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Diagnostic Value of S100B and Neuron-specific Enolase in Distinguishing Acute Central and Peripheral Vertigo

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Abstract

Aim: Vertigo is a common presenting complaint to the emergency department (ED). Distinguishing between acute central and peripheral vertigo can be challenging. During recent years, several biomarkers have been introduced for use in distinguishing central and peripheral vertigo. The current study determined whether S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) serum concentrations could effectively predict the central causes of vertigo.

Materials and Methods: This was a prospective study performed on 117 patients with acute vertigo who were admitted to the ED. All patients underwent magnetic resonance imaging (MRI) and the results of the MRI were considered the gold standard. S100B and NSE from blood samples taken <8 h after the onset of symptoms were measured in all patients.

Results: Finally, 117 patients were enrolled in the study, of which 43 patients had central vertigo and 74 patients had peripheral vertigo. The serum levels of S100B and NSE in the central group were significantly higher (60.62 vs 28.01 pg/mL, and 11.86 vs 7 ng/mL, $p<0.001$, respectively). The receiver-operating characteristic analysis demonstrated an AUC of 0.91 [95% confidence interval (CI): 0.84-0.96] and 0.93 (95% CI: 0.87-0.97) for S100B and NSE for predicting central vertigo and reported a sensitivity of 97.7% and 93% and a specificity of 87.8% and 89.2% for detecting the central cause of vertigo with S100B and NSE.

Conclusion: The serum S100B and NSE concentrations in central vertigo were significantly higher, and could be useful markers in screening central from peripheral vertigo in the ED.

Keywords: Neuron-specific enolase, S100B, central vertigo, peripheral vertigo, emergency department

Introduction

Dizziness and vertigo are the most common chief complaints referred to the emergency department (ED), with a prevalence of 1.8% among young adults and more than 30% in the elderly (1,2). Among patients with acute vertigo and dizziness, about 25% have a potentially life-threatening condition, such as a stroke in 4-15% (1,3).

Although vertigo does not usually increase the risk of death, it can affect the quality of life. Central vertigo is the cause of dizziness in approximately one-fourth of patients who experience dizziness (2). Therefore, we need a reliable, safe, and cost-effective method to differentiate between central and peripheral vertigo in the ED (4).

Cerebrovascular diseases such as transient ischemic attack or stroke, cerebellopontine angle tumor (i.e., acoustic neuroma), multiple sclerosis, neurodegenerative disorders, and migraine are the most common central causes of vertigo (5,6). In one case series on fifteen cases of misdiagnosed cerebellar infarction, half of the patients were less than 50 years old, had 40% overall mortality and had disabled deficits in about 50% of all survivors (7).

Brain imaging in patients with acute-onset vertigo is indicated in the following cases: in patients with vertigo that begin suddenly

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and the patient is suspected of having central causes of vertigo, or the patient has signs or symptoms of brainstem dysfunction or the patient cannot stand or walk. Magnetic resonance imaging (MRI) with diffusion weighting (DWI), which reliably detects new infarcts, is the modality of choice (8). DWI is widely considered an important imaging sequence for detecting various brain lesions, especially in the diagnosis of infarct lesions.

Although brain computed tomography (CT) is widely used in the ED setting to rule out potentially life-threatening disorders in patients whose examination is not completely typical of a peripheral vestibulopathy, it is significantly less sensitive in the assessment of a patient in the early phase of infarction, and in subjects with lacunar or posterior fossa infarction and for pathologies affecting the brainstem or vestibular nerve. Therefore, the diagnostic efficiency of brain CT was low in isolated vertigo (9,10). Biomarkers help distinguish central and peripheral vertigo and provide a strategy for identifying a subset of patients for MRI (11-13). Serum biomarkers are useful for distinguishing central from peripheral vertigo because of their association with the cause of central vertigo (11-13). MRI is not always available or cost-effective (14). Biomarkers are a strategy for identifying a subset of patients in need of MRI (12,13).

