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Value of copeptin and S100B protein in the differential diagnosis of central vertigo and peripheral vertigo

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Main Article

Dr F Cakmak takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To investigate the usefulness of copeptin and S100B levels in the differentiation of central and peripheral vertigo.
Methods. Ninety patients were included in the study. Copeptin and S100B levels were measured using the enzyme-linked immunosorbent assay method.
Results. The time between symptom onset and presentation to the emergency department was longer in the patients diagnosed with central vertigo. S100B and copeptin levels were significantly higher in central vertigo patients. The confirmed cut-off value was 17 for the S100B level and 1.65 for the copeptin level.
Conclusion. Quick and reliable differentiation between central and peripheral vertigo is important to reduce the length of hospital stay of patients in the emergency department, and for patient comfort. S100B and copeptin levels are potential biomarkers in the differential diagnosis of central vertigo and peripheral vertigo for patients whose aetiology of vertigo cannot be differentially diagnosed with history-taking and physical examination.

Introduction

Clinical conditions described as 'dizziness' by patients are divided into four subtypes; vertigo (dizziness), light-headedness (wooziness), presyncope and disequilibrium (imbalance). These conditions are among the most common reasons for presenting to the emergency department. Vertigo, which is one of these clinical conditions, can be defined as the illusion of motion that the patient feels but which does not exist.[1] Dizziness is a non-specific complaint, and it can emerge as a result of the dysfunction of many organs, the effects of drugs and psychogenic factors. Therefore, many patients present to the emergency department complaining of dizziness. In the USA, 3–5 per cent of patients using the emergency department complain of dizziness. This is equivalent to 10 million patients per annum. The incidence in the community is estimated to be between 20 and 30 per cent. The cause of vertigo is often diagnosed by history-taking and examination, but further investigations are required in some clinical situations.[2–4]

Materials and methods

Ethical committee approval for this study was obtained from Bülent Ecevit University Clinical Research Ethics Committee (protocol number 2014-5-14/01, dated 11 March 2014). Support was additionally received from the Karabuk University Coordinatorship of Research Projects.

All patients who presented to the Emergency Department of Karabuk Training and Research Hospital and Samsun Training and Research Hospital complaining of dizziness between 1 July 2015 and 30 June 2016 were evaluated by emergency medicine specialists. All evaluated patients with pre-diagnosis vertigo were included in this study. Exclusion criteria were based on anamnesis (Table 1). Detailed information about the study was given to patients and/or their caregivers after exclusion. Patients who were willing to participate signed the volunteer consent form.

The demographic data of the patients and the time between symptom onset and presentation to the emergency department were recorded on the patient form. Venous blood samples of 6 ml were taken from all patients. Samples were centrifuged for 3 minutes at 6000 revolutions per minute, and blood sera were separated. The blood sera were numbered and stored at −60 °C until the end of the study.

The diagnosis and treatment duration of the patients were not considered; only observation was performed. Patients whose diagnosis was confirmed by magnetic resonance imaging (MRI) were included in the study. Patients without a diagnosis of vertigo and those who did not complete MRI were excluded from the study. The findings were recorded on the patient form.

Table 1. Exclusion criteria

Cerebrovascular diseases (except cerebellar, pons & basilar stroke)
Chronic obstructive pulmonary disease
Liver failure
Decompensated heart failure
Epilepsy
Drug-related vertigo
Renal failure
Malign tumour disease
Age <18 years
Pregnancy

Forty-five patients with a definitive diagnosis of central vertigo were included in the study. The number of patients with a diagnosis of peripheral vertigo was 227, and MRI was performed for these patients. We aimed to make the number of patients with central vertigo and peripheral vertigo equal; randomisation was performed, and 45 peripheral vertigo patients were also included in the study.

At the end of the study, copeptin and S100B levels were examined in blood sera samples, using the enzyme-linked immunosorbent assay method.

