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Neuron specific enolase as a marker of seizure related neuronal injury

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ABSTRACT

Background: and purpose: Neuron specific enolase (NSE) is an established biomarker of neuronal damage. It is not clear how much seizures contribute to the neuronal damage, morbidity or mortality in critically ill neurology patients. The aim of this study is to determine the impact of seizures on neuronal injury in critically ill neurology patients by using neuron specific enolase as a biomarker.

Material and methods: Forty patients with clinical evidence of acute central nervous system disease associated with seizures were included as critically ill neurology patients with seizures [CINPS] (age in years 38.8 ± 17.54, mean ± SD; 22 males) and 43 age and sex-matched acute central nervous system disease without seizures were recruited as critically ill neurology patients [CINP] (age in years 37.84 ± 17.38 years mean ± SD; 24 males) The serum NSE assays were performed in CINPS (within 24 h of last seizure) and in CINP using an enzyme immunoassay kit.

Results: The level of serum neuron specific enolase was significantly higher in CINP with seizures compared to those without seizures. The length of ICU stay was more prolonged in those with seizures. There was a close correlation between the NSE levels and frequency of seizures. There was no significant difference in the mortality between both the groups.

Conclusions: NSE a marker of neuronal injury was elevated in patients with acute central nervous system diseases. It is significantly higher in patients with seizures in comparison to those without seizures. This warrants further studies to document aggressive treatment of seizures in acute neurologically ill patients can reduce neuronal damage.

1. Introduction

The estimated prevalence of seizures in neurology intensive care ranges from 11 to 16 percent (Acute Symptomatic Seizures, 2012). There is a well-documented evidence that generalized convulsive status epilepticus causes significant neuronal injury (Acute Symptomatic Seizures, 2012; Aicardi and Chevrie, 1970; Fujiwara et al., 1979; Corsellis et al., 1983; DeGiorgio et al., 1992). However, there is a less substantial evidence to prove the ill effects of both recurrent partial or generalized seizures. In an acute neurointensive care unit, how much the acute symptomatic seizures contribute to neuronal injury is not clear. There is clinical debate among clinicians whether treatment (usage of multiple antiepileptic or anaesthetic medication) is more harmful than the seizures itself in acutely ill patients (Parent et al., 2008).

The main challenge in these critical situation is to determine the severity of neuronal injury. Currently it is the clinical condition supported by radiological findings which determines the neuronal damage. Attempts are being made to identify a reliable biomarker for the early detection of neuronal damage in these patients for appropriate and aggressive management.

Various biomarkers have been studied in the context of epilepsy and brain damage. However, no validated marker has yet been established. Brain derived neurotropic factor (BDNF) (Toro et al., 2007) myelin basic protein (MBP), glial fibrillary acidic protein (GFAP) (Gurnett et al., 2003), microfilament (Lamers et al., 2003), and different enzymes (enolase, aldolase, pyruvate kinase, lactate dehydrogenase, creatine phosphokinase) (Royds et al., 1983) have been studied. Among all, neuron-specific enolase (NSE) is the most widely investigated biochemical markers of nervous tissue damage, as it is present only in low concentrations outside the nervous system (Kato et al., 1982) and found to be relevant and reliable biomarker in assessing the brain injury (El-

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Maraghib et al., 2013). Its role in differentiating seizure or syncope was evaluated by Lee SY et al. and suggested that increased NSE was associated with seizure activity thus estimating the NSE levels serve as a diagnostic marker (Lee et al., 2010).

Studies have shown that high levels of NSE are seen with status epilepticus (SE); De Giorgio CM et al. have demonstrated that levels of NSE were increased in all the types of SE studied, while complex partial (23.88 ng/ml) and subclinical subgroups (37.83 ng/mL) were associated with highest levels of NSE compared to controls (5.02 ng/mL). Incidentally these two subtypes recorded worse outcomes which indirectly indicated the severity and longer duration of underlying neuronal injury (DeGiorgio et al., 1999).

There are very few studies with regards to elevation of NSE in critically ill patients admitted to neuro-intensive care (El-Maraghib et al., 2013). Neuron-specific enolase has been used as marker of brain damage in various neurological disorders and other clinical conditions. Thus, we undertook this study to study the role of Serum NSE (sNSE) as a marker of Seizure related neuronal injury.

