Evaluation of thiol / disulfide homeostasis and ischemia modified albumin levels in the differential diagnosis of central and peripheral vertigo

Oxidative stress and albumin in vertigo

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Abstract

Aim: We evaluated the role of ischemia-modified albumin (IMA) levels and thiol/disulfide homeostasis (TDH) parameters in the differential diagnosis of central and peripheral vertigo. Thus, we aim to present a new approach to the differential diagnosis of vertigo, especially in centers where magnetic resonance imaging (MRI) cannot be performed.

Material and Methods: The study was conducted in the emergency department (ED) using a prospective, non-randomized method. Patients with complaints of acute onset vertigo over 18 years old who underwent brain MRI were included in the study. Patients with acute ischemia with MRI were included in the central vertigo and with normal MRI in the peripheral vertigo group. Blood samples for native thiol (NT), total thiol (TT), disulfide, and IMA were collected at admission. Statistical analyzes were performed with the SPSS for Windows 16.0 Package Program.

Results: Age medians were found to be significantly higher in the central vertigo group compared to the peripheral vertigo group (65 vs 46; p<0.001). NT and TT levels were significantly lower in the central vertigo (n=29; 19.0%) group compared to the peripheral vertigo (n=124; 81.0%) group; Index-1 (D/NT) and IMA were significantly higher (p<0.05). In multiple regression analysis, age, Index-1 and IMA were found to be independent predictors in the differential diagnosis of central and peripheral vertigo (Odds: 1.061 [1.030-1.093], 2.423 [1.196-4.906], 1.060 [1.003-1.121]; respectively).

Discussion: It is possible to say that IMA and TDH parameters can be used in the differential diagnosis of vertigo when evaluated with the age of the patient.

Keywords

Age, Central Vertigo, Ischemia Modified Albumin, Peripheral Vertigo, Thiol/Disulfide Homeostasis

Introduction

Vertigo is a common complaint in the emergency department (ED) and is mentioned in 10% of all admissions [1]. The differential diagnosis of vertigo is difficult and critical in ED. There are many serious causes of vertigo with poor outcomes [1]. The rate of central etiology is approximately 3% [2]. In patients with isolated acute vertigo, peripheral vestibular system-related etiology is usually the first consideration. However, approximately 20-30% of vertebrobasilar or posterior system-originated stroke patients present with isolated vertigo without neurological deficit [3]. This leads to misdiagnosis of central vertigo [3].

Magnetic resonance imaging (MRI) is important in the differential diagnosis of vertigo [1,4]. However, MRI is not available in many EDs. In addition, false-negative results can be obtained using MRI in the first 48 hours, especially for the ischemic lesions of the posterior fossa [5]. In previous studies of stroke cases, many biomarkers have been evaluated for diagnostic or prognostic purposes [6-11]. However, not a single parameter has yet been established that can determine the indication of MRI in stroke patients and contribute to the clinical approach in practice [1].

Thiols in the plasma thiol pool form disulfide bridges as a result of oxidant stress. These disulfide bridges can also be reduced back to thiol groups. In this way, the thiol/disulfide balance works. It can be said that as the thiol/disulfide ratio increases, the status shifts to the antioxidant side; so, index-1 can give better information about antioxidant status [12]. In many diseases, it is known that this balance is collapsed in various ways. Bektaş et al expressed significant changes in stroke cases in terms of TDH parameters [9]. Şahin et al also showed that oxidative stress is on duty in benign paroxysmal positional vertigo cases [13].

The N-terminal of human serum albumin is an unstable segment; although this segment deteriorates when exposed to oxidative stress, its predisposition to bind some heavy metals such as cobalt increases. This is expressed as IMA. With ischemia and oxidative stress in stroke cases, this binding is increased and this reaction can be measured quantitatively [10,11].

In this study, we aimed to determine the value of TDH and IMA parameters in terms of the differential diagnosis of vertigo. A different approach can be provided using these biomarkers, especially in centers without MRI. It may be possible to avoid the cost of MRI through these biomarkers.

Material and Methods

Study Design

The study was carried out in the ED using a prospective, observational method from 01.07.2018 to 31.12.2018. The study was approved by the local ethics committee of Ankara Yıldırım Beyazıt University Faculty of Medicine (25.06.2018/137). Informed consent was obtained from each participant.

Study Setting and Population

Patients who were admitted to the ED with acute onset (within the last 24 hours) of vertigo and who underwent brain MRI for the differential diagnosis of peripheral/central vertigo were included in the study. Patients for whom MRI was contraindicated, under 18 years of age, pregnant and/or tobacco users were excluded from the study. Patients with significant neurological symptoms and/or signs such as motor/sensory neurologic deficits, speech disorder, unconsciousness and seizure, with all types of lesions (hematoma, mass, cyst, aneurysm, arteriovenous malformation, etc.) other than ischemic infarcts on MRI, acute ischemic lesions other than posterior fossa lesions, and with all infections and previous diagnosis of peripheral vertigo were excluded. The causes of lightheadedness other than central and peripheral vertigo, such as traumatic emergencies, acute crisis of cardiovascular and metabolic diseases, were also excluded.