Statistical analysis

The descriptive statistics data collected comprised average, standard deviation, lowest and highest median, frequency, and ratio values. The Kolmogorov–Smirnov test was used to evaluate the distribution of the variables. The unpaired *t*-test and Mann–Whitney U test were used in the analysis of independent quantitative data. When the chi-square test and its conditions were not met, the Fisher's exact test was used in the study of independent qualitative data. The receiver operator characteristic curve analysed the effect level and cut-off values. SPSS® version 22.0 statistical software was used for the analysis.

Results

The average age of the central vertigo group was significantly higher than that of the peripheral vertigo group ($p < 0.05$). The proportion of male patients was significantly higher in the central vertigo group than in the peripheral vertigo group ($p < 0.05$). The time from symptom onset to presentation at the hospital was significantly higher in the central vertigo group ($p < 0.05$). One of the central vertigo patients died (Table 2).

In the differential diagnosis of the patients, it was observed that S100B level had significant efficiency in detecting central vertigo (area under the curve, 0.981 µg/l (95 per cent confidence interval (CI), 0.960–1.000 µg/l)). When the cut-off value for the S100B level was taken as 17, it had significant efficiency in differentiation between the central and peripheral vertigo groups (area under the curve, 0.933 µg/l (95 per cent CI, 0.873–0.993 µg/l)). The accuracy was 86.7 per cent, positive predictive value was 100 per cent, specificity was 100 per cent and negative predictive value was 88.2 per cent (Table 3 and Figure 1).

The copeptin level was found to have significant efficiency in the diagnosis of central vertigo (area under the curve, 0.792 pmol/l (95 per cent CI, 0.702–0.882 pmol/l)). Copeptin level was effective for differential diagnosis when the cut-off value was taken as 1.65 pmol/l (area under the curve, 0.722 pmol/l (95 per cent CI, 0.615–0.830 pmol/l)). The accuracy was 95.6 per cent, positive predictive value was 65.2 per cent, specificity was 91.7 per cent, and negative predictive value was 48.9 per cent (Table 4 and Figure 2).

In the differential diagnosis of central and peripheral vertigo, S100B and copeptin levels were found to be significantly higher in the central vertigo group ($p < 0.05$) (Table 2).

Discussion

Differential diagnosis of vertigo is essential, because the cerebellar and brainstem ischaemic diseases that may cause dizziness can be serious and potentially deadly. Vertigo can be classified as central or peripheral. The causes of central vertigo may be life-threatening; because of this, it is vital to establish a differential diagnosis for peripheral and central vertigo in patients with dizziness (Table 5).[5]

It has been reported that between 0.7 and 3.2 per cent of patients who presented to the emergency department in the USA with dizziness had ischaemic disease (central vertigo). The cost of diagnosing dizziness in the USA was, in 2013, estimated to exceed $10 million. Emergency service medics try to diagnose the diseases as quickly as possible and with the lowest cost. However, in some cases, it is difficult to diagnose them based on anamnesis and physical examination, and, because of this, further examination and imaging findings are needed. This leads to prolonged hospital stays and overcrowding in the emergency department.[2,3,6]

It is essential that differential diagnosis of life-threatening vertigo be performed rapidly and safely, which should also prevent emergency department overcrowding. Furthermore, the quality of life of vertigo patients can be significantly increased with appropriate treatment. The most important thing is the differential diagnosis of peripheral and central vertigo. A differential diagnosis can be made with good anamnesis and physical examination, but computed tomography (CT) and MRI of the brain are required in some clinical situations.[7,8] Magnetic resonance imaging is not available in many emergency departments; CT imaging is more common. In a study by Pavlović *et al.*, CT imaging was not helpful in vertigo patients without focal neurological signs.[9] In patients who cannot be differentially diagnosed, MRI imaging is required, leading to extended length of stay in the emergency department and increased cost of diagnosis.

