Biochemical Serum Markers in Head Injury: An Emphasis on Clinical Utility

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Tissue damage can be diagnosed and monitored a number of ways. However, the assessment of traumatic brain injury (TBI) still remains less than optimal. A modality that has been of considerable interest is the assessment of certain brain specific biochemical markers in serum after TBI. This has been used in myocardial injury using creatine kinase-MB and troponin, which provide valuable information in diagnosis and determining the extent of the infarction, the effect of treatment, and the prognosis of the patient. The same principle has been applied by a number of researchers to establish a correlation between certain brain-specific serum markers and TBI as seen by imaging studies. A number of brain-specific biochemical markers are available like S-100B, neuron-specific enolase (NSE), glial fibrillary acidic protein, lactate dehydrogenase, myelin basic protein, and creatine kinase-B.[1-4] The assessment of these markers can be done in cerebrospinal fluid (CSF) and blood. An ideal marker is one that is quickly and simply measured in the serum. Serum is preferred over CSF because serum is more readily available than CSF. Above all, however, ideal markers of brain damage should be both highly brain specific and sensitive.

We selected 2 biochemical serum markers for our study, namely S-100B, which is a marker of astroglial tissue, and NSE, which is a marker of neuronal tissue, to provide a complete spectrum of neuroglial injury after TBI.

The objectives of this work were to study the temporal trend of the 2 serum markers after TBI, to compare the role of the 2 serum markers in an assessment of TBI, to identify patients who may benefit from early surgical intervention, and to prognosticate the outcome with the markers.

METHODS AND PATIENTS

After obtaining the necessary approval from hospital ethics committee, we began our prospective study. It included 40 patients between the ages of 15 and 50 years with mild to moderate closed TBI (Glasgow Coma Scale [GCS] > 9) with no gross systemic injury.[5] All patients were admitted within 6 hours of the primary injury. The following were exclusion criteria: gross systemic injury such as fracture or extracranial visceral injury; compound head injury; comorbid illness such as diabetes mellitus, hypertension, ischemic heart disease, or known cancer; and known psychiatric or other neurological illnesses. Patients with shock or postresuscitation and patients outside the time frame, ie, 6 hours, also were excluded.

On the basis of admission GCS, patients were divided into 2 groups: the mild head injury group (GCS, 14-15) and moderate head injury group (GCS, 9-13).

Computed tomography (CT) brain plain and venous sample of the 2 serum markers (S-100B and NSE) were taken on days 0, 3, and 5. Biochemical analysis was done with a commercially available kit (Fujirebio Diagnostics EIA Kit, USA/Sweden). It used the solid-phase noncompetitive direct sandwich assay technique for analysis. The results for S-100B and NSE were obtained in 4 and 2 hours, respectively. S-100B concentrations of 45 ng/L or above and NSE concentrations of 13 μg/L or above were considered abnormal.

Outcome assessment was done at 3 months with the Glasgow Outcome Scale (GOS). The patients were grouped into 2 categories: good outcome (GOS, 4-5) and poor outcome (GOS, 1-3). Data analysis was done with SPSS version 13.0 software with the Kolmogorov-Smirnov Z test, χ^2 test, independent-samples t test, analysis of variance, the Friedman test, the Duncan test, and receiver-operating characteristics curves.

RESULTS

All 40 patients were male. Eighty-five percent (n = 34) of the patients were in 20 to 40 years of age. Ten percent of patients (n = 4) were >40 years of age, and only 5% of patients (n = 2) were <20 years of age.

On the basis of admission GCS, there were more patients in the mild head injury group (n = 26) than in moderate head injury group (n = 14). Twenty-five percent (n = 10) of the patients had a normal CT scan on day 0, whereas 75% (n = 30) of the patients had evidence of parenchymal injury.

On serial CT scan findings over the next 5 days, it was observed that the patients fell into 3 broad categories. The first was the progressive category, which accounted for 33% (n = 13) of the patients. In these patients, the contusions kept

evolving over 5 days, or there was an appearance of a new contusion on an initially normal or abnormal scan. One patient with an initial normal CT had evidence of parenchymal damage on the day 3 scan. The second was the resolving category. In these patients, the contusions were either static or resolving. This category accounted for 45% (n = 18) of patients. The third category (n = 9) was made up of the CT-negative patients in whom the CT scan was normal.

