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ORIGINAL ARTICLE

Value of Neuron-Specific Enolase in Pediatric Acute Encephalopathy

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ABSTRACT

Background: Neuron-specific enolase is a dimeric isoform of the glycolytic enzyme that is mostly present in neurons is important as a diagnostic and a prognostic value in pediatric encephalopathy which is common and is potentially life threatening, previous studies were done worldwide to detect its diagnostic and prognostic value in acute encephalopathy among adult and pediatric age groups. The current study aimed at evaluation of serum neuron specific enolase for early diagnosis of pediatric acute encephalopathy. **Methods:** This case control study was carried out in pediatric intensive care unit and the inpatient pediatric department, faculty of medicine, Zagazig University and was conducted on 24 patients suffering from acute encephalopathy and 24 patients presented with seizures without encephalopathy. serum neuron-specific enolase was measured. **Results:** Serum neuron-specific enolase level had sensitivity 95%, specificity 88.5%, PPV 94%, NPV 90% and accuracy 93% in prediction of encephalopathy. **Conclusions:** There was statistically significant increase in serum NSE levels in encephalopathy group more than seizures group.

Keywords: Neuron-Specific Enolase; Encephalopathy**;** Seizures.

INTRODUCTION

Acute encephalopathy, which can be caused by focal lesions or generalized brain injuries, is a change in mental status that affects cognition or level of alertness in the patient **[1]**. It frequently leads in death or serious neurological after effects in previously healthy children **[2].** With an overall mortality rate of ~5%, so detection and treatment of acute encephalopathy early is of significant importance to decrease the mortality rate **[3].**

A glycolytic enzyme called enolase is primarily found in neurons. A dimeric isoform of enolase called neuron-specific enolase (NSE) exists. It can be found in neurons, platelets, erythrocytes, and other neuroectodermal cells **[4].**

It is one of the laboratory biomarkers that could be investigated in cases of encephalopathy, which can be found in both blood and cerebrospinal fluid, might be a helpful biomarker for determining brain injury prognosis and neuronal damage **[5].**

In this study we tried to detect the value of serum neuron specific enolase in diagnosing acute encephalopathy in pediatrics which is not well covered in pediatric field.

METHODS

This case control study was carried out in Pediatric Intensive Care Unit (PICU) and the inpatient pediatric department, Faculty of Medicine, Zagazig University from April 2021 to October 2021 and was conducted on 24 patients suffering from acute encephalopathy and 24 patients presented with seizures without encephalopathy, 30 were admitted to PICU and 18 were admitted to the inpatient pediatric department of Zagazig University Hospital.

Patient aged from 1 month: 14 years, both sexes and patients presented with encephalopathy that is a term used to describe diseases, injuries, or malfunctions of the brain. A wide range of symptoms associated with encephalopathy can appear, from minor ones like memory loss or subtle personality changes to severe ones like dementia, seizures, coma, or even death **Carmona-Aparicio et al. [6]** and patients presented with seizures without encephalopathy the study's participants had seizures, which are described as a brief, involuntary change in awareness, behavior, motor activity, sensation, or autonomic function brought on by an excessive

rate and hypersynchrony of discharges from a group of brain neurons **[7]** were included in the study.

Patients presented with traumatic brain injury, patients presented with attack of hemolysis and patients with brain tumor were excluded from the study.

Patients who fulfill the inclusion criteria was divided into two equal groups (the first group includes patients with acute encephalopathy, the second one includes patients presented with seizures without encephalopathy) and were subjected to: full history taking including name, age and sex, antenatal, natal and post-natal history, nutritional history, growth history, mental and physical developmental history, history suspecting neurological disorders and family history. Clinical examination: including: general (weight, length, cyanosis, pallor, jaundice, rash, edema or fever, level of consciousness, reflexes, tone, irritability or convulsions), modified Glasgow Coma Scale (GCS) was assessed for every patient at admission, respiratory (tachypnea, chest abnormalities, grunting or apnea), cardiovascular (tachycardia, bradycardia, murmurs (CHD) or hypotension) and gastrointestinal (diarrhea, vomiting, distension or organomegaly). Laboratory work up including complete blood cell count (CBC), liver function tests, kidney function tests, and C- reactive protein (CRP) coagulation profile and serum neuron-specific enolase.

