Original Research Article

Protein S100B and Amplitude-Integrated EEG as Early Predictive Methods for Brain Injury and Seizures in Preterm Neonates

Abstract:

Background: Neonatal brain injury (NBI) is a serious adverse outcome in premature neonates. The most common form of neonatal brain injury (NBI) are intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). Improved survival of preterm infants leads to short- and long-term hazards of neurological, cognitive, respiratory, digestive, renal, cardiovascular, metabolic, immune, and psychosocial disturbances. We sought to determine the levels and prognostic value of serum S100B and the role of aEEG during the first three days of life in premature neonates (< 37 weeks) that later developed NBI in the form of intraventricular hemorrhage (IVH) or neonatal seizures to rule out the sensitivity and specificity of them in early detection of brain lesions in preterm neonates

Aim of the Study: to evaluate the role of Protein S100B as an early predictor for neonatal brain injury in preterm neonates and the predictive and prognostic value of amplitude-integrated electroencephalography for neonatal brain injury susceptibility and severity.

Subject and Method: This study was carried out on 50 preterm neonate (less than 37 weeks GA) who were divided according to presence or absence of brain injury into case and control groups. They were admitted in Neonatal Intensive Care Unit (NICU) of Tanta University Hospital during the period from March 2021 to March 2022.serum S100B at (Day 1 and Day 3), serial trans-cranial sonar and aEEG were done for all patients.

Results: Neonates with NBI, had significantly higher S100B concentration during the first three days of life, its level was higher in the third day than the first day, the cut-off value >810.4 ng/ml serum S100B performed a sensitivity of 72.7%and a specificity of 71.4% to predict adverse neonatal outcome. 60% neonates had normal aEEG and 40% had abnormal aEEG.72.7% of neonates with NBI had abnormal aEEG interpretation. There was a significant relationship between the electrografic seizures on aEEG and occurrence of clinical seizures as 96.7% of neonates who had abnormal aEEG suffered of clinical convulsion.

Conclusion: protein S100B has a good predictive value regarding NBI in premature neonates and aEEG has a great role in monitoring neonatal brain function and early detection of neonatal seizures.

Introduction:

"Preterm birth, defined as birth prior to 37 weeks' gestation, affects 15 million newborns every year" [1].

"The rate of preterm birth increased dramatically in the late 20th century, from less than 7% in the 1960s to a peak of 12.8% in 2006. However, there has been a recent decline to 11.4% in 2013, likely caused by a reduction in indicated late preterm deliveries" [2].

"Premature neonates < 33weeks of gestational age (GA) are at high risk of serious complications, such as brain injury, due to immaturity and inadequate reserves of their core organic systems" [3].

"The most common forms of neonatal brain injury (NBI) are intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and hypoxic-ischemic encephalopathy (HIE) and