In the concussion category, the S-100B values on days 0, 3, and 5 were 47.22 ± 1.39, 45.33 ± 1.32, and 43.67 ± 1.5, respectively. In the progressive category, the S-100B values on days 0, 3, and 5 were 97 ± 37.22, 177 ± 24.87, and 259.17 ± 58.89 in patients with mild head injury and 184 ± 58.09, 273.71 ± 42.22, and 396 ± 39.66 in patients with moderate head injury, respectively. In the resolving category, S-100B values on days 0, 3, and 5 were 104.64 ± 44.28, 79.18 ± 29.37, and 55.73 ± 19.92 in patients with mild head injury and 182 ± 68.68, 149.29 ± 65.43, and 108.71 ± 56.21 in patients with moderate head injury, respectively (Table 1).

In the concussion category, the NSE values on days 0, 3, and 5 were 12.19 ± 0.87, 11.86 ± 1.13, and 11.67 ± 0.89, respectively. In the progressive category, the NSE values days 0, 3, and 5 were 15.57 ± 2.33, 19.2 ± 3.71, and 22.35 ± 4.18 in patients with mild head injury and 27.34 ± 2.63, 31.06 ± 3.47, and 34.67 ± 4.49 in patients with moderate head injury, respectively. In the resolving category, NSE values on days 0, 3, and 5 were 18.09 ± 3.12, 16.93 ± 3.06, and 15.44 ± 2.21 in patients with mild head injury and 25.61 ± 4.98, 23.89 ± 5.25, and 22.4 ± 5.04 in patients with moderate head injury, respectively (Table 2).

Our next observation was the relationship of serum markers with serial imaging over 5 days as depicted in the histogram (Figure 1A and 1B). All 40 patients had elevated S-100B serum values on day 0 regardless of CT findings. By day 5, S-100B normalized in the majority of patients in the CT-negative category (n = 6 of 9) and a minority of patients in the resolving group (n = 3 of 15). In none of the patients with progressive contusions did the level return to normal. With NSE, a similar trend was not noted; a majority of CT-negative patients had normal values on day 0.

Figures 2 and 3 show the trend of the markers in the 3 categories. In the CT-negative category, there was a marginal

TABLE 1. S-100B[a]

Group	Type	Day 0	Day 3	Day 5
CT negative	Mild	9 (47.2222)	9 (45.3333)	9 (43.6667)
Progressive	Mild	6 (97)	6 (177)	6 (259.1667)
	Moderate	7 (184)	7 (273.7143)	7 (396)
Resolving	Mild	11 (104.6364)	11 (79.1818)	11 (55.7273)
	Moderate	7 (182)	7 (149.2857)	7 (108.7143)

[a]CT, computed tomography. Values are n (mean).

TABLE 2. Neuron-Specific Enolase[a]

Group	Type	Day 0	Day 3	Day 5
CT negative	Mild	9 (12.1889)	9 (11.8556)	9 (11.6667)
Progressive	Mild	6 (15.5667)	6 (19.2)	6 (22.35)
	Moderate	7 (27.3429)	7 (31.0571)	7 (34.6714)
Resolving	Mild	11 (18.0909)	11 (16.9273)	11 (15.4364)
	Moderate	7 (25.6143)	7 (23.8857)	7 (22.4)

[a]CT, computed tomography. Values are n (mean).

increase in markers above normal on day 0. Over the next 5 days, there was a gradual normalization of the value. In the progressive group, the high initial values corresponding to the degree of parenchymal injury on the day 0 scan further increased over the next 5 days as the contusion increased in size. A strong correlation exists between serum level of the 2 markers with the progression of head injury ($P < .001$). In the resolving group, the marker levels showed a decreasing trend.

Another important observation is that S-100B showed a steeper rise in concentration compared with NSE.

Figure 4 is 95 % confidence interval graph that reveals the performance of the 2 markers in the mild and moderate head injury groups over the 5-day period. The mean S-100B and NSE values in mild head injury patients were comparatively much lower than in patients with moderate head injury group on days 0, 3, and 5.

