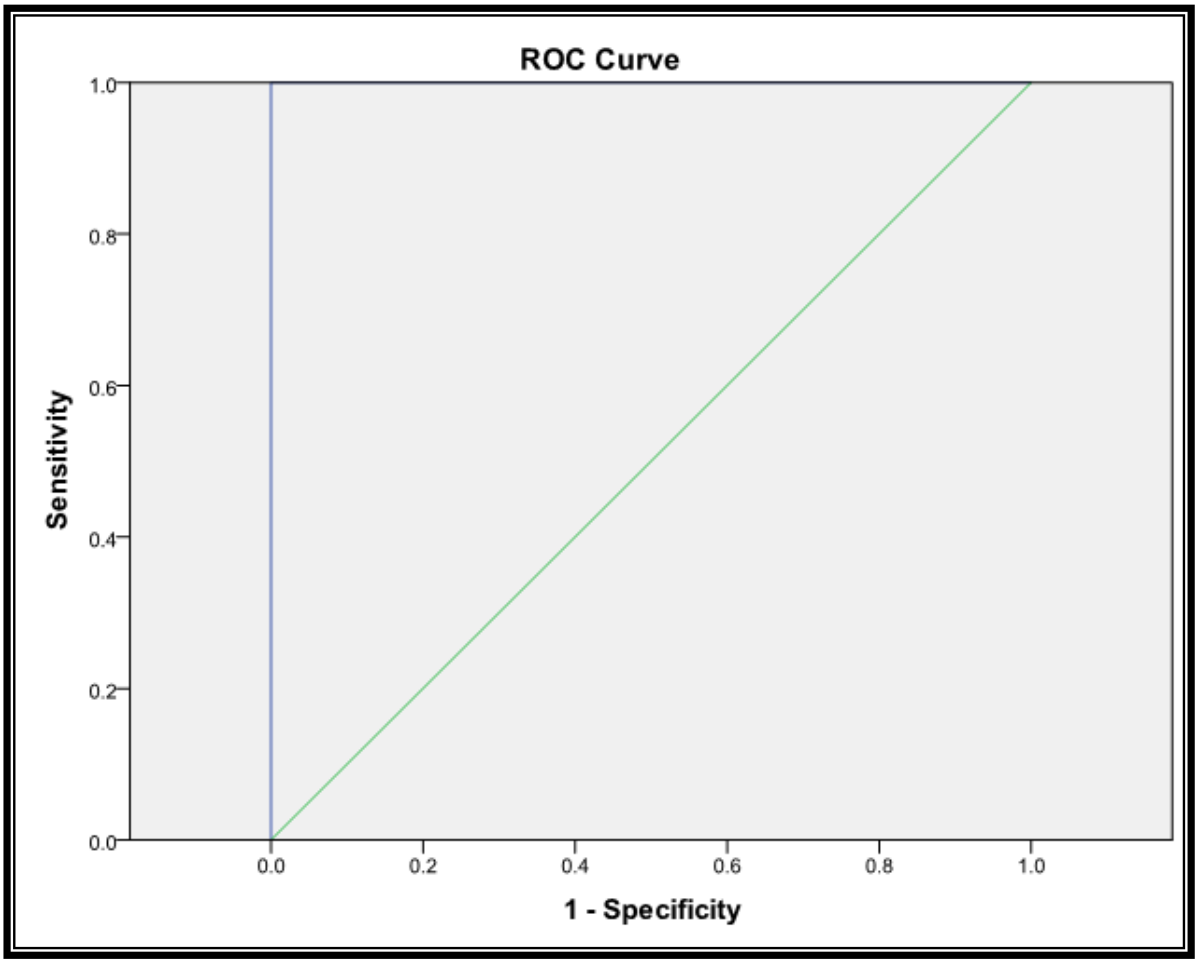

Figure-3. Receiver operating characteristics (ROC) graph for the sensitivity and specificity of SAA at day 7 in diagnosis of perinatal asphyxiated infants.