Approval was obtained from Institutional Review Board (IRB), Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants' parents. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of the study.

Statistical analysis:

Utilizing the IBM SPSS software package, version 24.0, data were input into the computer. Number and percentage were used to describe qualitative data. We utilized the independent t-test and the chi-square test. The 5% level of significance was used to determine the results' significance.

RESULTS

Table 1 showed that there was no significant difference between the two studied groups regarding age and sex (P > 0.05).

Table 2 showed that there was significant difference between the two studied groups regarding blood pressure, pulse, Respiratory rate and temperature.

Table 3 showed that there was significant difference between the two studied groups regarding morphological features (p value = 0.047), sensory affection that was higher in the first group than that of the second group (p value =0.002) and modified Glasgow Coma Scale (p value= 0.005). There was no significant difference between the two studied groups regarding Heart diseases, Chest disorders, GIT disorders, Skin changes, Musculo-Skeletal abnormalities and Motor deficit.

Table 4 showed that there was no statistical significant difference between the two studied groups regarding history, frequency and duration of seizures (P > 0.05)

Table 5 showed that there was significant difference between the two studied groups regarding WBCs (p value = 0.013), neutrophils (p value = 0.019), serum neuron-specific enolase level (p value = 0.001), PO2 (p value = 0.001), and PCO2 (p value = 0.01). It also showed that there was no significant difference between the two groups regarding lymphocytes, hemoglobin, CRP, ALT, AST, Albumin, Total & direct bilirubin levels, creatinine, urea, PT, PTT, INR, PH, SO2, HCO3, RBG, Na, K, Mg and Ca.

Table 6 showed that the most common cause of encephalopathy in the studied group was due to CNS infections (9 cases= 37.5 %).

Table 7 showed that serum neuron-specific enolase level in prediction of encephalopathy had sensitivity 95%, specificity 88.5%, PPV 94%, NPV 90% and accuracy 93% as shown figure 1.

Table 1: Comparison between the two studied groups regarding demographic data.

	Encephalopathy "n=24"	Seizures without encephalopathy "n=24"	P value
Age (years)			
Range	1.2-10.0	1.1-14.0	0.084
Mean±S.D.	4.35±2.7	5.70±3.9	
Median	4.22	5.9	
Sex			
Male	16 (66.7%)	15 (62.5%)	
Female	8 (33.3%)	9 (37.5%)	0.384

Table 2: Comparison between the two studied groups regarding the vital signs.

Vital sign	Encephalopathy "n=24"	seizures without encephalopathy "n=24"	t-test	P value
Blood pressure (mm/Hg)				
Systolic blood				
Range	75-110	90-170	2.23	0.0131*
Mean±S.D.	94.25±10.0	105.83±21.2		
Diastolic blood				
Range	40-80	70-100	1.96	0.022*
Mean±S.D.	65.83±11.0	76.67±8.7		
Pulse (bpm)				
Range	90-130	80-110	3.12	0.006*
Mean±S.D.	105.71±10.4	92.17±8.2		
Respiratory rate (bpm*)				
Range	20-45	18-32	3.65	0.002*
Mean±S.D.	34.46±6.8	23.38±4.1		
Temperature (°C)				
Range	37-39.5	37-38	2.98	0.0035*
Mean±S.D.	38.38±0.8	37.39±0.5		

Bpm=beat per minute bpm*= breathe per minute

Table 3: Comparison between the two studied groups regarding Clinical examination.

