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# Role of S100B, neuron-specific enolase, and adrenomedullin in differentiating central and peripheral vertigo

Biomarkers in central vs peripheral vertigo

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**Abstract**
Aim: This study aimed to evaluate S100B, adrenomedullin (ADM), and neuron-specific enolase (NSE) as diagnostic biomarkers to differentiate central and peripheral vertigo in patients with dizziness.
Methods: A prospective cohort study was conducted with 88 patients (58% women) presenting with dizziness. Patients were categorized based on MRI findings into two groups: those with acute lesions (central vertigo) and those without lesions (peripheral vertigo). S100B, ADM, and NSE levels were measured and compared between the groups to assess their diagnostic value for central vertigo.
Results: Significant differences were found in S100B, NSE, and ADM levels between the central and peripheral vertigo groups (p=0.003, 0.008, and 0.010, respectively). Factors predicting MRI-detected lesions included age, mean arterial pressure, movement-induced and positional vertigo, neurological findings, history of hypertension, lack of response to symptomatic treatment, and elevated S100B, ADM, and NSE levels. Logistic regression analysis identified the lack of response to symptomatic treatment as the only significant predictor (p=0.0148).
Conclusion: S100B, ADM, and NSE levels significantly differ between central and peripheral vertigo, suggesting their potential as diagnostic biomarkers. However, only the lack of response to symptomatic treatment was a significant predictor. Further research is needed to validate these biomarkers alongside clinical assessments and imaging.

**Keywords**
adrenomedullin, neuron-specific enolase, S100B protein

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## Introduction

Vertigo is a sensation of movement that is experienced as rotation or turning without any actual movement. It occurs due to an abrupt imbalance in tonic neural activity within the vestibular system. It may have a central or peripheral cause.[1] Dizziness and vertigo are among the most common symptoms that prompt individuals to consult physicians.[2] The underlying etiology cannot be determined in 40-80% of patients presenting to the emergency department with vertigo.[3] The patient's medical history, physical examination findings, and most advanced imaging methods, e.g., cranial computed tomography (CT) and/or magnetic resonance imaging (MRI), are employed in the differentiation of peripheral and central vertigo. Indeed, publications are showing that there is an ischemic lesion in the cranial imaging of patients considered to have peripheral vertigo.[4] Consequently, laboratory tests and imaging methods, along with clinical evaluation, are necessary in the differential diagnosis of vertigo.

MRI is a high-cost and time-consuming method for the differentiation of peripheral and central vertigo.[5] Therefore, there is a need for rapid, reliable, highly sensitive, specific, and low-cost tests that can be used to ascertain the diagnosis of a patient with dizziness complaints in the emergency department.[6] Recent studies have found some biomarkers that indicate neuronal damage in cranial pathologies and show a correlation with nerve damage.[7] S100B, neuron-specific enolase (NSE), and adrenomedullin (ADM) are particularly notable in this respect. Studies have been conducted on the levels of these parameters, especially in patients with stroke and head trauma, and a correlation has been detected between the increase in these biomarkers and the level of damage.[8,9,10]

This study aimed to determine whether S100B, ADM, and NSE could be used as diagnostic biomarkers as an alternative to radiological imaging methods that have diagnostic value in differentiating central and peripheral vertigo in patients presenting to the emergency department with complaints of dizziness or in the selection of patients requiring further examination.

## Materials and Methods

### *Study Design*

This prospective cohort study investigated the diagnostic test value of S100B, ADM, and NSE and was conducted between March 2014 and March 2015 at an adult emergency department receiving 655 emergency admissions daily.

### *Study Population and Sample Selection*

All patients who presented to the emergency department of our hospital with complaints of dizziness were evaluated by an emergency medicine physician. Due to the observational nature of the study, the physicians were not influenced in their decisions concerning examination methods and evaluation algorithms.

The patient's demographic information, medical history, medications, vital signs, and detailed physical and neurological examination findings were recorded. All patients were questioned regarding the character of the dizziness they experienced, the onset time, any accompanying complaints, prior history of dizziness, and factors that exacerbated their complaints. Following clinical assessments, the patients were requested to undergo electrocardiography, hemogram, biochemistry, and other tests as deemed necessary by the physicians.