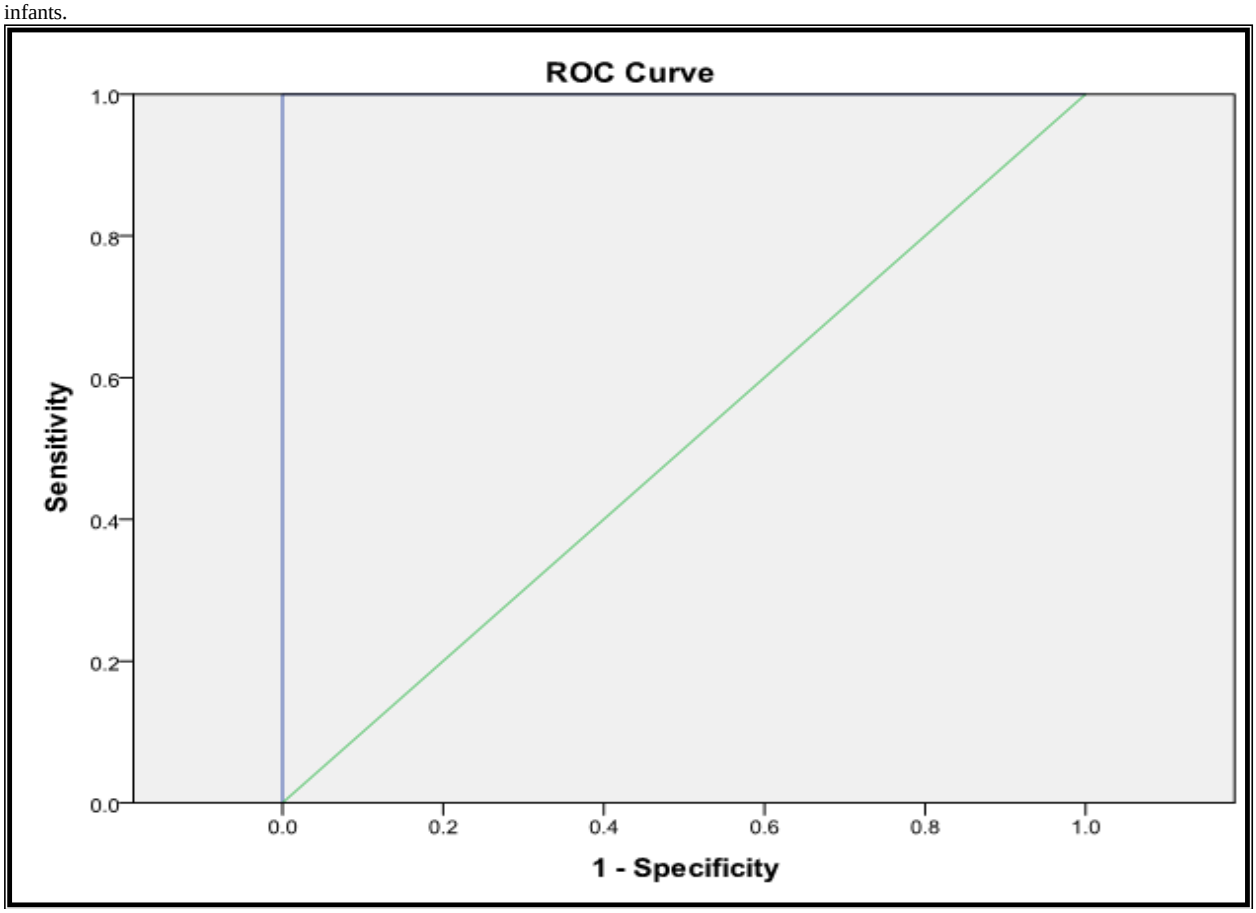

Table-12. Area under the Curve (AUC) and Confidence Interval of SAA for diagnosis of perinatal asphyxiated infants.

Biomarkers	AUC	95% Confidence Interval	p-value [a]
Serum amyloid 1st day	1	1-1	<0.001 **
Serum amyloid 7th day	1	1-1	<0.001 **

* Statistically significant at $p < 0.05$
[a] Null hypothesis: Area = 0.5

From table (12) and (11) and figures 2 and 3 we can conclude that SAA is the Gold standard for diagnosis of perinatal asphyxiated infants.