2. Materials and methods

This prospective observational study was conducted in the department of neurology in a tertiary care hospital, India after the approval of the Institutional Ethics Committee. Prospective patients were included from the Neuro-Intensive Care unit (NICU) from January 2015 to December 2015 over a period of one year. A written informed consent was taken from the close relative of the patients who participated in the study.

Patients having clinical, electrophysiological and imaging evidence of disease of central nervous system were termed as critically ill neurology patients. The CINP with record of at least a single seizure within 24 h prior to hospitalization and those who had seizure/s during the hospital stay were included as CINP with seizures. Those with evidence of CNS disease but without seizures are called as CINP without seizures and were matched for age and gender. Patients who had past history of epilepsy or chronic neurological condition were excluded.

Clinical information, medical history was obtained from reliable source (patients' family members). Routine blood biochemistry, hematological and other relevant Investigations were done. Electroencephalogram (EEG) was done in patients with seizures. Magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) studies were done where required. **APACHE II** ("Acute Physiology and Chronic Health Evaluation II") is a severity-of-disease classification system one of several ICU scoring system (KnausDouglas et al., 1991). It is applied within 24 h of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on a patient's age, PaO2,Temperature, Mean arterial pressure, Heart rate, Respiratory rate, Sodium (serum), Potassium (serum), Creatinine, Hematocrit, white blood cell count and Glasgow Coma Scale (GCS); higher scores correspond to more severe disease and a higher risk of death. The serum samples from patients with seizures were taken immediately after admission to NICU in patients who already had seizure prior to admission as their clinical manifestation. For patients who had seizures after hospitalization, the samples were obtained within 24 h of the seizure. The serum samples were stored at −80 °C till analysis. Three ml of blood was collected and centrifuged at 3000 rpm for 10 min. Haemolysed samples were excluded as it may cause false elevations of NSE levels. After separating serum, NSE assays were performed using an Enzyme Linked Immuno Sorbent Assay (ELISA) two-site sandwich technique. Critically ill neurology patients using EDI Human NSE kit.

Patients were considered to have a good outcome if the modified Rankin scale (mRS) score at the last follow up was 0–2 and a poor outcome if the mRS was > 2.

2.1. Statistical analysis

Mean and standard deviations (SD) were calculated for parametric variables and medians and quartiles for non-parametric variables. Pearson's correlation (parametric) and Spearman's correlation (non-parametric) were used to assess associations between variables. Statistical significance of differences between two groups was tested by independent two-tailed *t*-test. Frequency tables were compared with Pearson chi-square test (in 2 × 5 tables, 4 degrees of freedom) and Fisher's exact test (post-hoc comparisons in 2 x 2 tables, 1 ° of freedom). Statistical calculations were carried out using SPSS (ver. Win 5.1D, Statsoft Inc., Tulsa, OK, USA). Findings were considered statistically significant at $P < 0.05$.

3. Results

We included 83 patients meeting the selection criteria. There were 46 (55.42%) male and 37 (44.58%) female patients with a mean ± SD age of study population of 38.28 ± 17.36 years, minimum age was 11 years and maximum was 75 years. Both groups were comparable at baseline without any significant difference. Demographic characteristics of both groups are compared in Table 1.

In both groups, neuro-infection was the most common etiology (15 in CINPS and 16 CINP [both 37%] followed by cerebrovascular disease (Table 1)).

Out of 40 patients with seizure: 55% (n = 22) had generalized tonic clonic seizure/s followed by focal seizures with dyscognitive features in 27% (n = 11), Status Epilepticus in 10% (n = 4) and myoclonic seizures in 8% (n = 3).The average duration of seizure/s in cases was 9.12 ± 3.21 min. The maximum duration of clinical/electrographic seizure was 30 min and minimum was 5 min(Table 1).

Glasgow coma scale was compared between the two groups at the time of NSE level measurement. They were divided into three groups based on the scores (GCS between 13 and 15, 8–12 and < 8.) Both groups had similar distribution of scores in the GCS (Table 1).