Excluded from the study were patients with newly developed ataxia and those with speech and/or vision disorders based on anamnesis and physical examination findings, as well as those with deficits in the neurological examination, given that the cause of dizziness is most likely central in these cases. Other exclusion criteria were being aged below 18; being pregnant; having a history of cerebrovascular events; having a known brain tumor, cranial pathology/space-occupying lesion, a history of epilepsy or anti-epileptic use, any neurological disorder (multiple sclerosis, leukodystrophy, etc.), or malignancy; having any contraindications to CT or MRI (having platinum metal in the body or a pacemaker or stent in the heart); and not providing consent, The study was conducted within one year after receiving ethics committee approval.

The patients were divided into two groups according to whether acute lesions were detected on MRI. The patients with acute lesions were considered as having central vertigo, and those without acute lesions were accepted as having peripheral vertigo.

### *Ethical Approval*

This study was approved by The Ethical Committee of Fatih Sultan Mehmet Training and Research Hospital (Date: 13.03.2014, Decision No: 2014/10).

### *Statistical Analysis*

Continuous variables were reported using mean, standard deviation, and confidence interval values, and categorical variables were expressed as frequencies and ranges. Student's t-test was used to compare the mean values of normally distributed variables between two groups, and the Mann-Whitney U test was used to compare the means of non-normally distributed parameters between two groups. The suitability of the variables for a normal distribution was evaluated with the Shapiro-Wilk test. Fisher exact test or Chi-square test and the continuity (Yates) correction were used to compare the frequencies of categorical variables between groups. The values and relationships of all variables in terms of predicting central vertigo diagnosed by MRI, which was the primary endpoint of the study, were evaluated with the Pearson correlation analysis and reported with r coefficients. A model was created using the variables determined to be highly related by correlation analysis and Fisher's exact test, and the percentage of explanation of this model for the population with the primary endpoint was calculated using a logistic regression analysis and the Nagelkerke R square test. For each measured biological marker, cut-off values with specificity to diagnose central vertigo or sensitivity to exclude it were determined through receiver operating characteristic (ROC) analysis. For the study, type I error was accepted as 5%, and type II error as 80%. The cases in which the p-value was below 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS v. 22.0 (IBM SPSS, USA) and MedCalc statistical packages.

*Reporting Guidelines*

The study was reported in accordance with STROBE guidelines.

## Results

A total of 122 patients who presented to the Emergency Department of Fatih Sultan Mehmet Training and Research Hospital with complaints of dizziness from March 2014 to March 2015 were examined. Three patients whose MRI findings could not be obtained, 28 patients whose complaints were determined not to be dizziness or whose dizziness was determined to have a neurological (e.g., epilepsy) or cardiac (e.g., arrhythmia) origin, and three patients with pathologies known to increase the S100B level were excluded from the study. As a result, the study was completed with a total of 88 patients, of whom 51 (58%) were women and 37 (42%) were men. The ages of the patients ranged between 22 and 90 years, and the mean age was 55.61±16.98 (95% confidence interval: 52.02-59.21) years. Clinically compatible lesions were seen on MRI in 23 of the cases, and this group constituted the central vertigo group. The comparison of the central and peripheral vertigo groups in terms of descriptive characteristics is shown in Table 1. Analysis of biomarker levels between central and peripheral vertigo groups revealed significant differences. The S100B levels were 712.95±294.23 ng/ml in the peripheral group and 1,569.39±1,120.13 ng/ml in the central group (p=0.003). Pre-adrenomedullin levels were found to be 263.50±173.60 ng/ml in the peripheral group and 546.99±470.48 ng/ml in the central group (p=0.008). Additionally, neuron-specific enolase levels measured 11.94±6.39 ng/ml in the peripheral group and 24.55±17.63 ng/ml in the central group (p=0.010). These findings suggest that these biomarkers may be useful in differentiating between types of vertigo. Logistic regression analysis of MRI findings