4. Discussion

Hypoxic-ischemic injury is the most important consequence of perinatal asphyxia. [9].

The extent of systemic organ involvement does not correlated with the severity of encephalopathy, except that severe HIE often is accompanied by other organ involvement. This can be transient and reversible. In fact, the CNS is often the only organ system that has residual sequelae at long term follow-up [10].

In this respect, early markers of brain injury would be relevant for therapeutic intervention and identification of infants at high risk [11].

By neurological examination of our patients, poor reflexes, convulsions and decressed level of consciousness were found by their order of frequencies and there is highly significant difference between them and control group.This agree with [12] and also,study made by Groenendaal and Vries [13] supported our results by finding that central nervous system was the organ most frequentiy involved (72%) in asphyxiated neonates.

Seizures are the most common manifestation of brain injury in newborns with reported incidence of 1 to 3.5 per 1,000 live births Miller, *et al.* [14]. Typically the first occur at 12-24 hr post delivery; if they occur within the first 6 hr, they are most likely of non-hypoxic origin or hypoxia occurred prepartum Korthals and Colon [15].

Our study showed that cases with HIE had significantly higher incidence of occurrence of convulsion and the chance increases with the increase of the severity of the disease, this is in agreement with [16] who postulated that eighty percent of neonatal convulsion occurs in the first 1 to 2 days to the first week of life and hypoxic – ischemic encephalopathy is the most common cause. Also [17] Study showed that birth asphyxia is the main cause of neonatal convulsion.

In our study SAA increased significantly in asphyxiated infants when compared to controls during the first day of life. SAA measured on day one, correlated significantly with the clinical degree of severity of asphyxia.

SAA was not previously monitored as a marker for neonatal asphyxia, yet we had enough leads to investigate such a relationship. SAA is part of acute phase response is part also of the innate defense system of an animal against trauma, inflammation, and infection [18].

Human studies have shown that damage to the myocardium is the most powerful stimulus for SAA induction, followed by traumatic events,arthritis, viral infections, and malignant diseases. It seems therefore that although acute response is considered a generalized reaction, it is not completely independent of the localized events which induce it. Among the known parameters, SAA is the most sensitive marker for monitoring the intensity of events [4].

Hypoxia with ischemia is one of the most injurious and stressful conditions in the neonatal period. Hypoxia ischemia is considered a major cause of brain injuries that occurs in two phases [19]. therefore it is justifiable to try to find a correlation between SAA as an acute phase reactant in response to brain injury in asphyxia.

Since hypoxia ischemia is considered one of the oxidative stresses where the production of damaging free radicals and other oxidative molecules exceeds the capacity of the body's antioxidant defenses [20]. therefore SAA could be related to hypoxia ischemia as a stress in neonates.

Although, delivery itself even if smooth might be considered as a stress, yet stress due to parturition does not form a stimulus for the production of acute-phase proteins in the fetus [21]. Also, Plasma levels of serum amyloid A protein is not elevated in pregnant women whether preeclamptic or normal [22]. In our study, the stress of delivery did not affect the SAA in controls. SAA increases in response to the combination of injury, stress and inflammation, all of which are found in asphyxiated infants. Multiple mechanisms of injury are involved in asphyxia, including genetic vulnerability, acquired inflammatory responses, and clotting defects that can lead to ischemic-induced brain damage [23].

In our study the level of SAA at day 1 & 7 in patient subgroups according to the Sarnat score. Sarnat stage I patients had a mean level of 58.1 ± 21.5 at day 1 and 17.7 ± 20.7 at day 7 of life. The mean level of SAA for Sarnat II patients at day 1 was 79.8 ± 24.7 and 54.7 ± 46 at day 7, whereas Sarnat III subgroup had a mean SAA level of 146.9 ± 56.4 and 133 ± 41 at day 1 & 7 respectively.

Many physiopathological mechanisms involved in the brain damage related to hypoxic-ischemic encephalopathy of the newborn. Early assesment of the severity of an acute cerebral lesion secondary to hypoxia-ischemia may provide a very useful basis for preventive or therapeutic decisions in affected neonates Naithani and Simalti [24].