	Encephalopathy "n=24"		Seizures without encephalopathy "n=24"		Test of significant	P value
Dysmorphology						
No	19	79.2	23	95.8	3.933	0.047*
Yes	6	25.0	1	4.2		
Heart diseases						
No	20	83.3	22	91.7	0.7619	0.221
Yes	4	16.7	2	8.3		
Chest disorders						
No	14	58.3	17	70.8	0.8197	0.069
Yes	10	41.7	7	29.2		
GIT disorders						
No	15	62.5	18	75.0	0.8727	0.106
Yes	9	37.5	6	25.0		
Skin changes						
No	21	87.5	23	95.8	1.0909	0.089
Yes	3	12.5	1	4.2		
Genito-urinary system						
Normal	22	91.7	24	100.0	0.4	
Renal colic	2	8.3	0	0.0		0.098
Musculoskeletal (muscles and joints)						
No	21	87.5	22	91.7	0.2233	0.247
Yes	3	12.5	2	8.3		
Neurological exam						
Motor deficit						
Yes	5	20.8	1	4.17	3.0476	0.11
No	19	79.2	23	95.83		
Sensory affection						

No Yes	14 10	58.3 41.7	22 2	91.7 8.3	7.111	0.002*
Modified GCS Range Mean±S.D.	3-12 8.11±3.66		12-15 13.62±1.05		T=3.54	0.005*

GCS= Glasgow Coma Scale

Table 4: Comparison between the two studied groups regarding history, frequency and duration of seizures

	Encephalopathy "n=24"		**seizures without encephalopathy "n=24"**		**X^2**	**P value**
	NO.	**%**	**No.**	**%**		
History of seizures						
Yes No	20 4	83.3 16.7	24 0	100.0 0.0	1.468	0.062
Frequency of seizures (from admission)						
1 time **2-3 times** **>2-3 times** **>5-10 times**	4 6 10 0	16.7 25.0 41.7 0.0	6 8 8 2	25.0 33.3 33.3 8.3	1.08	0.165
Duration of episodes						
< 5 min **5, < 15 min** **15, < 30 min** **30 min, < 1 hr** **≥1 hr**	4 4 6 6 0	16.7 16.7 25.0 25.0 0.0	3 6 9 6 0	12.5 25.0 37.5 25.0 0.0	1.56	0.0954

Table 5: Comparison between the two studied groups regarding laboratory finding.

	Encephalopathy "n=24"	**Seizures without encephalopathy "n=24"**	**t-test**	**P value**
WBC (×10^3/µl) Range Mean ±S.D.	7.60-24.80 16.85±4.06	7.20-15.18 12.11±2.24	2.41	0.013*
Neut. (×10^3/µl) Range Mean ±S.D.	2.333-19.300 9.65±2.07	1.5-12.18 7.01±2.65	2.01	0.019*
Lymph. (×10^3/µl) Range Mean ±S.D.	0.9 - 8.890 3.29±2.11	1.786-8.0 4.21±2.78	1.28	0.166
Hb. (g/dl) Range Mean ±S.D.	8.70-13.50 10.50±1.25	9.2-14.00 11.18±1.68	0.968	0.119
CRP (mg/L) Range Mean ±S.D.	0.0-170.0 25.20±43.37	0.00-100.0 15.65±32.76	0.854	0.484
ALT (U/L) Range Mean ±S.D.	9.0-50.0 18.74±11.47	10.0-18.0 13.13±2.74	1.71	0.074
AST (U/L) Range Mean ±S.D.	9.6-64.40 28.08±12.01	18.0-30.0 21.38±4.68	1.81	0.068
Albumin (g/dl) Range	3.12-4.40	3.22-4.21	0.032	0.984