Neuron-specific enolase (NSE), a neuronal form of the glycolytic enzyme enolase, and the S100 calcium-binding protein B (S100B), a glial cytoplasmic protein, have been studied as useful biochemical markers to indicate brain damage observed under conditions such as head injury, cerebral infarction, cardiac arrest, and heart surgery (11).

Few studies have examined S100B and NSE in subjects with acute vertigo in the ED to differentiate peripheral from central vertigo (12-14). These biomarkers can be effective for emergency physicians in identifying the need for neuroimaging.

This study investigated the screening values of S100B and NSE in distinguishing central from peripheral causes of acute-onset vertigo in the ED.

Materials and Methods

Study Design

This prospective cross-sectional study was performed between January 2015 and March 2016 in the adult ED of Al-Zahra and Kashani Hospitals in Isfahan, Iran. The study was approved with Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1394.3.049) the and informed consent was obtained from each subject.

Study Setting and Population

Adult patients (>18 years) with the chief complaint of acute-onset vertigo who presented to the ED within 8 h of the onset of symptoms and signed a consent form to participate were eligible for the study.

Patients who had a previous history of vertigo and known cranial or auditory system disorders and a history of recent head trauma or malignancies were excluded. Patients with any persistent neurological deficits at admission and with contraindications for performing MRI were also excluded.

Study Protocol

All participants were examined by an Emergency Medicine Specialist at their arrival and the medical history, examination, and electrocardiograms of each patient were obtained. After the initial evaluation, blood samples for NSE and S100B levels were taken by a trained research assistant nurse at the same venipuncture that was used to measure hemoglobin and electrolytes.

Then brain diffusion-weighted MRI (DWI) was performed for all patients. A radiologist who was blinded to the biomarker results interpreted the MRI.

The patients with abnormal MRI findings related to central vertigo were in the central group, and the others were in the peripheral group. Biomarker levels were compared between the two groups. Emergency care has not been modified in this study. Figure 1 shows a flow chart of the study.

Biomarker Assessments

Peripheral venous blood (10 mL) from the patients with vertigo was sampled in plain tubes containing separation gels. The sampled blood was allowed to clot for 30 min and then centrifuged at 2,500 rotations per minute for 10 min. Serum samples were diluted with 1 mL of distilled water and then transferred to test tubes. The serum was frozen and then stored at -20 °C until further testing.

Electrochemiluminescence immunoassay was used to detect the NSE and S100B proteins serum levels. S100B and NSE levels were measured using a commercial kit (Elecsys® analyzer, Roche Diagnostics, Mannheim, Germany).

Results for NSE and S100B are expressed as nanogram per milliliter (ng/mL) and picograms per milliliter (pg/mL), respectively. Laboratory personnel were blinded to imaging findings and baseline characteristics of the patients.