In terms of the role of serum markers on day 0 in the outcome assessment, it was observed that there is an inverse relationship between the 2, ie, patients with poor outcome had higher concentrations of markers. GOS was good for 72% of patients (n = 29) and poor in 28% of patients (n = 11) (Figure 5).

A strong statistical significance exists between day 0 serum levels of biochemical markers and outcome assessment ($P = .003$ between GOS and S-100B and $P < .001$ between GOS for NSE). On comparison between the 2 markers, NSE seems to be more reliable in this regard, as indicated by the minimal overlap of values and statistical significance ($P < .001$).

Figure 4 depict a clinical scenario of a patient in whom there is progression in the all 3 assessment methods, ie, clinical, radiologic, and biochemical. Corresponding values of the GCS and biochemical markers are shown in Table 3.

DISCUSSION

The S-100 protein is called so because of its solubility in 100% saturated ammonium sulfate at neutral pH. It was first described by Moore in 1965.[6] It is a calcium-binding protein (molecular weight = 21 kDa), which is localized in astroglial and Schwann cells.[7,8] It is implicated in a number of calcium-dependent regulations of a variety of intracellular activities.[9] The β subunit is more specific for the astroglial cells of the
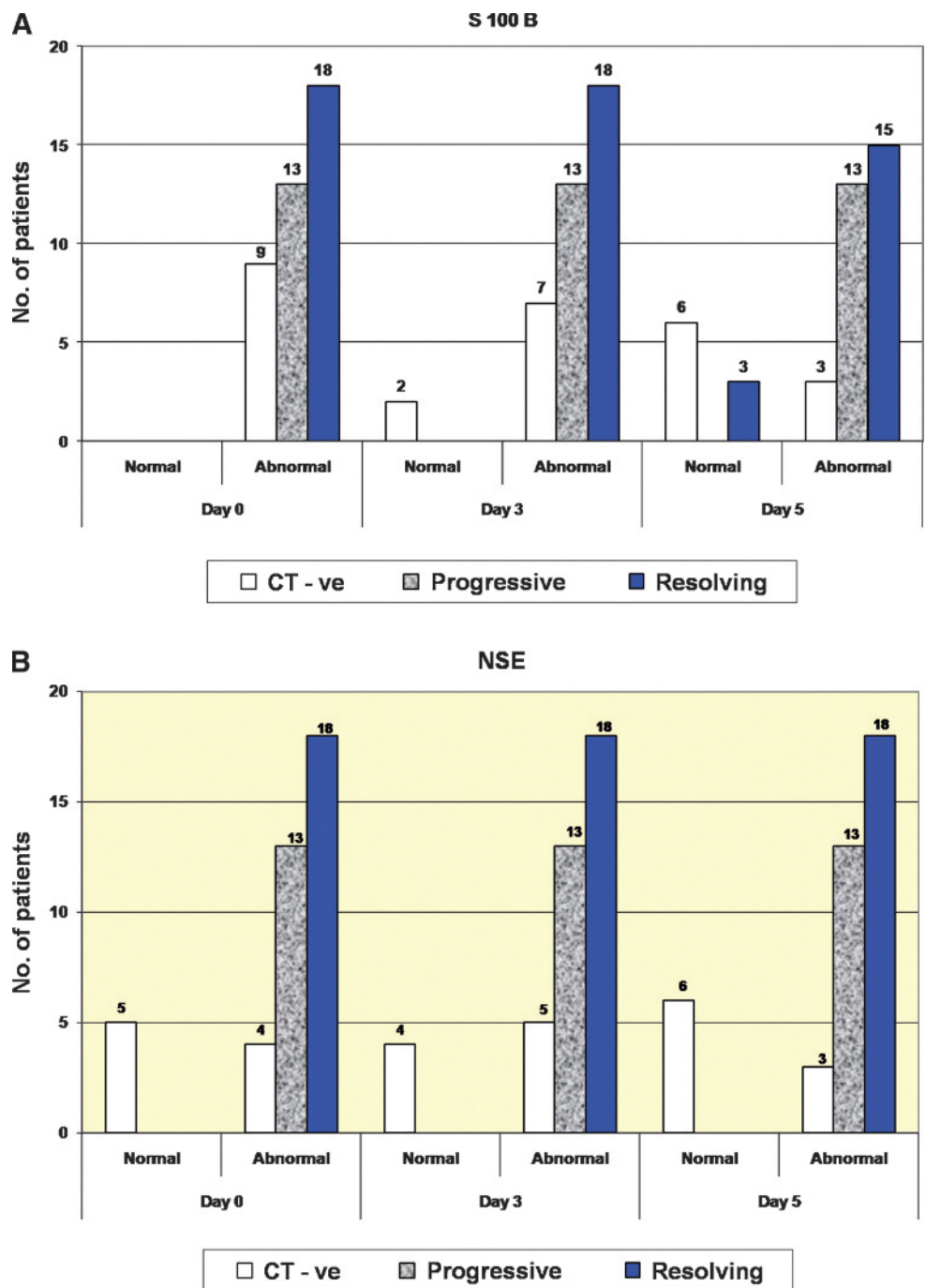
FIGURE 1. The histographic relationship of serum markers (A for S-100B, B for neuron-specific enolase [NSE]) with serial computed tomographic (CT) imaging over 5 days (days 0,3, and 5). The y axis represents the number of patients, and the x axis represents serum levels of the markers. Each day is divided into normal and abnormal serum levels. All 40 patients had elevated (abnormal) S-100B serum values on day 0 regardless of CT findings. By day 5, S-100B normalized in the majority of patients in the CT-negative category (n = 6 of 9) and a minority of patients in the resolving group (n = 3 of 15). In none of the patients with progressive contusions did the level return to normal. With NSE, a similar trend was not noted; a majority of patients in the CT-negative category had normal values on day 0.