	Encephalopathy "n=24"	Seizures without encephalopathy "n=24"	t-test	P value
Mean ±S.D.	3.76±0.50	3.77±0.47		
Total Bilirubin (mg/dl) Range Mean ±S.D.	 0.08-0.71 0.34±0.23	 0.28-0.41 0.35±0.05	0.105	0.956
Direct bilirubin (mg/dl) Range Mean ±S.D.	 0.04-0.3 0.15±0.11	 0.017-0.13 0.09±0.05	0.711	0.330
Serum total protein (g/dl) Range Mean ±S.D.	 5.9-7.85 6.72±0.83	 4.2-7.1 5.81±1.23	0.865	0.268
Creatinine (mg/dl) Range Mean±S.D.	 0.20-2.50 0.68±0.48	 0.40-0.90 0.65±0.20	0.107	0.812
Urea (mg/dl) Range Mean ±S.D.	 13.00-82.00 31.22±17.63	 12.00-60.00 28.46±16.61	0.744	0.671
PT (sec) Range Mean ±S.D.	 10.90-11.60. 11.20±0.36	 10.90-12.00. 11.17±0.41	0.045	0.909
PTT (sec) Range Mean ±S.D.	 28.80-41.40. 34.39±4.38	 32.00-38.00. 35.06±2.62	0.411	0.711
INR Range Mean ±S.D.	 0.90-1.17 0.96±0.09	 0.88-1.00 0.93±0.05	0.963	0.392
Serum neuron-specific enolase level (ng/ml) Range Mean ±S.D.	 18.80-56.20 36.08±11.18	 15.80-26.20 20.20±2.67	2.54	0.001*
PH Range Mean±S.D.	 7.21-7.50 7.32±0.16	 7.25-7.52 7.38±0.14	0.895	0.661 N.S.
PO2 (mmHg) Range Mean ±S.D.	 39-40 39.50±0.71	 22-24 23.00±0.82	3.11	0.001*
PCO2(mmHg) Range Mean±S.D.	 22-39 33.33±5.89	 23-26 24.60±1.14	2.41	0.01*
SO2 (%) Range Mean ±S.D.	 60-95 81.67±18.93	 94-96 95.00±1.00	0.952	0.290
HCO3 (mmol/L) Range Mean ±S.D.	 24-26 25.00±1.00	 24-28 26.00±2.00	0.785	0.325
RBG (mg/dl) Range Mean ±S.D.	 68-152 98.00±30.71	 60-99 81.60±15.36	0.965	0.308
Na (mmol/L) Range Mean ±S.D.	 115-149 133.60±8.47	 121-134 129.20±5.07	0.911	0.291
K (mmol/L) Range Mean ±S.D.	 3.2-4.5 3.62±0.45	 3.1-4.6 3.35±0.19	0.871	0.255

	Encephalopathy "n=24"	Seizures without encephalopathy "n=24"	t-test	P value
Mg (mmol/L) Range Mean ±S.D.	 1.5-2.3 1.90±0.18	 1.6-2.4 1.78±0.28	0.612	0.419
Ca (mg/dl) Range Mean ±S.D.	 8.9-10 8.22±0.38	 9-9.6 9.20±0.11	0.711	0.247

WBC= white blood cells, RBG= random blood glucose, Hb. = hemoglobin, CRP= C-reactive protein, ALT= Alanine transaminase, AST= Aspartate aminotransferase, PT =Prothrombin time, PTT= partial thromboplastin time, INR= international normalized ratio, TLC= total leucocytic count.

Table 6: Relation between serum neuron-specific enolase level and type of encephalopathy.

Type of encephalopathy	N	Percent	Mean±S.D
CNS infection	9	37.5	39.84±13.76
Encephalopathy with guillain barre syndrome	1	4.2	36.20±.0.0
Epileptic encephalopathy	6	25.0	34.78±9.64
Metabolic encephalopathy	2	4.2	28.60±4.10
Organophosphorus poisoning	1	4.2	27.50±.0.0
Unclassified	5	20.8	35.56±11.77
ANOVA (Analysis of variance). P value	0.458 0.802		

Table 7: Sensitivity, specificity and accuracy of Serum Neuron- specific enolase level in predict Encephalopathy

Area	Cut off value	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.939	>25	.0001	.866	1.000
Sensitivity Specificity PPV NPV Accuracy	95.0 88.5 94.0 90.0 93.0			