can affect neonates born at any GA. However, neonates born < 32 weeks of GA are more prone to IVH and PVL while neonates born > 35 weeks of GA to HIE" [3].
"Intraventricular hemorrhage (IVH) is a major complication of prematurity. IVH typically initiates in the germinal matrix, which is a richly vascularized collection of neuronal-glial precursor cells in the developing brain" [4].
"Some infants manifest with subtle abnormalities in the level of consciousness, movement, tone, respiration and eye movement; and uncommonly, there is a catastrophic deterioration presenting with stupor, coma, decerebrate posturing, generalized tonic seizure, and quadriparesis" [4].
"Periventricular leukomalacia is the commonest white matter brain injury in preterm infants. It has a typical distribution at the watershed areas adjacent to the lateral ventricles. PVL occurs because of ischemic injury to periventricular oligodendrocytes of the developing brain" [3].
"Periventricular leukomalacia (PVL) is the leading cause of non- hemorrhagic neuropathological abnormality in the cerebral white matter of a premature infant" [5].
Although clinical seizures are rare, may be seen in severe forms of PVL.
"Intraventricular haemorrhage and its complications are the main cause of neonatal seizures in very and extremely preterm newborns (< 32 wGA), and the risk increases with increasing severity of brain injury (grades III and IV intraventricular haemorrhage)" [4].
"Seizure activity in neonates is often difficult to observe, making the detection of seizures particularly challenging. Clinical observation alone can lead to underdiagnosis of neonatal seizures, as nearly 80% of seizures can be occult. It is for these reasons that effective methods for seizure detection are of fundamental importance in neonatal care" [5].
Although advances in neonatal intensive care have greatly improved the survival and outcome of these 'micro' patients, brain injury remains of major concern.
Early diagnosis is important for optimal treatment, and neurological outcome.
Currently, there is no available effective predictive model which can provide early detection of neonates at high risk to develop NBI.
"In an effort to provide prognostic data on survival, density of residual deficits and effectiveness of early therapeutic intervention, a number of biomarkers have been tested since brain injury can exist subclinically at a stage when routine brain imaging is still silent" [6].
Based on previous studies, "S100 Calcium Binding Protein B (S100B) seems to be a promising early biomarker of NBI" [7] "It is an astroglial calcium-binding protein, released in the circulation of neonates when brain injury occurs, long before suggestive clinical symptoms are evident and in advance of neuroimaging findings" [7].
"S100B is a member of the S100 family. Because it is soluble in 100% saturated ammonium sulfate solution, it was named "S100. S100 protein is a cytosolic calcium-binding protein with a molecular weight of 21 kDa consisting of 2 monomers, α and β, which are present in various cells and concentrated mainly in the glial cells of the central nervous system.6-8 Because of its molecular weight, only S100B will be detected in peripheral blood" [8]. "It is predominantly released from the astroglial cells after there is hypoxic ischemic damage to the brain, and the ongoing glial cell death will increase the serum concentrations of S100B protein" [8].
"Studies in different biological fluids, have demonstrated adequate effectiveness in predicting adverse neonatal outcomes or NBI. Yet, there is still no consent on which biological fluid or method (one sample or multiple longitudinal sampling) is the most effective for the early detection of premature neonates at high risk to develop NBI when using S100B as a predictor" [9].
"Although S100B protein will come from other organs, that is, muscle, heart, fractured bone, and adipose tissue, extracerebral sources of S100B do not contribute to the increase in serum

concentrations Hence, serum S100B protein is considered a specific protein of brain damage. S100B acts as a neurotrophic factor and neuronal survival protein, and overproduction of S100B can lead to exacerbation of neuroinflammation and neuronal dysfunction. It is possible that increased S100B protein level might be considered as a sensitive and specific indicator to predict early brain damage in newborns" [10].

Another early predictor and prognostic method for Neonatal Brain Injury is amplitude-integratedEEG.

"Electrophysiological brain activity, as measured by amplituded-integrated electroencephalography (aEEG), is well established as a tool for providing information regarding the functional and metabolic state of the brain and the occurrence of epileptic seizure episodes" [11]. "In neonatal care, aEEG has been used for estimation of the degree of cerebral maturation in preterm infants and for detection of abnormal patterns indicating focal and global cerebral lesions" [11].

"Amplitude-integrated EEG (aEEG) is a technique for simplified EEG monitoring. Its main value lies in allowing real-time detection of electrographic seizures, providing the opportunity for treatment at the time they occur as in the neonate, electrographic seizure patterns vary widely, electrical seizure activity does not accompany all behaviors considered to be seizures, and electrographic seizures frequently occur without evident clinical seizures" [12].

So, aEEG will provide early information about the cerebral function and will be used as a prognostic model for the severity of the brain injury as there's significant association between seizure duration and severity of brain injury.

In our study we will use serum S100B as an early predictor biomarker for neonatal brain injury in premature neonates and aEEG as apredictor and prognostic model for NBI.

Patients and Methods:

- **Type of the study**: case-control study.
- **Place of the study:** Tanta University Hospital NICU.
- **The duration of the study:** 1 year from 1March 2021 to 1 March 2022.

Subjects:

This study was carried out on fifty preterm neonates (less than 37 weeks gestational age) who were admitted in Neonatal Intensive Care Unit (NICU) of Tanta University Hospital.

Our preterm neonates were classified according to CUS findings into two groups:

Group 1 with neonatal brain injury (case group).

Group 2 without neonatal brain injury (control group).

Inclusion criteria:

- Neonates less than 37-week GA.
- Neonates with electrographic seizures.
- Neonates with brain injury (IVH, PVL).
- Neonates with clinical seizures.