central nervous system and commonly referred to as the brain-specific S-100B protein. It is also found in nonnervous cells such as adipocytes, chondrocytes, and melanoma cells, which may be a serious source of error.[10] The half-life is about 30 minutes.[11] Levels increase with advancing age even in patients with no previous history of neurological disorders.[12]

Age and sex variability is insignificant.[13,14]

NSE is a maker of neuronal integrity. It is glycolytic enzyme first described by described by Moore and McGregor in 1965.[15] The isoforms $\gamma\gamma$ and $\alpha\gamma$ are restricted to neurons.[16]

The molecular mass of NSE is 78 kDa, and its biologic half-life is probably >20 hours.

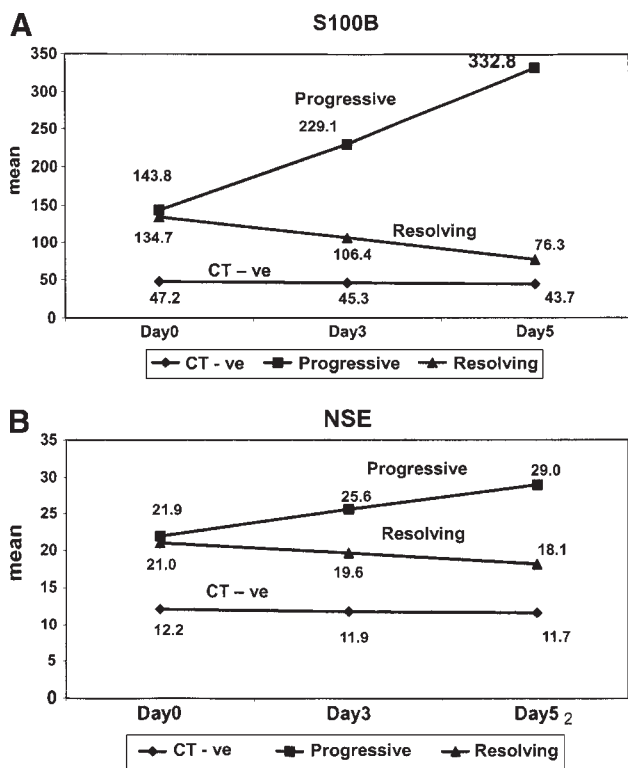NSE is also released in the blood by hemolysis of erythrocytes, which may be a serious source of error.[17]

A

B

FIGURE 2. The trend of the markers in the 3 categories. In the computed tomographic (CT)–negative category, there was a marginal increase in markers above the normal on day 0. Over the next 5 days, there was a gradual normalization of the value. In the progressive group, the high initial values corresponding to the degree of parenchymal injury on the day 0 scan further increased over the next 5 days as the contusion increased in size. A strong correlation exists between serum level of the 2 markers with progression of head injury ($P < .001$). In the resolving group, the marker levels showed a decreasing trend. A, S-100B. B, Neuron-specific enolase (NSE).