APACHE II scores were used to evaluate the severity of the illness in critically ill patients. The mean APACHE II SCORE in cases was 11.8 ± 3.65 vs 11.14 ± 5.48 in controls (p = 0.52) (Table 1).

Table 1
Demographic characteristics of study population.

	CINP–S	CINP	P value
No Of Patients	40	43	NA
Male/Female	22:18	24:19	NA
Age,Mean(Range)	38.77 ± 17.54 (13–72 years)	37.84 ± 17.38 (11–75 years)	0.8
Type of Seizure			
a)Generalized tonic clonic seizures	*22(55.0%)*	*NA*	
b) Focal seizure/s	*11(27.0%)*	*NA*	
c) Status Epilepticus	*2(5.0%)*	*NA*	
d)NonConvulsiveStatus Epilepticus	*2(5.0%)*	*NA*	
d) Myoclonus	*3(08.0%)*	*NA*	
Etiology			
Neuroinfection	15 (37.5%)	16 (37.21%)	0.97
Vascular	14 (35%)	15 (34.8%)	0.98
Demeylination	1 (2.5%)	1 (2.3%)	0.95
Toxic	01 (2.5%)	00	NA
Tumours	0	1 (2%)	NA
Metabolic	0 2 (5%)	1 (2%)	0.45
Others	07 (17.5%)	9 (21%)	0.68
APACHE II Score	11.8 ± 3.65	11.14 ± 5.48	0.67
GCS:			
13–15	9	10	0.93
8–12	24	26	0.96
3–7	7	7	–

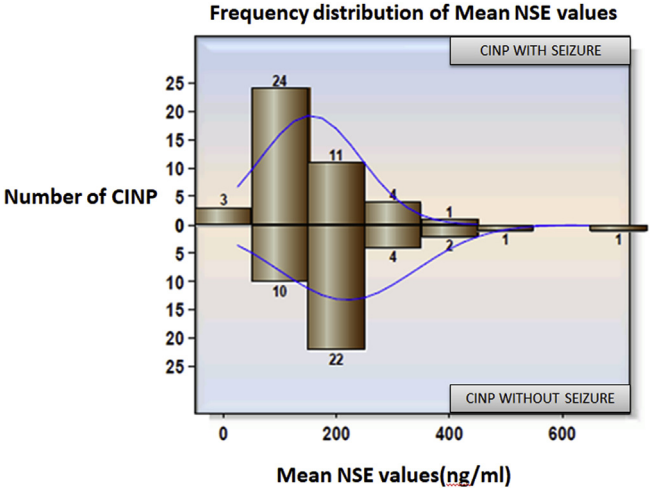

Fig. 1. Frequency Distribution Chart of serum NSE levels in critically ill neurology patients with seizures (CINPS) and without seizures (CINP).

3.1. NSE level in CINPS vs CINP

Mean ± SD sNSE level in cases was 206.96 ± 120.164 ng/ml vs 142.346 ± 88.67 ng/ml in controls (p = 0.006). Fig. 1 depicts the frequency distribution of sNSE levels among the study population.

3.2. NSE levels and the frequency of seizures

Mean sNSE level was less in those with 1–3 episodes of seizure, while higher levels were seen in those with status epilepticus (Fig. 2).

3.3. NSE levels and outcome

3.3.1. Duration of ICU stay

The mean duration of ICU stay was 9 ± 3.92 days in CINPS vs 6.97 ± 4.72 days CINP (p = 0.037) suggesting significantly prolonged ICU stay in patients with seizures (Fig. 3 and Table 2).

3.3.2. Time to discharge

The average time to discharge was 19.87 ± 11.51 days in cases vs 13.86 ± 8.13 days in control group. The two tailed P value = 0.007(Significant).

3.3.3. Modified rankin score

The modified rankin score at the time of discharge was significantly better in patients without seizures (CINP with seizures Vs CINP without seizures 3.45 ± 1.17 vs 2.69 ± 1.18) (p = 0.0042), whereas it was clinically insignificant after 3 month follow up (p = 0.6839) (CINPS Vs CINP: 1.83 ± 1.30 Vs 1.95 ± 1.37) (Table 2).