PPV = Positive predictive value, NPV = Negative predictive value

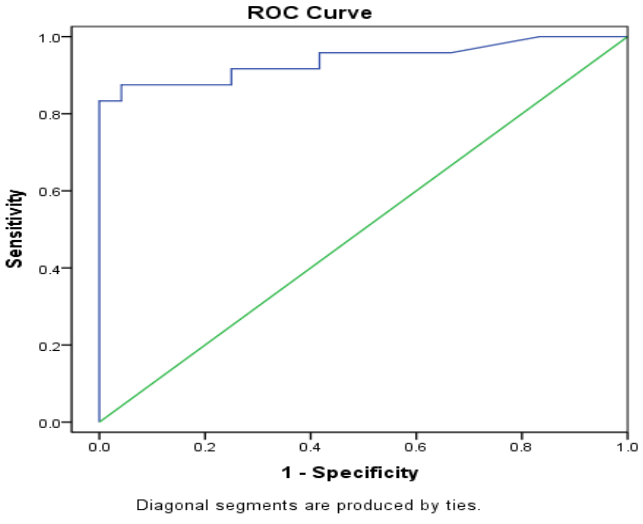

Figure 1: ROC curve to determine the sensitivity, specificity and accuracy of Serum Neuron- specific enolase level in predict Encephalopathy.

DISCUSSION

The term "acute encephalopathy" refers to immediate brain dysfunction brought on by a variety of factors, include hepatic or renal impairment, infection, metabolic problems, and hypertension **[8].** This dangerous condition has an overall fatality rate of less than 5% **[3].**

Acute encephalopathy is characterized by broad or widespread non-inflammatory cerebral edema as the pathogenic substrate. Magnetic resonance imaging (MRI), including diffusion-weighted images, is more sensitive than computed tomography for the diagnosis of acute encephalopathy. The use of MRI has helped to distinguish a number of acute encephalopathy subtypes **[8].**

Acute stroke, head trauma, and hypoxia ischemic injury are a few neurological illnesses that have been studied using serum or cerebrospinal fluid (CSF) biomarkers **[9].**

NSE, a highly specific marker for neurons, is expressed by granule cells, Purkinje cells, projection neurons, and both sensory and autonomic neurons **[10].**

The amounts of NSE have been evaluated in blood serum and CSF in adults, children, and infants with HIE. It is a well-known indicator of neuronal damage **[11].**

The aim of the work was to detect the diagnostic value of neuron-specific enolase in pediatric acute encephalopathy.

Patients were divided into two equal groups (the first group includes 24 patients with acute encephalopathy, the second one includes 24 patients presented with seizures without encephalopathy) attending the PICU and inpatient pediatric department of Zagazig University Hospital.

Our study's findings showing there was no significant difference in age or sex between the encephalopathy group and the seizures without encephalopathy group, these results were important to eliminate the effect of demographic data on the final outcome.

Also, the results of our study showed that there was a significant increase in blood pressure in the second group more than the first group - (systolic blood pressure range in the first group = 75-110 mmHg compared with 90-170 mmHg in the second group, while diastolic range = 40-80 mmHg and 70-100 mmHg in the first and second groups respectively with a P value of 0.0131) according to table 2, on the other hand the pulse, respiratory rate and temperature were significantly higher in the first group (the pulse ranged from 90-130 bpm and 80-110 bpm, respiratory rate ranged from 20-45 bpm and 18-32 bpm, temperature ranged from 37-39.5°C and 37-38°C in the first and second groups respectively with P values of 0.006, .002 and .0035 respectively).

In a study carried out by **Ng et al. [12]**, they found that hypertension is a risk factor for unprovoked seizures, although seizures sometimes accompany hypertensive encephalopathy, hypertension per se has not been regarded as a risk factor for epilepsy. Risk of seizure associated with hypertension is often thought to be mediated through intermediate events such as stroke or intracranial bleeding. Inclusion of prior stroke in multivariate analysis does in fact reduce the univariate association of hypertension with seizure. Nonetheless, among both those with and without a history of stroke, the risk of seizure with hypertension remains elevated. Especially among those with prior stroke, hypertension is a very strong independent risk factor for seizure. This is consistent with a study which shows that a history of hypertension is the single most important risk factors for the development of epilepsy after subarachnoid hemorrhage and neurosurgery.