Levels of S-100B rise immediately and steeply after TBI. S-100B is a more reliable marker of the severity of primary injury that causes disruption of the blood-brain barrier through which brain-specific markers are released into the bloodstream. The early concentration peak of these markers reflects the mechanical disruption of brain tissue, ie, primary brain damage.[18] In contrast, rising NSE serum levels indicate secondary brain damage.

Our findings of raised serum level associated with low GCS scores and positive scan findings are similar to those available in the literature. Herrmann et al[19] and Raabe et al[20] demonstrated a positive correlation between the S-100B levels in serum and GCS, CT scan findings, and volume of brain contusions. However, we did not assess the volume of the contusions, neither did we correlate it with intracranial pressure. The correlation of serum levels of NSE with admission GCS, CT scan findings, and long-term outcome has been conflicting in the available literature. However, our assessment revealed a positive correlation. Ergün et al[21] and Skogseid et al[22] observed increased NSE serum levels in 18% and 31% of their patients, respectively, but control groups were not included.

One study failed to detect differences in serum NSE levels between mild head injury patients and control subjects. Similar findings were seen in our study.[23-33]

Some authors believe that very early serum values, obtained < 12 hours after the injury, might give false-positive results. Therefore, values obtained > 12 hours after the injury may give results more accurate for outcome prediction.[34]

Patients with good outcome and moderate disability demonstrated a similar pattern of S-100B levels, with high initial values and no secondary increase. Initial values were clearly associated with outcome; higher initial values were associates with moderate disability; and lower values were associated with

FIGURE 3. A 95 % confidence interval graph revealing the performance of the 2 markers in the mild and moderate head injury groups over the 5-day period. The bottom half of each graph represents the performance of markers in patients with mild head injury on days 0, 3, and 5; the top half of each graph represents the performance of markers in patients with moderate head injury on days 0, 3, and 5. The mean S-100B and neuron-specific eno-lase neuron-specific enolase (NSE) values in mild head injury patients were much lower than in patients with moderate head injury on days 0, 3, and 5.
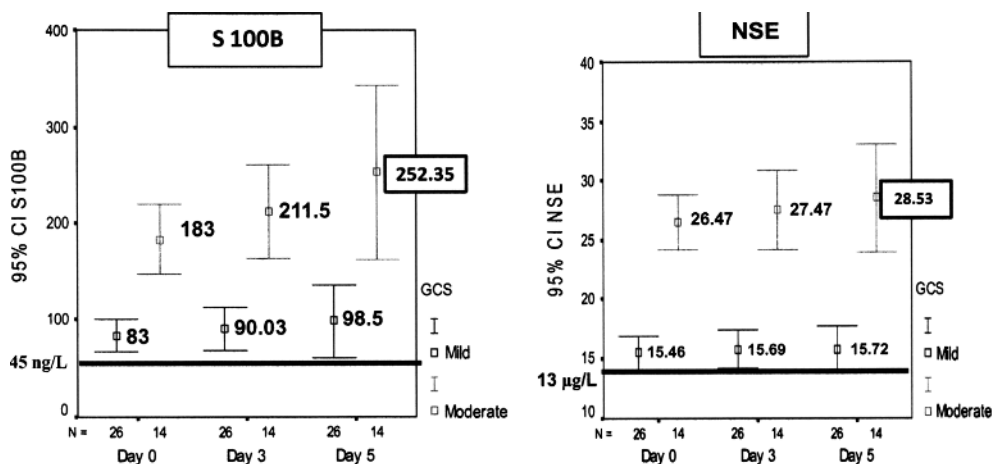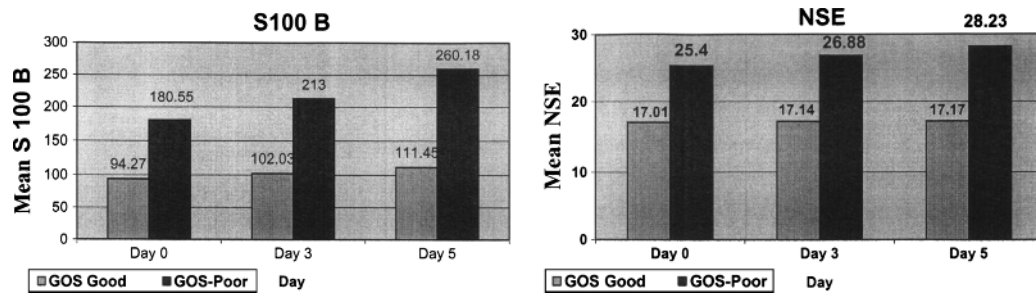
FIGURE 4. The role serum markers on day 0 in an outcome assessment. An inverse relationship was observed between the 2, ie, the patients with poor outcome had higher concentrations of markers. NSE, neuron-specific enolase. The lower half of each graph represents performance of markers in patients with mild head injury on days 0, 3, and 5 while the upper half of each graph represents the performance of markers in patients with moderate head injury on day 0, 3, and 5. The mean S 100B and NSE values in mild head injury patients were comparatively much lower than in patients with moderate head injury group on day 0, 3, and 5 respectively.