Exclusion criteria:

- Neonates more than 37-weeks G.A.
- Neonates with multiple congenital anomalies.
- Neonates with CNS malformation.
- Neonates exposed to hypoxic insult during delivery and Suspected to be HIE.

All the studied group were subjected to the following:

- Full medical history:
- Thorough Clinical examination:

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Results:

Regarding cases group, the median serum S100B was 695.95 with IQR from 609.35 to 776.075 at day 1 which significantly increased at day 3 to have a median of 871.4 and IQR from 818.275 to 934.05. In terms of control group, the median serum S100B was 567.05 with IQR from 460.375 to 656.075 at day 1 which changed insignificantly at day 3 to have a median of 520.15 and IQR from 467.375 to 557.625. By comparing between both groups at days 1 and 3, the concentration of serum S100B was significantly higher in patients with NBI compared to those without NBI (P value<0.001) as shown in [Table 1].

Table 1: Comparison between the two studied groups according to S100B

		Cases (n=22)	Control (n=28)	P between groups
Day 1	Median	695.95	567.05	<0.001*
	IQR	609.35 - 776.075	460.375 - 656.075	
Day 3	Median	871.4	520.15	<0.001*
	IQR	818.275 - 934.05	467.375 - 557.625	
P between day1&3		0.005*	0.074	

There was a statistically significant relation between aEEG and C.U/S as patients with normal aEEG had more normal ultrasound than those with abnormal aEEG at all-time evaluation (P values<0.001) as shown in [Table 2].

Table 2: Relation between aEEG and C.U/S (n= 50)

		aEEG		
		Normal (n=31)	Abnormal (n=19)	P value
Day 1	No IVH	25 (80.65%)	6 (31.58%)	<0.001*
	IVH I	5 (16.13%)	1 (5.26%)	
	IVH II	0 (0%)	6 (31.58%)	
	IVH III	0 (0%)	5 (26.32%)	
	IVH IV	0 (0%)	0 (0%)	
	PVL	1 (3.23%)	1 (5.26%)	
Day 3	No IVH	24 (77.42%)	4 (21.05%)	<0.001*
	IVH I	2 (6.45%)	1 (5.26%)	
	IVH II	4 (12.9%)	2 (10.53%)	
	IVH III	0 (0%)	8 (42.11%)	
	IVH IV	0 (0%)	3 (15.79%)	
	PVL	1 (3.23%)	1 (5.26%)	

At day 1, S100B can significantly discriminate patients with NBI with AUC of 0.572, P value<0.001. At cut off >612.6ng/ml, it has sensitivity of 73.73%, specificity of 64.29%, PPV of 61.5 and NPV of 75. At day 3, S100B can significantly discriminate patients with NBI with AUC of 0.774, P value<0.001. At cut off >810.4ng/ml, it has sensitivity of 72.73%, specificity of 71.43%, PPV of 66.7 and NPV of 76.9 [Table 3].

Table 3: Predictive performance (AUC, sensitivity, specificity) for S100B D.1 and D3 to discriminate patients with NBI

	Cut off*	Sensitivity	Specificity	PPV	NPV	AUC	P value
Day 1	>612.6	72.73	64.29	61.5	75	0.572	**<0.001***
Day 3	>810.4	72.73	71.43	66.7	76.9	0.774	**<0.001***

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, * Statistically significant as P value ≤ 0.05.

There was a statistically significant relation between aEEG and clinical convulsion as patients with abnormal aEEG had significantly more convulsions than those with abnormal aEEG (P values<0.001) as shown in [Table 4].

Table 4: Relation between aEEG and clinical convulsion

		aEEG		
		Normal (n=31)	Abnormal (n=19)	P value
Clinical convulsion	No	25 (80.65%)	4 (21.05%)	<0.001*
	Diaphragmatic	2 (6.45%)	1 (5.26%)	
	G.T.C	4 (12.9%)	11 (57.89%)	
	G.T.C + Death	0 (0%)	3 (15.79%)	

Discussion:

In the view of this study: the age of our neonates was < 37week G.A among them 28 neonate without NBI and 22 with NBI and there was statistically significant difference between levels of serum S100B between both groups. Serum S100B was higher in the group with NBI than the other group ($p < 0.001$).