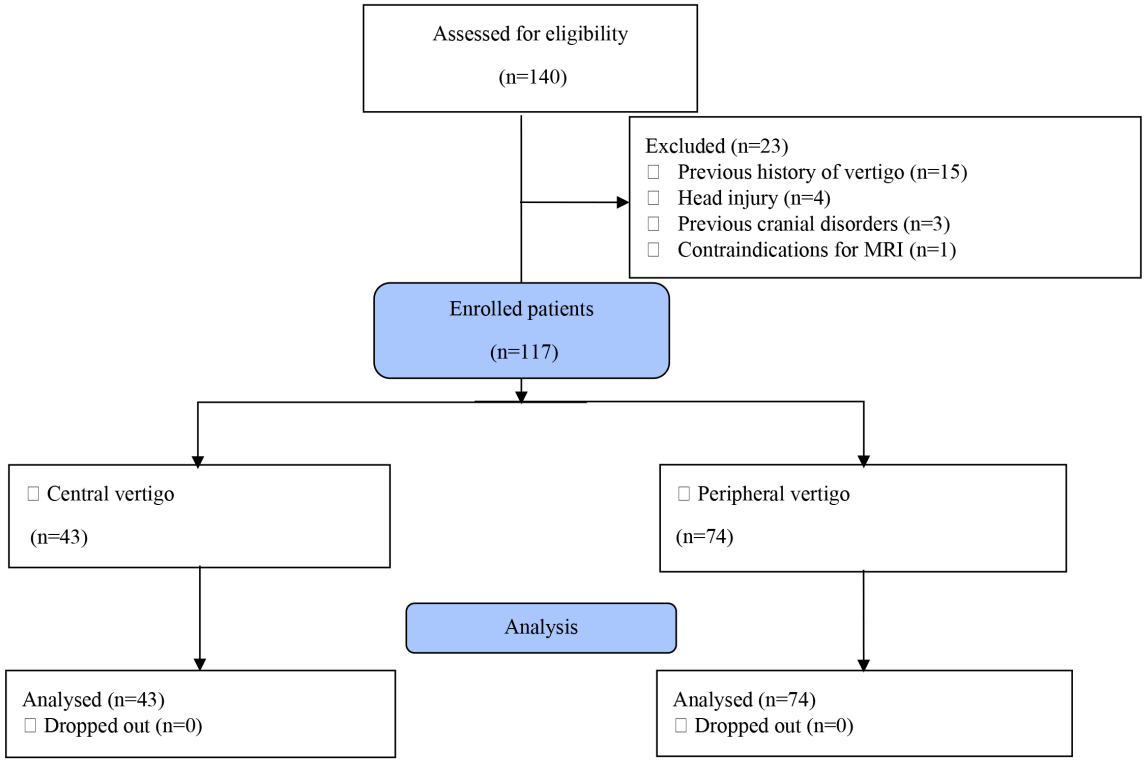

Figure 1. Study flowchart
MRI: Magnetic resonance imaging

Statistical Analysis

Data analysis was performed using the IBM Statistical Package for the Social Sciences software (version 22, NY, USA). Kolmogorov-Smirnov test was performed to check the normal distribution of variables. The chi-square test was used for the comparisons between qualitative variables. Student's t-test and paired t-test were performed for normally distributed variables, and Mann-Whitney and Wilcoxon tests were used for nonparametric data. Receiver-operating characteristic (ROC) analysis was performed to predict the accuracy with 95% confidence interval (CI) of each serum biomarker for differentiating central and peripheral vertigo. The cut values of serum NSE and S100B were calculated according to Youden's index. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

Out of 140 eligible patients, 117 subjects with acute-onset vertigo were finally enrolled in the study. Of them, 43 (36.8%) had MRI findings related to central causes of vertigo (placed in the central group) and the MRI findings didn't indicate the central causes of vertigo in 74 (63.2%) patients (placed in the peripheral group). Of the 43 patients with central causes of vertigo, 31 had an acute infarct of posterior circulation, 8 had an ischemic attack of the brainstem due to vertebrobasilar insufficiency, 3 had a cerebellar hemorrhage, and one patient had a cerebellar mass. Serum biomarker levels were not significantly different between these subgroups.

The mean age of the patients was 53.72±11.86 years in the peripheral group and 55.62±10.43 years in the central group. There was no statistically significant difference between the two groups in terms of age, gender, and vital signs ($p>0.05$). The baseline characteristics of the subjects are reported in Table 1.

The S100B serum levels in the central and peripheral groups were 60.62±10.63 pg/mL and 28.01±8.16 pg/mL. The serum level of NSE was 11.86±2.01 ng/mL for the central group and 7.00±1.47 ng/mL for the peripheral group. The serum levels of NSE and S100B in the central group were statistically significantly higher than those in the peripheral group ($p<0.001$).

