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ORIGINAL RESEARCH ARTICLE

Serum Neuron Specific Enolase as predictor of neurological disability and short term outcome in Ischemic Stroke

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ABSTRACT

Background and Purpose: The prediction of neurological outcome in acute cerebral infarction has enormous ethical and socioeconomic implications. The purpose of the present study was to investigate the relation between initial serum Neuron Specific Enolase (NSE) level and neurological disability and short term outcome. **Methods:** Serial analysis of serum NSE levels was performed in 90 patients resuscitated from witnessed, nontraumatic, normothermic, in- or out-of-hospital stroke. The neurological outcome was evaluated with the use of the National health stroke scale within 72 hours symptoms onset. The student's' test was used to compare patients and control. To study the correlation between quantitative variables, Pearson test was used. A probability value $p<0.05$ was considered statistically significant. **Results:** Serum NSE levels were significantly elevated in patients with acute cerebral infarction compared with the health control. The initial serum was higher in deteriorate group than in the non-deteriorate group. NIHSS on admission and on the 7th day correlated with the initial serum NSE level. **Conclusions:** This study shows that initial serum NSE level may be a useful marker for severity in acute ischemic stroke and that it may be well correlated with neurological disability and short term functional outcomes.

Keywords: Stroke, Neuron Specific Enolase, National Health Stroke Scale.

INTRODUCTION

Stroke is a form of cardiovascular disease affecting the blood supply to the brain. Also referred to as cerebrovascular disease or apoplexy, stroke actually represents a group of disease that affects about one out of five people in the United States. In India, the stroke accounts for 0.9 to 4.5 % total medical admissions and 9.2 to 30 % of admitted to neurological wards. The World Health Organization defines stroke as "rapidly developed clinical signs of focal (or global) disturbance of

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cerebral function, lasting for more than 24 hours or leading to death, with no apparent cause other than vascular origin (WHO: 1980). Many substances are released into the blood during this process, but the ideal marker would have to satisfy certain requirement; to be localized intracellular, to be present in high concentration in brain tissue, and finally to be relatively easy for detection. Neuron specific enolase (NSE) is mentioned as a possible reliable marker of neuronal tissue damage. NSE or the γγ dimmer of the glycolytic enzyme enolase is present in high concentrations in neurons, where it catalyses the conversion of 2-phosphoglycerate into phospho-enol-pyruvate. NSE is released in the cerebro-spinal fluid and blood in response to different forms of brain injury, including ischemic stroke, and can serve as a peripheral indicator of ongoing neuronal damage.[1-4] NSE has been the subject of many clinical studies and of experiments in animals setting.[5] Previous reports have focused on the release and the kinetics of NSE after acute cerebral infarction in humans[6-9] and animals[10], and in other types of brain damage caused by traumatic brain injury[11], hypoxia[12] cardiac surgery[13] and status epileptics.[14]

The objective of this study was to examine the association between posttraumatic serum NSE level and the short-term outcomes of physical disability measured by the National Institute of Health Stroke Scale (NIHSS), in patients with Ischemic stroke.

Patients

We included 90 patients (60 men and 30 women) with first-ever ischemic stroke admitted within 72 h of the onset of stroke symptoms to the intensive care unit of the Department of Neurology, Sri Aurobindo Hospital, Indore, India. All patients were treated according to the guidelines of the American Heart Association and none of them underwent surgical procedures. Our exclusion criteria were 1) CNS infection 2) Stroke more than 72 hours. The study protocol was approved by the appropriate institutional Ethical Committee and informed consent was obtained from all study participants. We also enrolled a group of 101 control individuals with no history of stroke, admitted to our hospital for routine checkups. Some controls were recruited from the hospital staff.

METHOD

Blood samples were collected at time of admission for the measurement of NSE. Blood was allowed to clot at room temperature, and serum was obtained immediately by centrifugation at 3500 rpm for 10 min. Serum was aliquoted into plastic tubes and stored at -20°C until assayed. NSE was measured with commercially available quantitative ‘‘sandwich’’ enzymelinked immunosorbent assay kits obtained from R&D Systems, according to the instructions of the manufacturer. Sensitivity of the assay was 1μg/L for NSE. A neurologist blind to all patient information, including the serum NSE level,

performed the examination. The degrees of neurological deficit during the acute phase were evaluated by the NIHSS at the time of admission and second evaluation was done after 7 days of admission.

We divided patients in two groups on the basis of neurological worsening at the time of admission and after 7 days.

1) Deteriorate ischemic stroke patients: - This group contains patients in which NIHSS Score increased more than 3 after second evaluation.

2) Non deteriorates ischemic stroke patients: - Remain patients in which NIHSS score decreased or increased but less than 3 after 7 days .