A number of parameters have been studied in the aim to provide an early and reliable marker of tissue injury for diagnostic and prognostic purpose. Some authors have even suggested that biochemical indicators may be more effective than the results of clinical, Apgar score, pH in cord blood, electroencephalographic and neuroimaging data. [25].

Hypoxia ischemia of the newborn can trigger an acute phase inflammatory response which involves the expression of different acute amyloid A is not only a reactant to initial inflammation, but also reflect the degree of cell death *[5]*.

The resuts of our study detected that SAA values were raised significantly in HIE as compared to non hypoxic group, and its level were correlated with the severity of HIE. This agreed with the study which stated that the increased serum amyloid A in asphyxia is a true marker for the amount of tissue damage and cell death and it also represent the acute inflammatory response that follows hypoxia ischemia [22].

Also our study agree with [26], also detected that SAA was significantly increased in neonates with HIE than normal neonates and related with the prognosis of HIE, moreover they concluded that determining SAA was important in early phase diagnosis and evaluate prognosis.The same results were found by Aly, *et al.* [27] as they reported that SAA concentrations were significantly related with the severity of HIE .

Also our study agree with, asphyxia can increase SAA proteins level in the neonate, but most this occurs in the first few days after birth [28].

In our study CT scan, 24 (66.7%) were normal, 4 (11.1%) had brain odema,and 8(22.2%) had sever ischemia .

Our study agree with the observation made by Volpe [29] that infants with normal CT scans rarely exhibit major neurological deficits on follow-up and infants with scans demonstrating marked diffuse hypodensity are rarely normal on follow-up.

Our study disagree with Tippin, *et al.* [30] Although CT scan may occasionally show early changes, it is most often normal hours after the insult and may remain unremarkable at later stages, even in patients with extensive neurological damage. [31].

CT is the least sensitive modality for evaluation of HIE because of the high water content in the neonatal brain and high protein content of the cerebrospinal fluid, which result in poor parenchymal contrast resolution. In addition, CT has the inherent disadvantage of radiation exposure. However, with present CT technology, it provides a rapid mode of cranial screening for hemorrhage in a sick neonate without the need for sedation [32].

The most sensitive and specific imaging technique for examining infants with suspected hypoxic- ischemic brain injury is MR imaging Barkovich [32].

In our study was found there is significantly difference among serum amyloid A at day 1 and CT brain and there is significantly difference among serum amyloid A at day 7 and CT brain.

In our study was found milestone at age 3 months (gross motor development),28(77.8%) able to lift head ,8(22.2%) unable to lift head,(vision and fine motor),24(66.7%) follows moving object by turning the head,12 (33.3%) unable to follows moving object,(hearing, speech and language),24(66.7%) vocalises alone say (aa,aa),12(33.3) unable to vocalises alone and (social, emotional and behavioral development),24(66.7%) smiles responsively,12(33.3%) unable to smiles responsively.

Also in our study was found milestone at age 6 months (gross motor development),28(77.8%) sits with support ,8(22.2%) unable to sits with support,(vision and fine motor),24(66.7%) palmar grasp,12(33.3%) absent palmar grasp ,(hearing,speech and language), 24(66.7%) turn to soft sounds,12(33.3) unable to turn to soft sounds and (social,emotional and behavioral development),24(66.7%) puts food in mouth ,12(33.3%) unable to puts food in mouth.

In our study ,we found that means of SAA at day1 level were significantly different in gross motor development, vision , fine motor, hearing, speech, language, Social, emotional and behavioral development milestones of cases at age 3 and 6 months.

Because of the possibility of damage of the posterior visual pathway, including the primary visual cortex, the indications for early referral to a paediatric ophthalmologist include the following: stage 3 HIE, stage 2 HIE with an abnormal neurological examination or reduced visual awareness at hospital discharge, and stroke associated with HIE.

5. Conclusions

SAA correlates with the severity of HIE and higher SAA expression is a prognostic marker for morbidity in these infants.

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