Epilepsy and hypertension are both common, chronic disorders that can coexist in the same person, according to a different study by **Gasparini Sara, et al. [13].** It is possible for hypertension to play a direct or indirect pathogenic role in the development of seizures and epilepsy. The discovery that medications that can inhibit RAS decrease seizures in animal models suggests that the renin-angiotensin system (RAS) may be a key player in the direct connection between hypertension and epilepsy. Furthermore, independent of vascular injury, hypertension is a predictor of late-onset epilepsy. Indirectly, hypertension may cause cerebrovascular illnesses like stroke and posterior reversible encephalopathy syndrome (PRES), which increase the risk of developing acute symptomatic epilepsy or chronic epilepsy.

Table 3 shows that while there was no statistically significant difference between the other clinical exams between the two groups, there was for dysmorphology, sensory affection, and modified GCS, with p values of 0.047, 0.002, and 0.005, respectively.

Table 4 demonstrates that there was no statistically significant difference between the two studied groups in terms of the frequency, duration, or history of seizures, with P values of 0.062, 0.165, and 0.0954, respectively.

Table 5 demonstrates that the WBC, serum neuron-specific enolase level, PO2, and PCO2

were statistically different between the two study groups.

Table 6 showed that the most common cause of encephalopathy in the studied group was due to CNS infections (9 cases= 37.5 %) but it also shows that there was no statistical significant difference between serum NSE levels and types of encephalopathy.

Serum neuron-specific enolase level in pediatric Encephalopathy has sensitivity 95%, specificity 88.5%, PPV 94%, NPV 90% and accuracy 93%.

In agreement with our study, **Shaik et al. [14]** found that NSE is raised in patients with acute central nervous system illnesses and that patients with seizures have higher levels of NSE than patients without seizures. NSE is therefore linked to brain injury and seizures, however it is yet unknown whether NSE levels rise before or after convulsions.

Additionally, in line with our study, **Attia et al. [15]** examined the blood level of neuron-specific enolase's predictive usefulness for newborns with birth asphyxia. In this study, the encephalopathy group's mean serum NSE level was considerably greater than the control group's [15.8 g/l], [P=0].003].

A number of other investigations shown that serum NSE may be a predictor of the severity of encephalopathy and a bad prognosis. On the other hand, other investigations revealed a significant correlation between NSE concentrations in CSF and the severity of encephalopathy stage, the degree of brain injury, and the ensuing neurological prognosis.

Wong et al. [16], studied the Cerebrospinal fluid neuron-specific enolase following seizures in children: role of etiology. Only children with severe neurologic diseases experienced elevated NSE levels; in these kids, It was impossible to determine whether element contributed most to the neuronal damage the seizure, the underlying cause, or another aggravating circumstance.

It is necessary to consider the technological confounders. These factors include sample processing, the impact of storage duration since concentrations in CSF may significantly fall after six months at -80°C, and, in particular, the hemolysis effect **[17].**

The blood NSE levels of infants with no or mild encephalopathy and those with moderate or severe encephalopathy did not significantly differ, according to **Nagdyman et al. [18].** However, in the same study, NSE's sensitivity, specificity, positive, and negative predictive values were shown to be 83, 65, 42, and 93%, respectively, in predicting moderate or severe encephalopathy (cut-off value 46 mg/l). This is not significantly different from our findings (cut-off value: 40.0 mg/l; respective values: 79, 70, 51, and 89%).

In a study carried out by **Celtik et al. [19],** they found that while the sensitivity and specificity rates were found to be rather high for the evaluation of diagnosis and poor prognosis of encephalopathy, the positive and negative predictive values of NSE were comparatively low.

The findings of this study show that NSE is raised in patients with acute central nervous system illnesses and that it is linked to seizures and brain injury.

CONCLUSIONS

There was statistically significant increase in serum NSE levels in encephalopathy group more than seizures group.

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