Also, in the group with NBI serum S100B was higher in D3 than D1 with a significant value ($p < 0.005$).

Regarding cases group, the median serum S100B was 695.95 with IQR from 609.35 to 776.075 at day 1 which significantly increased at day 3 to have a median of 871.4 and IQR from 818.275 to 934.05.

In terms of control group, the median serum S100B was 567.05 with IQR from 460.375 to 656.075 at day 1 which changed insignificantly at day 3 to have a median of 520.15 and IQR from 467.375 to 557.625.

The ROC curve in our study of serum S100B concentrations and brain damage revealed that in day 1 the AUC was as high as 0.572 ($p < 0.001$). The serum S100B cutoff value of <0.612.6 ng/L had a sensitivity of 72.7% and specificity of 64.29% in detecting brain damage, the PPV was 61.5%and the NPV was 75% while in day 3 the AUC was as high as 0.774. The serum S100B cutoff value of >810.4.6 ng/L had a sensitivity of 72.7% and specificity of 71.4% in detecting brain damage, the PPV was 66.7%and the NPV was 76.9%.

This was in agreement with a prospective longitudinal case-control study done by Metallinou et al. [13] which was applied on 58 preterm neonates with GA <34 weeks who were classified into two groups, those with normal cranial U/S (without NBI) and another group with abnormal cranial U/S showing either PVL or IVH.

The study approved that serum S100B levels during the first three days of life are significantly elevated in premature neonates that will later on develop NBI in the form of either PVL or IVH and S100B seems to be a very potent biomarker of NBI regardless the type of brain injury and higher levels of S100B are associated to higher grade of brain injury.

Another study done by Huang et al. [9] on 121 preterm neonates with GA<34 weeks and were classified into normal group (without PVL)and abnormal group (with PVL) according to head

U/S resulted in S100B levels of PVL infants were significantly increased at 1, 3, and 7 days, and were highest on the 7th day. There was a significant difference between the normal group and the PVL group. As the infants' condition improved, the S100B serum level decreased in the PVL group. There was no significant difference between the two groups on the 14th day.

Chiang et al. [14] showed "in their study that was done on 22 preterm neonates with GA<32 weeks and Seventeen well near-term infants who were enrolled in the reference group that S100B concentrations at 3 days of age were significantly higher in the extreme preterm infants than in the near-term infants ($p < 0.05$).The serum S100B concentrations of infants in the brain damage group was significantly elevated at age 7 days, 14 days, and 21 days, compared to the concentrations at the age of 3 days ($p < 0.05$) in the other group. In addition, the S100B concentration was highest at age 14 days ($p < 0.05$)".

The ROC curve in this study of serum S100B concentrations and brain damage showed that the AUC was as high as 0.985 ($p < 0.001$). The serum S100B cutoff value of 1.0 µg/L had a sensitivity of 93.8% and specificity of 90.5% in detecting brain damage, and the serum S100B cutoff value of 1.5 µg/L had a sensitivity of 84.4% and specificity of 98.3% in detecting brain damage.

Lu et al. [15] who studied "the relationship between premature brain injury and multiple biomarkers in cord blood and amniotic fluid included 130 preterm with GA<34 weeks and proved that cord blood S100B was a better predictor of NBI when compared to amniotic fluid S100B".

This study showed that there was 30 neonates had normal aEEG while 20 had abnormal aEEG.

We demonstrated that there was a significant relationship between abnormal cranial U/S (PVL, IVH I, IVH II, IVH III, IVH IV) and abnormal aEEG either abnormal background or seizure activity.

Our study revealed that there was 22 patients had brain injury with different grades IVH ranging between (IVH II, IVH III, IVH IV), 16(68.2%) of them had abnormal aEEG.

The most seen abnormality was Several discrete seizure episodes on adiscontinuous background pattern (37.5), Several discrete seizure episodes on a Continuous background pattern (18.7), then equally Several discrete seizure episodes on burst suppresion pattern and burst suppression (12.5%), respectively with one neonate with Isoelectric or flat tracing background and another one with Multiple marked seizures on a background of burst suppression (status epilepticus).

In patients with NBI, the highest percentage that showed abnormal aEEG interpretation were those with IVH III, IVH IV, IVH II respectively. Hence, there's a significant value between abnormal cranial U/S and abnormal aEEG ($p<0.001$).