Serum levels of NSE and S100B were good biomarkers for differentiating central and peripheral vertigo with the sensitivity of 93.0% and 97.7%, the specificity of 89.2% and 87.8%, the PPV of 83.3% and 82.4%, the NPV of 95.7%, and 98.5%, and overall

Table 1. The baseline characteristics in acute vertigo patients				
Group variables		**Brain MRI findings**		**p value**
		Peripheral vertigo (n=74)	**Central vertigo (n=43)**	
Age (year)		53.72±11.86	55.62±10.43	0.43
Sex (male)		35 (47.3%)	24 (55.8%)	0.45
Vital signs	Systolic blood pressure (mmHg)	143.7±26.8	150.6±28.5	0.323
	Diastolic blood pressure (mmHg)	82.4±16.2	82.5±21.3	0.928
	Pulse rate (/minute)	84.5±14.1	81.1±15.3	0.311
	Respiratory rate (/minute)	17.27±2.26	17.01±1.58	0.423
	Peripheral oxygen saturation (%)	98.6±2.1	98.7±2.2	0.756
Biomarker level	S100B (pg/mL)	28.01±8.16	60.62±10.63	<0.001
	Neuron specific enolase (ng/mL)	7±1.47	11.86±2.01	<0.001

Values are expressed as the mean ± standard deviation or number (%).
S100B: S100 calcium-binding protein B, MRI: Magnetic resonance imaging

Table 2. Diagnostic value of S100B and NSE in distinguishing central from peripheral vertigo		
Variables	**S100B**	**NSE**
True positive	42	40
False positive	9	8
True negative	65	68
False negative	1	3
Sensitivity	97.7 (87.7-99.9)	93.0 (80.9-98.5)
Specificity	87.8 (78.2-94.3)	89.2 (79.8-95.2)
Positive likelihood ratio	8.03 (4.35-14.84)	8.61 (4.45-16.64)
Negative likelihood ratio	0.026 (0.004-0.184)	0.078 (0.026-0.234)
Positive predictive value	82.4 (71.6-89.6)	83.3 (72.1-90.6)
Negative predictive value	98.5 (90.3-99.8)	95.7 (88.0-98.5)
Accuracy	91.5 (84.8-95.8)	90.6 (83.8-95.2)
AUC	0.928 (0.865-0.967)	0.911 (0.844-0.956)
Cut-off level	42.65 pg/mL	8.6 ng/mL

Values are expressed with 95% CI.
AUC: Area under the curve, NSE: Neuron specific enolase, S100B: S100 calcium-binding protein B, CI: Confidence interval

accuracy of 90.6% and 91.5%; respectively (Table 2). The cutoff concentration for serum NSE and S100B was 8.6 ng/mL and 42.65 pg/mL, respectively. The ROC analysis demonstrated an AUC of 0.91 (95% CI: 0.84-0.96) for S100B and an AUC of 0.93 (95% CI: 0.87-0.97) for NSE to predicting central vertigo (Figure 2).

Discussion

Finding a quick and accessible method to diagnose central vertigo in the ED is crucial. NSE, and the S100B, have been studied as useful biochemical markers to indicate brain damage observed under conditions such as head injury, cerebral infarction, cardiac arrest, seizure, and heart surgery (11,15). Several studies have evaluated the efficacy of serum biomarkers for differentiating central and peripheral vertigo (11-16). Akinci et al. (16) performed a study on 116 patients who sought treatment for vertigo and showed that serum levels of D-dimer, fibrinogen, and C-reactive protein cannot be significant markers for differentiating central and peripheral vertigo. However, few studies have been performed on the diagnostic accuracy of the S100B and NSE in this area.

In this study, one hundred and seventeen patients with acute-onset vertigo were evaluated. According to our results, the serum levels of NSE and S100B in the central vertigo were significantly higher than those in peripheral vertigo. S100B is found in the nervous system, particularly in astrocytes and NSE is a biomarker of neuronal loss (13). Therefore, NSE and S100B concentrations are elevated in central nervous system disorders. Consistent with this study, it was demonstrated in several studies (12-14).