3.3.4. Glasgow coma scale (GCS) & NSE

GCS was recorded in all cases and correlated with mean sNSE levels; lower GCS was associated with higher sNSE levels of sNSE and were statistically significant (Fig. 4).

3.3.5. In hospital death

There were five deaths (cases –n = 03, 7.5%) and controls (n = 02, 4.65%) during the period of hospitalization (Z-Score = 0.5451, p = 0.582). However, the mean sNSE in these patients was statistically insignificant (p = 0.6774) (Table 2).

4. Discussion

There are three distinct enolase isoenzyme in brain; neuron specific enolase (NSE), formerly referred to as neuron specific protein, which is specifically localized in neurons, a nonneuronal enolase (NNE) and a third hybrid form. NSE and NNE can be used as specific metabolic markers for neurons and glial cells respectively (Pickel et al., 1976; Schmechel et al., 1998). Kirino T et al. proposed NSE as a reliable marker of axonal injury, nerve regeneration, target innervation and reinnervation (Kirino et al., 1983). It was found to be sensitive biomarker in ischemic neuronal injuries. DeGeorgio CM et al., in 1996 provided first evidence that increased serum NSE levels correlate with brain injury in humans (DeGiorgio et al., 1996). In 1995, its role in nonconvulsive status epilepticus was studied by Rabinowicz et al. who concluded that NSE was increased in this condition too (Rabinowicz et al., 1995). DeGiorgio CM et al. reported that NSE is increased in status epilepticus and concluded that it is a promising biomarker that correlates with duration of the insult and outcome (DeGiorgio et al., 1995).

There are inconsistent reports on the reliability of the estimation of serum NSE levels to denote neuronal injury compared to CSF NSE (cNSE), particularly in conditions of inflammation wherein the blood brain barrier is damaged (Lima et al., 2004). Though cNSE would give a clear picture of the underlying pathology, it is not feasible and convenient in many cases particularly in centre lacking the necessary

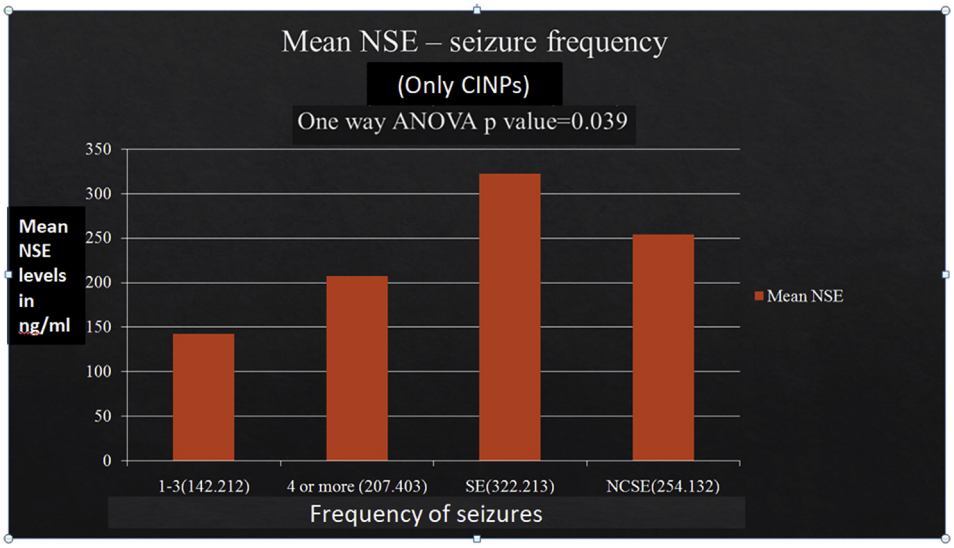

Fig. 2. Mean sNSE levels seen in study population in respect to the frequency of seizures.