Through correlation analysis and univariate comparisons,

**Table 1.** Descriptive characteristics of the patients and comparison of the central and peripheral vertigo groups

| Demographic characteristics | | Total | Peripheral vertigo | Central vertigo | p |
|---|---|---|---|---|---|
| Gender, n (%)** | Female | 51 (58) | 40 (61.5) | 11 (47.8) | 0,327 |
| | Male | 37 (42) | 25 (38.5) | 12 (52.2) | |
| Age, mean ± SD (95% CI) (year)* | | 55.61 ± 16.98 | 52.35 ± 15.76 (48.45–56.26) | 64.83 ± 17.25 (57.36–72.29) | **0.002** |
| **Vital signs, mean ± SD (95% CI)*** | | | | | |
| SAP (mmHg) | | 144.14 ± 34.39 | 137.86 ± 29.16 (130.64–145.09) | 161.87 ± 31.29 (148.34–175.40) | **0.001** |
| DAP (mmHg) | | 83.49 ± 15.70 | 80.71 ± 14.85 (77.03–84.39) | 91.35 ± 15.67 (84.57–98.12) | **0.005** |
| MAP (mmHg) | | 103.71 ± 19.51 | 99.76 ± 17.93 (95.32–104.20) | 114.86 ± 19.87 (106.26–123.45) | **0.001** |
| Body temperature (°C) | | 36.28 ± 0.29 | 36.28 ± 0.30 (36.20–36.35) | 36.29 ± 0.25 (36.18–36.40) | 0.880 |
| Pulse (/min) | | 81.84 ± 16.42 | 81.43 ± 15.25 (77.65–85.21) | 83.00 ± 19.68 (74.49–91.51) | 0.696 |
| Respiratory rate (/min) | | 16.99 ± 1.31 | 16.86 ± 1.17 (16.57–17.15) | 17.35 ± 1.61 (16.65–18.05) | 0.126 |
| **Physical examination findings, n (%)**** | | | | | |
| GCS score: 14 | | 3 | 1 (1.5) | 2 (8.7) | 0.166 |
| GCS score: 15 | | 85 | 64 (98.5) | 21 (91.3) | |
| Nystagmus | | 54 (61.3) | 40 (61.5) | 14 (60.9) | 1.000 |
| Horizontal nystagmus | | 54 (61.3) | 40 (61.5) | 14 (60.9) | 1.000 |
| Vertical nystagmus | | 1 (1.1) | 1 (1.5) | 0 (0.0) | 1.000 |
| Movement and positional vertigo description | | 79 (89.8) | 62 (95.4) | 17 (73.9) | **0.009** |
| Tinnitus | | 4 (4.5) | 4 (6.2) | 0 (0) | 0.569 |
| Number of attacks First attack | | | 40 (61.5) | 14 (60.9) | 1.000 |
| >1 attacks | | | 25 (38.5) | 9 (39.1) | |
| Response to symptomatic treatment | | | 58 (89.2) | 5 (21.7) | <0.0005 |
| Lesion on computed tomography | | | 0 (0.0) | 6 (26.1) | <0.0005 |

*SD: standard deviation; CI: confidence interval; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure; GCS: Glasgow Coma Scale*

factors predicting whether vertigo was caused by a lesion detected on MRI were determined to be age, mean arterial pressure, presence of both movement-induced and positionally described vertigo, neurological examination findings, history of hypertension, lack of response to symptomatic treatment, and S100B, pre-ADM, and NSE levels. These factors were included in a logistic regression model. The Nagelkerke R square value of the logistic regression model was found to be 0.707, which was statistically significant (p <0.0001), and the model was able to identify 92.05% of the cases accurately. In the model, only failure to respond to symptomatic treatment was found to be statistically significant (p=0.0148). Not responding to symptomatic treatment increased the likelihood of detecting a lesion that could cause vertigo on MRI by 8.83 times (Table 2). Although positive neurological examination findings were very strong predictors, they did not have a statistically significant effect on the model that included all the above-mentioned variables (p=0.0811). The power of the created model to accurately distinguish the presence of a lesion on MRI was extremely high, with an area under the curve (AUC) value of 0.934 (95% confidence interval: 0.861-0.976).

According to the results of the ROC analysis, the AUC values of S100B, pre-ADM, and NSE for predicting MRI abnormalities related to vertigo were calculated and compared with each other. The results of this evaluation are shown in Table 3.

## Discussion

This study aimed to ascertain the potential of S100B, ADM, and NSE as biomarkers for differentiating between central and peripheral vertigo and to evaluate their reliability compared to radiological imaging methods. There are only a few studies on the utilization of such markers in the emergency department. It has been suggested that such markers can be used as more specific diagnostic tools in the rapid evaluation of patients in emergency department settings. To the best of our knowledge, the current study is the first to evaluate the utility of ADM in the distinction between central and peripheral vertigo.