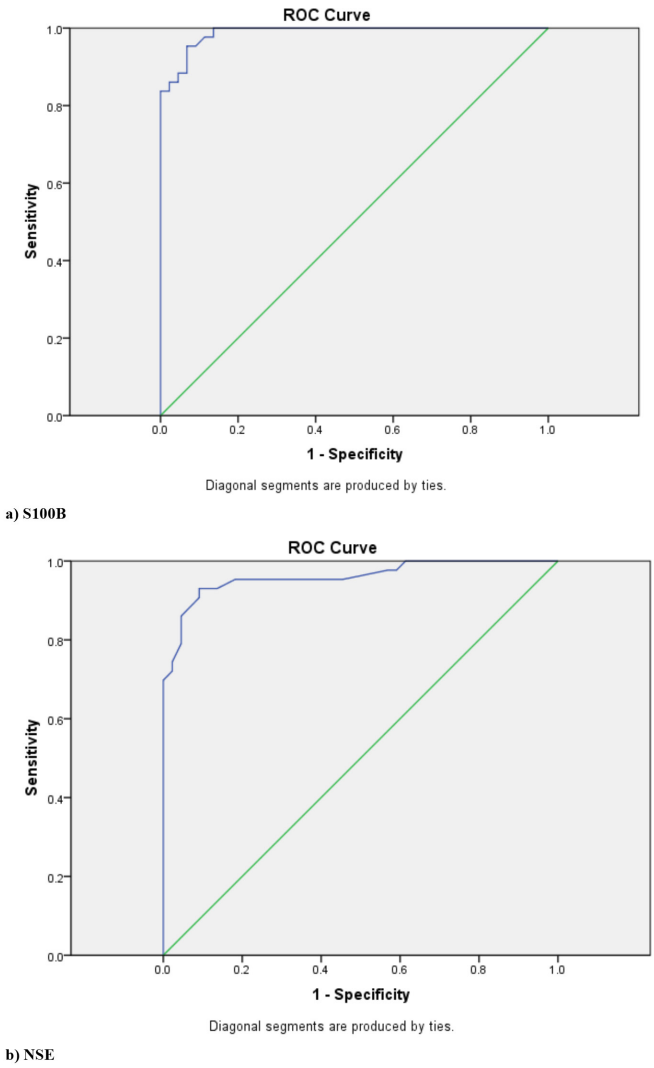

Figure 2. S100B (a) and NSE (b) the ROC curve of biomarkers in distinguishing central from peripheral vertigo

S100B: S100 calcium-binding protein B, NSE: Neuron-specific enolase, ROC: Receiver-operating characteristic

Moreover, S100B with a cut-off point 42.65 pg/mL and NSE with the cut-off point 8.6 ng/mL had high and acceptable sensitivity, specificity, PPV, and NPV for differentiating central and peripheral vertigo etiologies. S100B and NSE had good NPV (98.5% and 95.7%) to rule out central vertigo etiologies. Due to the high sensitivity (93.0% and 97.7%) and NPV, NSE and S100B may be useful diagnostic biomarkers in the diagnosis of central vertigo.

Kartal et al. (12) examined the serum S100B levels in 82 subjects with acute vertigo and demonstrated that the median serum S100B levels were significantly lower in patients with normal MRI compared to cases with abnormal MRI (27.00, vs. 60.94 pg/mL, p=0.04). Moreover, serum concentrations above 30 pg/mL had the sensitivity, specificity, PPV, and NPV of 83.89%, 51%, 51%, and 83.9%, for S100B in predicting the central cause of vertigo. They showed an AUC of 0.774 for S100B for predicting central vertigo. Finally, they reported that serum S100B levels were not sensitive enough to exclude patients for cranial MRI. This finding is contrary to the results of the present study.