Statistical Analysis

Statistical Package for the Social Sciences 16 (SPSS 16.0) for Windows was used for all statistical analysis. Results are presented as mean ± standard deviation (S.D.). Significance of age difference between groups was tested using the parametric Student's t test. The statistical significance of the difference between categorical variables was tested with the Chi-square test. We compared the serum NSE levels of patients with cerebral infarction with those of the normal controls using the independent sample t-test. Differences in serum NSE level between the Deteriorate group and Non Deteriorate group were also analyzed using the independent sample t-test. The correlation between the serum NSE concentration and the NIHSS score on admission and on the 7 evaluated by using regression analysis with Spearman's rank coefficient. Only p values < 0.05 were considered significant.

RESULT

The demographic and clinical patient data with cerebral infarction are shown in table 1.

As compared with normal controls (67 male and 34 female with mean age 61.31 ± 12.37) patients with infarction (60 male and 30 female with mean age 59.71 ± 12.6) were no different in terms of age or sex as shown in table 2. 71 (79%) patients had hypertension, 24 (26 %) were smokers, 5 (6%) had atrial fibrillation and 29 (33%) were alcoholic. The level of serum NSE was significantly higher in those with acute cerebral infarction than in normal controls (7.48 ± 1.51 vs. 17.95 ± 4.54, p <0.001).

On comparing the initial serum NSE level in the deteriorate group and none deteriorate group, NSE levels were found to be significantly higher in the former group (23.9 ± 4.20 vs. 16.8 ± 3. 9, p < 0.005). In terms of an association between the initial level of serum NSE immediately after admission and short term clinical outcome we found that higher initial level of NSE correlated with the severity of neurological deficit (r = 0.901, p < 0.01) (Figure 1) and that short term neurological outcome was significantly correlated

with the initial level of serum NSE ($r = 0.883$, $p < 0.01$) (Figure 2).

Table 1: Demographic characteristics of the study

Parameter	**Stroke patients (n = 90)**	**Control (n = 101)**	**p value**
Age	59.71±12.6	61.31±12.37	0.375[a]
Sex (M/F)	60/30	67/34	0.542[b]
Hypertension (Y/N)	71/19 (79%)	30/61 (30%)	0.001[b]
Smokers (Y/N)	24/66 (26%)	26/75 (26%)	0.869[b]
Atrial fibrillation (Y/N)	5/85 (6%)	21/80 (21%)	0.004[b]
Diabetes Mellitus (Y/N)	28/62 (31%)	27/74 (27%)	0.526[b]
Alcohol (Y/N)	29/61 (33%)	26/75 (26 %)	0.341[b]

a = independent t test, **b** = chi sqaure test

Table: 2 % of Stroke patients group

NIHSS	Stroke patients group (%)
NIHSS at the time of admission	13.48 ± 7.18
NIHSS at 7 days after onset	12.3 ± 7.85
Types of group	
Deteriorate Group	14 (15%)
Not Deteriorate Group	76 (85%)
Serum NSE level at admission (ng/ml)	17.95 ± 4.54 †

(): % of total number; NIHSS, National Institute of Heath Stroke Scale; NSE, Neuron specific Enolase† Significant difference between patients and normal control (Independent t test, $p<0.05$)