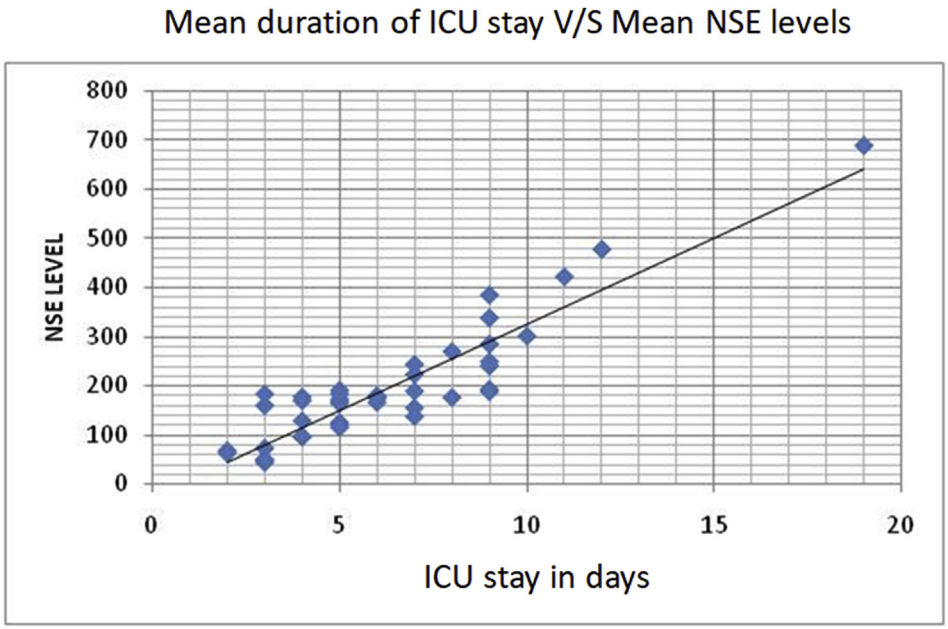

Fig. 3. Line Diagram Depicting Mean Duration of NICU stay vs NSE among our study population.

Table 2
Comparison of sNSE levels with NICU stay, mRS score at 3 months, mortality among the critically ill neurology patients with seizures (CINPS) and without seizures (CINP).

Parameter	CINP with seizures	CINP without seizures	p Value
NSE Level	206 ± 120.164	142.346 ± 88.67	0.006
ICU Stay	9 ± 3.92	6.97 ± 4.72	0.037
Mortality	3/40	2/43	0.58
NSE in patients who died	214.303 ± 47.67	210.827 ± 34.18	0.67
mRS at the time of discharge	3.45 ± 1.17	2.69 ± 1.18	0.0042)
mRs at 3 months	1.83 ± 1.30	1.95 ± 1.37	p = 0.6839

infrastructure; in such cases sNSE would be an alternative method.

Mounting evidences however suggest NSE can be a sensitive and reliable indicator of brain injury. Rabinowicz AL documented increased NSE levels in epileptic activity compared to non-epileptics, more so with complex partial seizures and generalized tonic clonic seizures (Rabinowicz et al., 1996). Elevated NSE was seen even with temporal lobe epilepsy also, though not to significant level (Palmio et al., 2008). Treiman DM has described the possible role of NSE as a sensitive indicator of neuronal injury associated with status epilepticus (Treiman, 1996). In post anoxic status epilepticus CSF NSE levels have been used as marker of neuronal injury (Simone BerettaAnna et al., 2018).

We studied the possible neuronal injury associated in critically ill patients with seizures in comparison to similar patients without seizures so as to know the effect of seizures on neuronal damage.

We estimated sNSE levels of cases (critically ill neurology patients associated with seizures) and compared with controls (critically ill neurology patients without seizures); enzyme levels were elevated in cases (CINP with seizures Vs CINP without seizures 206.96 + 120.16 ng/ml vs 142.35 + 88.67 ng/ml, p = 0.006). This indicates that seizures can worsen the brain damage in this critically ill neurology patients. We observed that the serum NSE levels correlated