Sohn et al. (13) in 77 patients with acute vertigo compared the serum S100B, NSE, glial fibrillary acidic protein (GFAP), brain-derived neurotrophic factor (BDNF), and interleukin-6 levels in to distinguish central from peripheral vertigo. Consistent with the present study, they reported that NSE and S100B levels were significantly higher in central vertigo compared with peripheral vertigo. The serum GFAP and BDNF levels were the same among the central and peripheral vertigo. They showed an AUC of 0.843 (95% CI=0.753-0.932) and 0.787 (95% CI=0.687-0.886) for NSE and S100B for predicting central vertigo. The sensitivity and specificity of NSE were 70.0% and 70.6% at a cut-off concentration of 73.1494 ng/mL and the sensitivity and specificity of S100B were 70.0% and 69.1% at a cut-off level of 766.9938 ng/mL in predicting the central cause of vertigo. The AUC of NSE and S100B to identify patients with central vertigo in this study was higher than that reported by Sohn et al. (13) and Kartal et al. (12).

Mozafari et al. (14) reported that serum S100B and NSE levels were significantly higher in acute central vertigo (217.13±119.28 vs. 77.39±31.67, p<0.001 and 30.90±7.34 vs.10.92±6.34, p<0.001), and could be used as accurate methods in the screening of these patients in the ED. The AUC was 90.3 (95% CI: 80.7-99.8) for S100B and 96.9 (95% CI: 93.7-100.0) for NSE in differentiating acute vertigo cases with a central cause. The serum S100B concentration cut-off of 119.68 pg/l gave sensitivity and specificity of 90.00% and 92.00%. At a cut-off NSE concentration above 18.12 ng/mL, the sensitivity and specificity of the test were 100.00% and 89.47% for detecting the central cause of vertigo. These findings are consistent with the results of this study.

Purrucker et al. (17) found that serum S100B levels were significantly higher in vascular vertigo cases (stroke) than in nonvascular vertigo cases. The sensitivity and specificity of S100B for indicating stroke in patients with acute vertigo were 94.4% and 31.8%.

The study by Zuo et al. (18) demonstrated that increased NSE (>11.85 ng/mL) was significantly higher in patients with cerebral infarction compared with non-infarcted subjects (45.7% vs. 22.5%, p<0.05) when evaluated in patients with acute vertigo.

Consistent with previous studies, we demonstrated that the serum NSE and S100B levels were significantly higher in patients with the central cause of vertigo. This study showed that serum levels

of S100B and NSE had an acceptable sensitivity for diagnosing the causes of peripheral vertigo from the central.

Study Limitations

In this study, biomarkers were measured only once. Repeated measurements at different times may provide a more accurate picture of each biomarker. The wide difference in time between the onset of symptoms and blood sampling may affect our calculated cut-off points.

Conclusion

The serum S100B and NSE concentrations were significantly higher in patients with central vertigo and could be useful markers with acceptable accuracy in screening central from peripheral vertigo in ED. These biomarkers are more cost-effective and easily accessible compared to MRI and provide a strategy for identifying a subset of patients for brain MRI as the gold standard tool.

1. NSE and S100B can serve as suitable screening tools in diagnosing central and peripheral vertigo in the emergency ward.
2. The NSE and S100B are more cost-effective and easily accessible as compared to MRI.
3. NSE and S100B do not need to be interpreted by a radiologist and the result is easily available to the physician.
4. NSE and S100B do not require the patient to leave the ED and can also be used in critically ill patients.

Ethics

Ethics Committee Approval: The study was approved with Ethics Committee of Isfahan University of Medical Sciences (approval no: IR.MUI.REC.1394.3.049, date: 30.06.2016).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.M., R.B., F.H., A.M., B.A., M.N-E., Concept: B.M., R.B., F.H., A.M., B.A., M.N-E., Design: B.M., R.B., F.H., A.M., B.A., M.N-E., Data Collection or Processing: B.M., R.B., F.H., M.N-E., Analysis or Interpretation: B.M., R.B., F.H., A.M., B.A., M.N-E., Literature Search: B.M., R.B., F.H., M.N-E., Writing: B.M., R.B., F.H., A.M., B.A., M.N-E.

Conflict of Interest: No conflict of interest was declared by the authors.

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