Our results were in agreement with Olischar et al., [16] who described the changes in aEEG in 56 preterm infants younger than 30 weeks GA with different grades of IVH. He applied cranial u/s for them on D 1,3,5,7 of life and aEEG weekly until they were discharged or transferred. Analysis of aEEG background activity showed that with higher degree of IVH, the relative amount of discontinuous low-voltage pattern increased whereas discontinuous high-voltage pattern decreased. The presence of suspected seizure discharges was more common in infants with IVH of higher degrees. Cyclical changes in aEEG background activity resembling early sleep-wake cycles were observed significantly less frequently in infants showing IVH, even at lower grades of hemorrhages, when compared those without hemorrhage($p<0.004$).

A Study done by Yang et al., [17] on "56 neonate with GA below 33 weeks with IVH and 31 gestational age-matched normal preterm without IVH revealed that the moderate-severe IVH group showed a decreased continuity of the voltage, an increased loss rate of SWC, and a lower aEEG score than the mild IVH and control groups ($P<0.017$)".

Hellström-Westas et al., [18] demonstrated "in their study that was applied on 64 preterm infants with IVH grade III – IV to investigate if early prediction of outcome is possible from aEEG in preterm infants with large IVH that there's a significant difference in the maximum bursts in aEEG between the infants who died and the surviving infants and hence the outcome may be predicted with aEEG already during the first days of life in preterm infants with large IVH".

Also, our study proved that there was significant relation between background activity and gestational age (GA).

Our study also found that there is a great role of aEEG in diagnosis of neonatal seizures as 96.7 % of patients with seizures activity in aEEG had clinical seizures in the form of generalized tonic colonic seizures (G.T.C) 57.89%, diaphragmatic seizures 5.26%, G.T.C and death 15.7% and only 21.05% of them had no clinical seizures.

On the other hand, there was 31 neonate with normal aEEG but some of them showed seizure activity in the form of diaphragmatic (6.45%) and G.T.C (12.9%) that with investigation proved to be due to other causes other than NBI like hypoglycemia and electrolyte disturbance and when these causes were treated, seizure activity stopped.

Hellström-Westas et al., [19] also found that "differentiating epileptic seizures from non-epileptic movements in severely ill newborns was possible with the use of aEEG".

Toso et al., [20] agreed with our results as he reported in his study that was carried on 21 neonates with neonatal encephalopathy or neurologic disturbances that, all children who had seizures had an abnormal aEEG background pattern at the start of monitoring. So, patients with an altered aEEG pattern were more likely to develop seizures, and this was not only observed with encephalopathy patients.

Chandrasekaran et al., [21] revealed that "Sensitivity and specificity of aEEG at 6 hrs of age were 96% (95% CI, 91 to 98) and 39% (95% CI, 32 to 46), respectively. Adverse neurodevelopmental outcome was associated with persistently abnormal aEEG at 48 hrs. or more. Normal 6 hrs. aEEGs had high negative predictive value but did not exclude adverse outcomes".

Also, Kadivar et al., [22] suggested that "aEEG is a very good screening tool for detecting neonates who need cEEG in the NICU but is not recommended for primary diagnosis and management of neonates with seizure".

Klebermass-Schrehof et al., [23] reported that "the presence of an abnormal aEEGpattern-score within the first 2 wk of life was highly predictive for adverse long-term outcome with a specificity of 94% and sensitivity of 81%".

In contrast, Osredkar et al., [24] reported that "in a study on 18 term newborns without severe hypoxic-ischemic encephalopathy, but with clinical signs suspicious of epileptic seizures the sensitivity of seizure detection of aEEG to standard EEG was 50%".

Conclusion:

Serum S100B varied significantly between preterm neonates with and without NBI in the first days of life, and this might successfully distinguish which neonates would later suffer a very poor outcome, such as mortality or grade II-IV IVH resulting in neonatal seizures and/or hypertonia. It's easy and applicable and can be done with routine lab. Investigation to any neonate.

At a cut off value >612.6 ng/ml (D1) and >810.4ng/ml (D3) attention should be paied that this newborn will develop brain injury in a great percentage.

Ethical Approval

Approval from Ethical Committee of Tanta Faculty of Medicine was obtained before starting the study.

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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