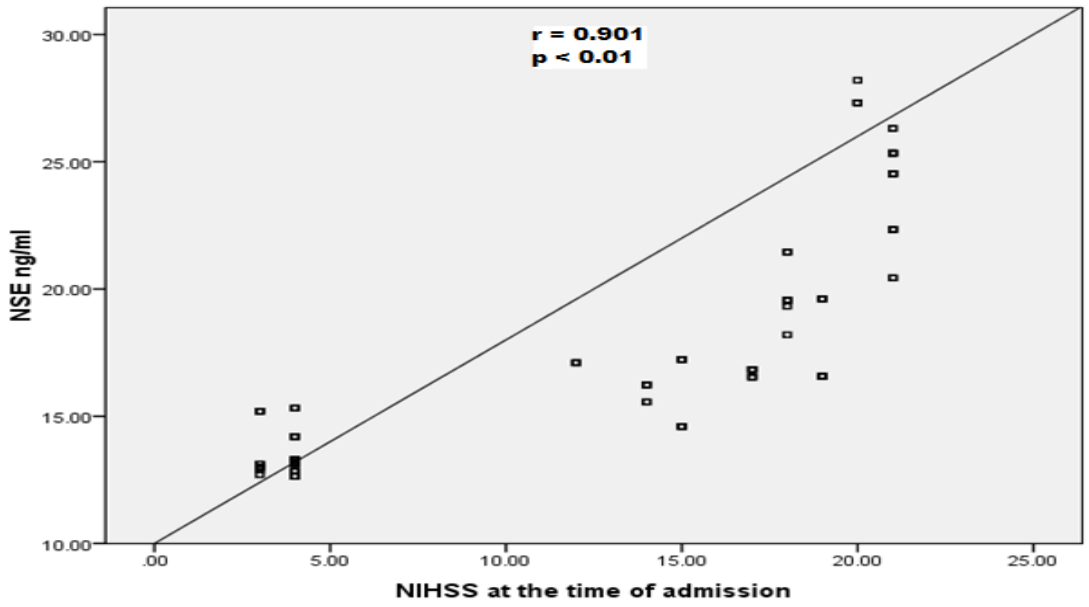

Figure 1: Scatter plot of serum NSE concentration against NIHSS scores at admission in acute cerebral infarction patients (Spearman rank correlation coefficient r = 0.901, p < 0.01)

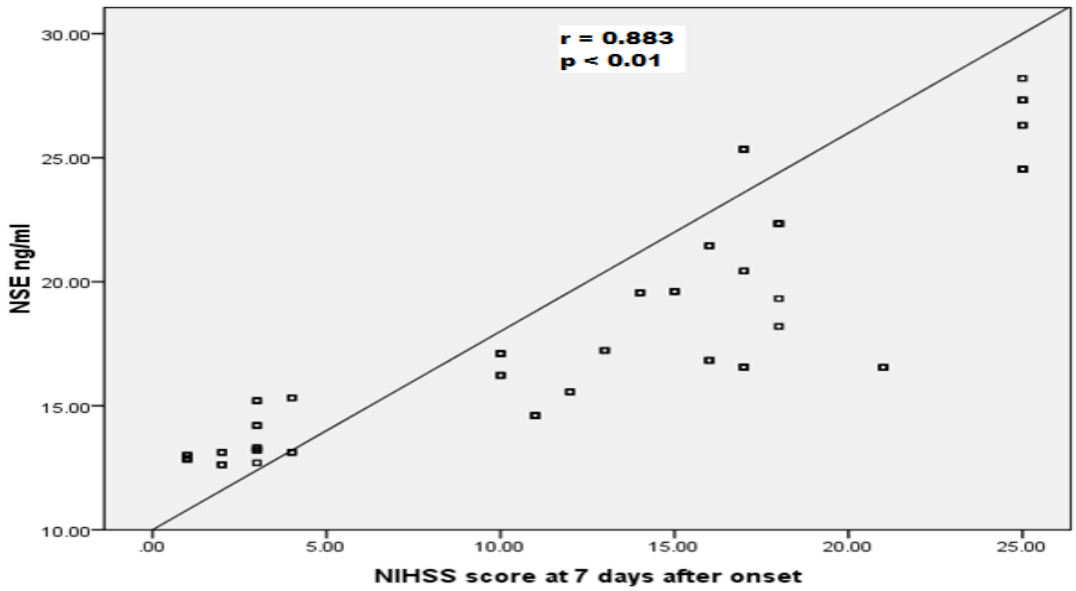

Figure 2: Scatter plot of serum NSE concentration against NIHSS scores on the 7th day after the onset (Spearman rank correlation coefficient r = 0.88, $p<0.01$)

DISCUSSION

NSE is the γγ-isoenzyme of the glycolytic enzyme enolase; it has a molecular weight of approximately 80000 Da and is present predominantly in neurons and neuroendocrine cell. [15] It has been found in several acute CNS insults, such as cerebral infarction during which changes in the brain-blood barrier and astroglial disintegration cause NSE to leak into the CSF and serum.[16] Increased NSE levels in the serum and CSF indicate neuronal damage. We evaluated the serum NSE level rather than the CSF level because the daily serum sampling was practical and posed no risk for older patients.

Our study expressed increased serum NSE levels within 72 hours of onset stroke versus the normal controls. This result suggests that the analysis of serum NSE during the acute phase of stroke is valuable for evaluating the neurological deficit of cerebral infarction patients. A previous report showed that patients with total anterior circulation stroke had higher initial NSE serum levels than patients with partial anterior circulation stroke or lacunars infarction. [17] In our study, the initial serum NSE level was significantly higher in patients in the deteriorate group than in none deteriorate group. This suggests that although the exact lesion size was not measured precisely in our present study, that the initial NSE level may be correlated with the degree of neurological deficit or short term

outcome. Whether NSE is good biochemical marker of short term outcome in patients with acute cerebral infarction is still controversial. Several previous studies have failed to demonstrate significance between NSE and short term outcome after infarction. The present study showed also good correlations between the initial serum NSE levels with short term out- come. And the results suggest that the patient's prognosis is worse if initial serum NSE level is higher and serum NSE may be used as an indicator of outcome in cerebral infarction patients.

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