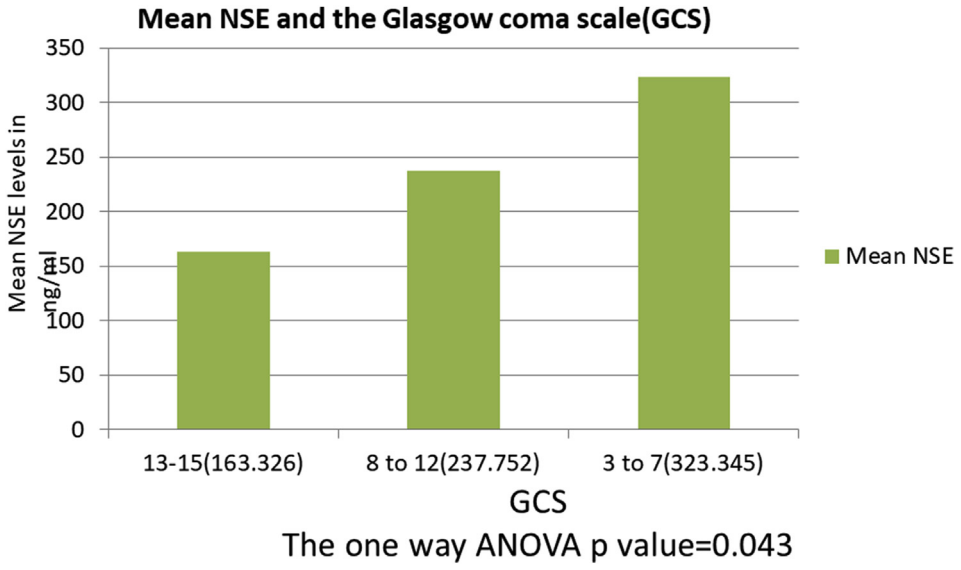

Fig. 4. Bar diagram showing the mean NSE levels in all CINP with different GCS scores.

with increased in number of episodes of seizure; highest levels being seen in status epilepticus (322.21 ng/mL) indicating the severity of the underlying injury. We could not document the serial changes in sNSE levels as the samples were drawn only once in this study.

The short-term morbidity, measured in terms of length of NICU stay ($p = 0.037$) and hospital stay ($P = 0.007$) were significantly higher in our cases than controls. The in-hospital mortality is not show any significant differences in both groups.

APACHE II score helps to monitor the quality of care given and is a useful tool in research studies because they allow comparison of outcomes among groups of critically ill patients with similar illness severity. There was no significant difference in APACHE score among cases and controls indicating that both groups had similar illness severity and there was no significant difference in the quality of care given to both the groups.

In critical conditions following neurological injury, it is often difficult to assess the prognosis. Meynaar IA et al. assessed the role of NSE in predicting the prognostic outcomes in those with post-anoxic coma; the results of this study demonstrated that elevated NSE in these patents indicate poor prognosis. They suggested assessing GCS in addition to NSE would provide more accuracy of neurological outcome (Meynaar et al., 2003). Our study too supports this fact as those with low GCS had high sNSE, and indicated poor prognosis.

There is emerging support for the use of CSF NSE to determine the severity of neuronal injury, particularly in conditions associated with minimal neuronal injury. Animal studies in pentylene tetrazol induced model of seizures also revealed raised CSF NSE levels after a seizure (Oses et al., 2004) This corroborates with finding of previous studies (DeGiorgio et al., 1995; Lima et al., 2004) and the present study in human beings indicating that seizures can cause neuronal damage.

Tumani H et al. report that serum NSE may not be a true indicator of neuronal injury in cases of single epileptic seizure (Tumani et al., 1999). Correlating CSF NSE levels with that of Serum levels would have helped us to draw a conclusion.

Ours is the first study assessing the sNSE in Indian population. This proves that sNSE levels are increased in any neuronal injury but significantly higher levels are seen in those with seizures, more so with status epilepticus.

5. Limitations of our study

The limitations of our study are smaller sample size and heterogenous study population with varied etiology of seizure, lack of serial serum NSE measurements. Correlation of neuronal injury with enzyme levels and radiological images could have thrown more light on the use of sNSE as a reliable indicator.

6. Conclusions

Thus serum NSE is a useful indicator of seizure related neuronal injury. The levels of sNSE positively correlated with severity of seizures, GCS, prolonged ICU stay and high morbidity. Further studies taking larger number of patients and serial measurements may help in establishing serum NSE as a prognostic tool.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2019.104509.

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