good outcome. Because S-100B has a half-life of 30 minutes, initially increased values of S-100B released by the primary damage should return to baseline levels rapidly unless there is ongoing damage. Rapid normalization of initially increased levels of S-100B has been found after minor head injury. S-100B showed a progressive rise in concentration in patients in patients with ongoing brain damage. The hypothesis of ongoing damage is supported by the observation of secondary increases even after day 3. Provided that there is a correlation between S-100B and ongoing secondary brain damage, the average time for the return of high S-100B values to normal levels may thus reflect the duration of secondary damage. This can be achieved only by serial assessment. Increasing or persisting high levels indicate ongoing damage despite current therapy, whereas quickly decreasing levels or persisting levels indicate no relevant ongoing secondary damage and sufficient therapy intensity.

Most studies of NSE levels in serum peak at the first measurement and decrease thereafter during the following

hours and days.[28,35] In mild head injury, NSE failed to separate patients from control subjects, suggesting that the sensitivity of this neuronal marker is inadequate. This might have been caused by the long (20 hours) biologic half-life. The slow elimination makes it difficult to assess the amount of primary damage and impossible to distinguish between primary and secondary injuries.

In the absence of secondary injury, S-100B normalizes at a faster rate than NSE because of its shorter half-life. Damage to glial cells after TBI is more extensive and occurs earlier than in neuronal cells, as evidenced by the acute rise in the concentration of S-100B compared with NSE.

This finding is in contrast to ischemic brain injury in which NSE levels rise earlier than S-100B, indicating the susceptibility of neuronal cells to ischemic injury. In comparison, glial cells are more resistant to ischemia.

Day 0 values for S-100 and NSE associated with a poor outcome were 180.54 $\pm$ 74.30 ng/L and 25.4 $\pm$ 5.52 μg/L,
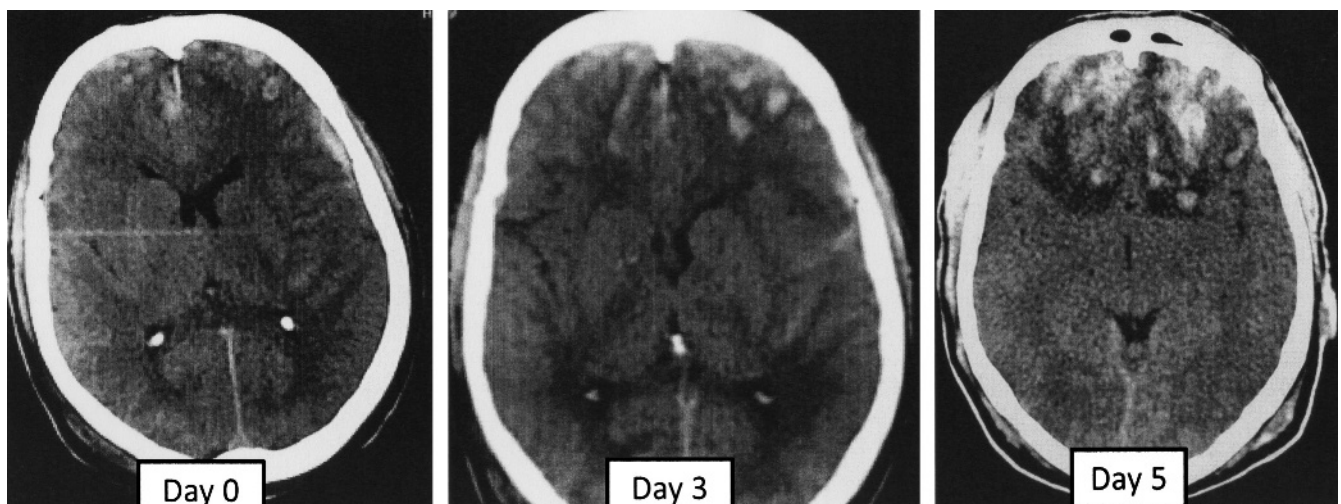