**Table 2.** Logistic regression analysis of differential of central peripheral vertigo

| | Odds ratio | 95% CI | p |
|---|---|---|---|
| Neurological examination finding present | 8.83 | 0.76-102.02 | 0.0811 |
| No response to systemic treatment | **8.83** | **1.53-50.95** | **0.0148** |
| Movement and positional vertigo described | 3.34 | 0.19-60.08 | 0.4131 |
| Hypertension | 1.36 | 0.14-13.37 | 0.7912 |
| Age | 1.05 | 0.97-1.14 | 0.2204 |
| Neuron-specific enolase (ng/ml) | 1.04 | 0.80-1.35 | 0.7594 |
| Mean arterial pressure | 1.03 | 0.97-1.08 | 0.1705 |
| S100B (ng/ml) | 1.00 | 0.99-1.01 | 0.4998 |
| Pre-adrenomedullin (ng/ml) | 1.00 | 0.99-1.01 | 0.7233 |

*CI: confidence interval*

S100B is responsible for regulating energy metabolism in the brain cell. It regulates the proliferation and differentiation of neurons and glia. It is involved in many immunological functions of the brain. Previous studies have shown that S100B increases in the acute phase of minor head trauma and stroke.[11,12] Furthermore, it has recently been demonstrated that the serum S100B level is increased in patients with vertigo of central origin.[13,14,15] Kartal et al. reported that the serum S100B level was statistically significantly higher in patients with central lesions on MRI compared to those with negative MRI results.[15] Similarly, in the current study, the serum S100B level of patients with lesions on MRI was statistically significantly higher than that of patients with negative MRI results. In addition, we determined that the specificity of S100B was high (98.5%), and its sensitivity was low (43.5%) in predicting central lesions. This shows that S100B can be used diagnostically to differentiate between central and peripheral vertigo, but it cannot be employed as an exclusion test. Our findings are supported by a study conducted in Germany investigating the usability of S100B in differentiating posterior circulation stroke from vertigo of non-vascular causes (specificity: 94.4%, sensitivity: 31%).

In a meta-analysis study, Li et al. found that NSE increased after cerebral infarction and showed a high level of correlation with acute cerebral infarction, especially in the Asian population.[16] In our study, consistent with the literature, the serum NSE level was found to be higher in patients with lesions detected on MRI than in those with negative MRI results.

Kaca-Orynska et al. reported that both NSE and S100B levels were statistically significantly higher in the stroke group than in the control group, but only the S100B level was associated with the volume of stroke, neurological status at admission, and functional/clinical outcomes.[17] In our study, the S100B and NSE values of the patients with lesions detected on MRI were determined to be significantly higher than those without lesions.

Many researchers have documented a correlation between NSE and the volume of cerebral stroke, including Herdemark et al., who compared S100B and NSE levels between traumatic and focal ischemic lesion injury groups; Hetfield et al., who experimented using a rat stroke model; Steinberk et al., who evaluated the NSE level in cerebrospinal fluid in an experimental ischemic brain injury model; and Bulut et al., who investigated the prognostic value of NSE in ischemic stroke.[18,19]

The results of two studies conducted in Iran in 2020 and 2022, which had a similar methodology to the current study, showed promising results for the use of the NSE level in the differentiation of central and peripheral vertigo. The sensitivity and specificity values of NSE for detecting the central cause of vertigo were reported to be 93% and 89.2%, respectively, in the study of Masoumi et al. and 100% and 89.47%, in the study of Mozafari et al.[13,14] According to the results of the current study, although the specificity of NSE was consistent with the literature, its sensitivity was lower than previously reported. According to our findings, NSE can be used as a diagnostic tool

**Table 3.** Receiver operating characteristic analysis of S100B, pre-adrenomedullin, and neuron-specific enolase in predicting central vertigo

| | S100B | Neuron-specific enolase | Pre-adrenomedullin |
|---|---|---|---|
| **AUC** | **0.706** | **0.682** | **0.687** |
| **95% CI** | **0.600- 0.799** | **0.574- 0.777** | **0.579 – 0.781** |
| **p value** | **0.0043** | **0.0139** | **0.0054** |
| **Cut-off value** | >1393.9 | >22.9 | >501.4 |
| **Sensitivity (95% CI)** | 43.5 (23.2-65.5) | 43.5 (23.2-65.5) | 43.5 (23.2-65.5) |
| **Specificity (95% CI)** | 98.5 (91.7-100.0) | 98.5 (91.7-100.0) | 89.2 (79.1-95.6) |
| **LR+ (95% CI)** | 28.3 (3.8-208.8) | 28.3 (3.8-208.8) | 4.0 (1.7-9.4) |
| **LR- (95% CI)** | 0.6 (0.4-0.8) | 0.6 (0.4-0.8) | 0.6 (0.4-0.9) |