S100B is a calcium-binding protein released from brain astroglial cells, and is detectable in cerebrospinal fluid and blood. High levels of S100B can be found in patients with infectious diseases, ischaemic conditions and traumatic brain injuries. It is also effective in detecting cerebral injury after stroke, successful cardiac resuscitation or cardiac surgery. There is a consistent correlation between the severity of ischaemic lesions and S100B level.[10,11]

Copeptin is a biomarker released as a precursor of arginine vasopressin from the posterior pituitary gland. It is easily detectable because of its stability in plasma and serum. It is estimated that copeptin could be widely used in emergency departments to ensure the diagnosis of life-threatening ischaemic diseases.[12,13]

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Table 2. Demographic and clinical features

Parameter	Central vertigo	Peripheral vertigo	*P*-value
Age (years)			0.025*
– Mean ± SD	68.2 ± 13.1	62.1 ± 12.4	
– Median	71.0	63.0	
Sex (*n* (%))			<0.001†
– Female	13 (28.9)	32 (71.1)	
– Male	32 (71.1)	13 (28.9)	
Time from symptom onset to presentation at hospital (days)			<0.001‡
– Mean ± SD	16.5 ± 19.0	5.2 ± 4.1	
– Median	6.0	3.0	
Patient mortality? (*n* (%))			1.000†
– No	44 (97.8)	45 (100)	
– Yes	1 (2.2)	0 (0.0)	
S100B level (μg/l)			<0.001‡
– Mean ± SD	27.5 ± 11.7	12.7 ± 2.7	
– Median	23.8	12.0	
Copeptin level (pmol/l)			<0.001‡
– Mean ± SD	4.1 ± 3.0	1.6 ± 1.0	
– Median	2.4	1.7	

*t-test; †Fisher's chi-square test; ‡Mann–Whitney U test. SD = standard deviation

Table 3. Efficiency of S100B in detecting central vertigo

Parameter	AUC	95% CI	*P*-value
Overall S100B level	0.981	0.960–1.000	<0.001
Cut-off value of 17	0.933	0.873–0.993	<0.001

Data represent S100B levels (μg/l), unless indicated otherwise. Accuracy, positive predictive value, specificity and negative predictive value were 86.7, 100, 100 and 88.2 per cent, respectively. AUC = area under the curve; CI = confidence interval

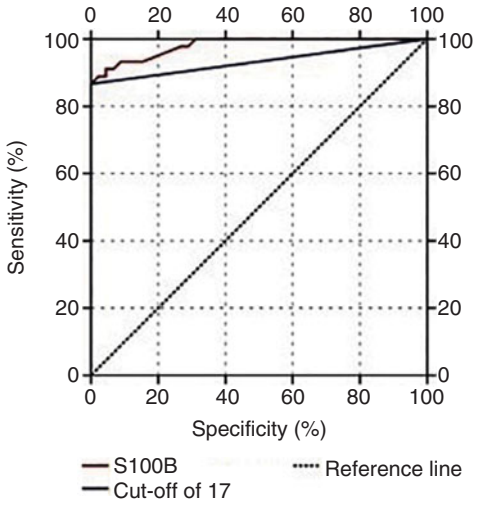

Fig. 1. Receiver operating characteristic curve of S100B levels, showing cut-off value, sensitivity and specificity for central vertigo.

Emergency departments in Turkey are quite crowded. Emergency physicians are not only trying to make a safe and rapid diagnosis; they are also trying to reduce the duration of stay in the emergency department. For this reason, a rapid, inexpensive and accurate diagnostic method is needed for patients who cannot be differentially diagnosed with central or peripheral vertigo. New biomarkers are also being analysed, and various algorithms are being created.

Vanni *et al.* evaluated the effectiveness of the 'STANDING' algorithm (i.e. (1) discrimination between spontaneous and positional nystagmus, (2) evaluation of nystagmus direction, (3) head impulse test and (4) evaluation of equilibrium) for a safe and effective diagnosis of the cause of vertigo in emergency department patients. The mean age of the patients was 58 ± 18 years, and 59.7 per cent of these patients were female. Patients with central vertigo were found to be older.[14] In a study by Perovic *et al.*, 46 of the 109 stroke patients were male. In addition, the mean age of the stroke patients was higher than in the control group.[12]

In a study by Kartal *et al.*, there were more male patients in the MRI-positive acute ischaemic group.[15] In contrast, the number of female patients was higher in the MRI-negative group without ischaemia. The mean age of patients with central vertigo was significantly higher than that of patients with peripheral vertigo. Regarding the difference between central and peripheral vertigo, gender was not found to be significant.