FIGURE 5. Computed tomographic imaging on days 0, 3, and 5, respectively.

TABLE 3. Corresponding Values of the Glasgow Coma Score and Biochemical Markers[a]

	Day 0	Day 3	Day 5
GCS	14	13	9
S-100B, ng/L	127	326	456
NSE, µg/L	24.6	28.9	32.6

[a]GCS, Glasgow Coma Score; NSE, neuron-specific enolase.

respectively. On the other hand, S-100 values of 94.27 ± 49.78 ng/L and NSE value of 17.01 ± 5.14 µg/L were associated with good outcome. Similar observations have been made by previous researchers.[36-41]

Predictions of outcome on the basis of NSE values have been conflicting in the literature. Whereas most other markers attempt to evaluate injury to the glial or Schwann cells of the central nervous system, NSE is the only marker that directly assesses damage to the functional cells of the brain (ie, the neurons). Its specificity for the brain is high.[35] The cutoff values for poor outcome were calculated on the basis of day 0 values of serum markers. Serum values of >195 ng/L for S-100B and >28.2 µg/L were associated with a poorer outcome.

Day 0 NSE values were considered more reliable in predicting outcome at 3 months because of the minimum overlap of the values. The day 0 specificity for outcome prediction for S-100B and NSE was 96% and 96.6%, respectively. The positive predictive value for outcome prediction for day 0 S-100B and NSE was 83.3% and 80%, respectively. Receiver-operating characteristics analysis revealed that the area under the curve for day 0 S-100B was 0.843 and 0.867, respectively.

This finding is in strong contrast to the study done by Li et al[37] in which they state that S-100B is clearly superior to NSE in terms of predictive value and appears to be a more promising serum marker in outcome prediction after severe head injury.[39,41]

Study Limitations

First, extraneural sources of these serum markers may give a false sense of a high degree of traumatic brain damage. Thus, the application of these makers may be restricted to a subpopulation of trauma patients with closed head injury and minimal systemic injury. Such a clinical scenario may be difficult to find. Second, we performed our study using a mechanical assay method that led to a long delay in obtaining the results. Compared with the other modalities of assessment (ie, clinical and radiological), the time lag made serum markers an inferior choice. However, an autoanalyzer is now available that can give results within 15 minutes. Third, these results were based on a small sample size. Further validation of these results needs to be

done with a large sample size. Fourth, no attempt was made for volumetric assessment of the hematoma with the biochemical markers. Fifth, long-term follow-up of the patients is lacking.

Future Applications

Future applications include decreasing unnecessary exposure to radiation by CT scans in a patient with normal initial values of biochemical markers; assessing the degree of disability and whether the disability or neuropsychological impairment after a traumatic event is really attributable to the head injury or to stress disorder, systemic injuries, or other causes; and determining the efficacy of treatment.

CONCLUSIONS

First, S-100B could be a more reliable marker of severity of injury compared with NSE. Second, day 0 NSE might be a more reliable predictor of outcome (GOS 3 months) compared with S-100B. Third, the usefulness of the markers in management decisions remains unclear.

We think that the results of our study are encouraging and provide the necessary foundation for continuing the study with a larger subject population. With continued improvement in the diagnostic techniques, these tests can be used in routine clinical management of TBI.

Disclosure

The author has no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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