*AUC: area under the curve; CI: confidence interval; LR: likelihood ratio*

for differentiating between central and peripheral vertigo, but it lacks significance as an exclusion test.

Current studies have shown that ADM indicates white matter damage and is a substance that prevents brain damage.[20,21] Robertson et al. reported a positive relationship between severe traumatic brain injury and the serum ADM level. The authors explained that when brain tissue damage occurred in patients with severe traumatic brain injury, ADM could pass into the cerebrospinal fluid, and from there, it could enter the bloodstream through cracks in the blood-brain barrier.[22] In a study from China, Cai et al. found that the serum ADM level of patients presenting to the emergency department with aneurysmal subarachnoid hemorrhage was statistically significantly higher than that of the control group formed by healthy volunteers. In the same study, higher ADM levels on admission are related to clinical severity and worse outcomes in patients with acute spontaneous aneurysmal subarachnoid hemorrhage.[23] In another study published in 2023 conducted in Germany, it was reported that a higher bio-ADM level might be a prognostic marker for fatal and nonfatal events in ischemic stroke cases.[24] In our study, consistent with the literature, the serum ADM level was found to be significantly higher in patients with lesions detected on MRI compared to those with negative MRI results. We determined that the specificity of ADM was 89.2%, and its sensitivity was 43.5%, indicating that this parameter had a low sensitivity and relatively high specificity for the identification of central lesions. This shows that ADM can be a diagnostic tool for distinguishing between central and peripheral vertigo, but it cannot be utilized as an exclusion test.

### *Limitations*

The most important limitation of our study is the insufficient number of patients. All patients presenting with vertigo could not be included in our study, mainly because imaging could not be performed on all patients with vertigo due to ethical reasons. Therefore, the results of the study cannot be generalized to all vertigo cases. Another reason for the small sample size is the use of stringent inclusion criteria. The study population consisted of patients with ischemic stroke who had lesions detected on MRI and a control group. There were no patients with hemorrhagic lesions in our sample; therefore, our results cannot be generalized to cases of hemorrhagic stroke.

### *Conclusion*

In this study, the sensitivity values of S100B, NSE, and ADM were similar in differentiating between central and peripheral vertigo in patients with lesions detected on MRI, but the selectivity values of S100B and NSE were slightly higher compared to ADM and found to be correlated. This supports the idea that these parameters can be used as diagnostic markers to distinguish between central and peripheral vertigo, but they cannot be employed as exclusion tests due to their low sensitivity levels.

***Ethics Declarations***
*The study was conducted in accordance with institutional ethical standards and the Declaration of Helsinki. Ethical approval was obtained from the relevant committee prior to study initiation.*

***Animal and Human Rights Statement***
*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.*

***Informed Consent***
*Written informed consent was obtained from all participants.*

***Data Availability***
*The datasets are available from the corresponding author on reasonable request due to privacy restrictions.*

***Conflict of Interest***
*The authors declare that there is no conflict of interest.*

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***Author Contributions (CRediT Taxonomy)***
*Conceptualization: B.O.*
*Methodology: S.Ö., M.K.*
*Formal Analysis: M.K.*
*Investigation: E.Ü.A., H.D.*
*Data Curation: T.C.Ö.*
*Writing – Original Draft Preparation: B.O.*
*Writing – Review & Editing: B.O., Ö.E.O.*
*Supervision: Ö.E.O.*

***Scientific Responsibility Statement***
*The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing,*

*and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.*

***Abbreviations***

*ADM: Adrenomedullin*
*AUC: Area Under the Curve*
*CI: Confidence Interval*
*CT: Computed Tomography*
*MRI: Magnetic Resonance Imaging*
*NSE: Neuron-Specific Enolase*
*ROC: Receiver Operating Characteristic*

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