In the current study, the time between symptom onset and presentation to the emergency department was significantly greater in the central vertigo group than the peripheral vertigo group. Patients with peripheral vertigo were more likely to have a severe clinical presentation and to present to the emergency department earlier.

Akoglu *et al.* found that the probability of cardiac or hypovolaemic syncope in patients increased with high S100B levels, and adverse events were seen more often in patients who presented to the emergency department with syncope.[10] In addition, patients with high S100B levels had more hypoperfusion in the brain, showing that adverse events of cerebral damage were

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Table 4. Efficiency of copeptin levels in detecting central vertigo

Parameter	AUC	95% CI	*P*-value
Overall copeptin level	0.792	0.702–0.882	<0.001
Cut-off value of 1.65	0.722	0.615–0.830	<0.001

Data represent copeptin levels (pmol/l), unless indicated otherwise. Accuracy, positive predictive value, specificity and negative predictive value were 95.6, 65.2, 91.7 and 48.9 per cent, respectively. AUC = area under the curve; CI = confidence interval

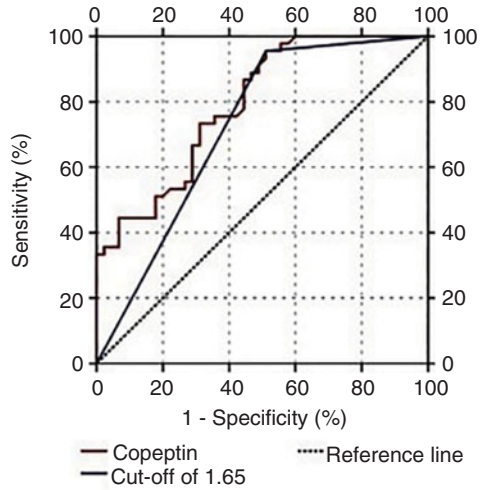

Fig. 2. Receiver operating characteristic curve of copeptin levels, showing cut-off value, sensitivity and specificity for central vertigo.

more frequent. In light of these findings, they reported that the S100B level could be used to predict the prognosis of patients with syncope.[10]

Rezaei *et al.* found that serum S100B level showed high sensitivity (94.4 per cent) but weak specificity (31.8 per cent) in the diagnosis of central vertigo.[11] Therefore, they concluded that serum S100B level is advantageous in diagnosis and follow up, and for estimating the likelihood of developing the complication of ischaemic stroke. Still, it should be noted that serum S100B level may give false positive and false negative results in the diagnosis of central vertigo.

Kartal *et al.* compared the MRI and S100B levels in the differentiation of peripheral and central vertigo, and concluded that the S100B level alone could not replace MRI sensitivity.[15] Still, it could be sufficient for differential diagnosis if the clinical symptoms and S100B levels were evaluated together.

In the current study, the S100B value was significant in the differential diagnosis of central and peripheral vertigo (area under the curve, 0.981 µg/l (95 per cent CI, 0.960–1.000 µg/l)). A cut-off value of 17 for S100B was found to be significant (area under the curve, 0.933 µg/l (95 per cent CI, 0.873–0.993 µg/l)). The accuracy was 86.7 per cent, positive predictive value was 100 per cent, specificity was 100 per cent and negative predictive value was 88.2 per cent in the differential diagnosis of central and peripheral vertigo. The S100B levels were significantly higher in patients with central vertigo than in those with peripheral vertigo ($p < 0.05$). This is consistent with other studies. S100B is a useful biomarker in the differential diagnosis of central and peripheral vertigo (Figure 1).

Katan *et al.* found that the level of copeptin is a better option compared with blood laboratory parameters such as blood glucose, C-reactive protein and white blood cells, as well as clinical measurements such as blood pressure and body temperature.[16] Copeptin is useful for the diagnosis and prognosis of patients with ischaemic stroke when it is evaluated with the National Institutes of Health Stroke Scale score.

Perovic *et al.* showed that ischaemic stroke patients had high copeptin levels, irrespective of age and sex. Their findings indicated that high copeptin level shows a poor prognosis.[12]

Table 5. Causes of vertigo

Peripheral vertigo
– Benign paroxysmal positional vertigo Ménière's disease
– Perilymph fistula
– Vestibular neuritis
– Labyrinthitis
– Chronic otitis media
– Vestibular ototoxicity
– Minor head trauma
– Vestibular migraine
– Psychogenic causes
Central vertigo
– Cerebellar stroke, haemorrhage or tumours
– Pons stroke, haemorrhage or tumours
– Thalamic stroke, haemorrhage or tumours
– Multiple sclerosis
– Central nerve system tumours
– Temporal lobe epilepsy
– Lyme disease
– Vertebrobasilar insufficiency

- This study investigated the usefulness of copeptin and S100B levels in the differentiation of central and peripheral vertigo
- The average age and ratio of male patients were higher in the central vertigo group than the peripheral vertigo group
- S100B level had significant efficiency in detecting central vertigo
- Accuracy, positive predictive value, specificity and negative predictive value for S100B were 86.7, 100, 100 and 88.2 per cent, respectively
- Copeptin level had significant efficiency in detecting central vertigo
- Accuracy, positive predictive value, specificity and negative predictive value for copeptin were 95.6, 65.2, 91.7 and 48.9 per cent, respectively

Dobša *et al.* studied copeptin's role in various diseases, and stated that C-peptide is a highly reliable biomarker in the diagnosis and follow up of cerebrovascular cases.[17] They concluded that other biomarkers (D-dimer, glutamate, matrix metalloproteinases and S100B) are also useful in early diagnosis and mortality estimation of intracerebral cases. Still, C-peptide is directly released into the systemic circulation, unlike the other biomarkers, so measuring it would be more meaningful.

Copeptin level was found to be significant regarding its efficacy in the differential diagnosis of central and peripheral vertigo (area under curve, 0.792 pmol/l (95 per cent CI, 0.702–0.882 pmol/l)). The cut-off value for copeptin was determined as 1.65 pmol/l (area under curve, 0.722 pmol/l (95 per cent CI, 0.615–0.830 pmol/l)). For copeptin in the differential diagnosis of peripheral vertigo and central vertigo, the accuracy was determined as 95.6 per cent, positive predictive value was 65.2 per cent, specificity was 91.7 per cent and negative predictive value was 48.9 per cent. Patients with central vertigo were found to have higher copeptin levels than those

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with peripheral vertigo ($p < 0.05$). The results obtained from this study are consistent with other studies. They indicate that copeptin is another biomarker that can be used to differentiate central and peripheral vertigo (Figure 2).

Limitations

A limited number of patients with cerebellar, pons and thalamus infarcts were included in the central vertigo group. Other causes of central vertigo could not be included in the study, and, in addition to the limited number of patients, this reduces the reliability of the results.

Conclusions

Rapid and safe differential diagnosis of central vertigo and peripheral vertigo is essential for patient comfort and finding the best treatment method. In this way, the duration of stay of patients in the emergency department can be reduced, and the workload of the emergency department, which is already too crowded, can be minimised. S100B and copeptin are highly efficient biomarkers for the differential diagnosis of central and peripheral vertigo in patients who cannot be diagnosed with history-taking and physical examination. However, in-depth studies with a large number of patients and more extended periods of follow up are needed. With routine use of S100B and copeptin, a more economical differential diagnosis of vertigo will be obtained.

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Competing interests. None declared

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