Study Protocol

When patients who met the criteria were admitted to the ED, blood samples were collected for TDH parameters and IMA within the first hour. MRI was performed in patients without contraindications. Patients without any pathology on MRI were included in the peripheral vertigo group. Patients compatible with acute ischemic infarct in the posterior fossa on MRI were included in the central vertigo group.

The TDH and IMA parameters were integrated into routine biochemical tests and were studied simultaneously. The TDH parameters consisting of native thiol (NT), total thiol (TT) and disulfide (D), were measured by an automatic spectrophotometric measurement method developed and defined by Erel and Neşelioğlu [12]. In this method, reducible disulfide bridges are reduced to thiol groups, and then the total thiol level, consisting of native and reduced thiols, is measured. Half of the difference between total and native thiol forms the amount of dynamic disulfide. The ratios of these parameters (Index 1: D/NT; Index 2: D/TT; Index 3: NT/TT) were also analyzed. Samples for IMA were analyzed using the Albumin Cobalt Binding test mentioned in the study of Bar-Or et al [14]. This test measures the capacity of human serum albumin to absorb reduced cobalt ions.

Sample Size

The sample size was calculated using the stroke group data from the study by Bektaş et al [9]; it was found that at least 19 patients should be included in each group for NT and TT parameters with 80% power and 5% Type-1 error. For IMA, the sample size was calculated using the data from the study by Jena et al [15]. In this calculation, the minimum required number of samples was calculated even lower. Based on these results, at least 20 patients were included in each group.

Data Analysis

Data were analyzed with the SPSS for Windows 16.0 Package Program. Comparisons of proportions for independent samples were made by the Chi-Square test. The normality analysis of continuous data was performed by the Shapiro-Wilk test. Independent Samples t-test was used for data showing normal distribution, and the Mann Whitney-U test was used for non-normal distribution of data; median, interquartile range (IQR) and minimum/maximum values were expressed. ROC analysis was performed for the parameters, which were statistically significantly different between the two groups. Multiple regression analysis was performed to evaluate the independent predictors in the differential diagnosis of vertigo. P <0.05 level was used for statistical significance.

Results

One hundred and fifty-three patients were included in the study, and 29 of them were diagnosed with acute ischemic stroke (19.0%; all had cerebellar infarct), and 124 of them were evaluated as peripheral vertigo (81.0%). While the age was found to be significantly higher in the central vertigo group, the gender distribution was homogeneous (Table 1).

NT, TT and index-3 levels were significantly lower in the central vertigo group compared to the peripheral vertigo group, and the IMA, index-1 and index-2 were significantly higher. Although D

was higher in stroke group, this difference was not statistically significant (Table 1).

We performed logistic regression analysis for the differential diagnosis of vertigo. According to the multicollinearity analysis, a significant relationship was detected between NT, D, TT and indices. In this regard, age, native thiol, Index-1 and IMA were included in the analysis in Step-1. The backward method and Wald statistics were used for the elimination of the variables. As a result, age, Index-1 and IMA were found to be independent predictors (Table 2).

Table 1. Demographic features and main parameters (all patients and age group over 52 years old)

Variables	All patients (n = 153)			Over 52-year of age patient group (n = 80)		
	Central vertigo n=29 Med (IQR)	Peripheral vertigo n=124 Med (IQR)	p-value	Central vertigo n=25 Med (IQR)	Peripheral vertigo n=55 Med (IQR)	p-value
Age (year)- Min-max	65 (20) 31-85	46 (26) 17-88	<0.001*	67 (17) 52-85	62 (12) 51-88	0.266*
Gender, male, n (%)	16 (55.2)	64 (51.6)	0.730†	14 (56.0)	27 (52.9)	0.802†
DM, n (%)	6 (20.7)	12 (9.7)	0.098‡	4 (16.0)	6 (11.8)	0.721‡
HT, n (%)	9 (31.0)	21 (16.9)	0.085†	7 (28.0)	18 (35.3)	0.525†
CKD, n (%)	5 (17.2)	8 (6.5)	0.073‡	5 (20.0)	6 (11.8)	0.489‡
NT (μmol/L)	340.0 (140.0)	432.7 (130.9)	0.001*	343.9 (155.7)	408.6 (124.7)	0.094§
D (μmol/L)	22.15 (12.35)	19.30 (18.68)	0.124*	22.15 (10.52)	18.90 (15.40)	0.097*
TT (μmol/L)	397.3 (138.0)	454.95 (119.4)	0.002*	401.1 (148.9)	444.0 (118.1)	0.171§
INDEX1	0.061 (0.046)	0.044 (0.038)	0.006*	0.061 (0.043)	0.043 (0.032)	0.015*
INDEX2	0.054 (0.036)	0.041 (0.033)	0.006*	0.054 (0.033)	0.039 (0.027)	0.015*
INDEX3	0.891 (0.072)	0.919 (0.065)	0.006*	0.891 (0.067)	0.921 (0.054)	0.015*
IMA (ABSU)	74.5 (12.0)	71.3 (8.3)	0.017*	74.5 (10.8)	71.8 (9.2)	0.042*

Med: Median; IQR: interquartile range; Min: minimum; Max: maximum; DM: Diabetes mellitus; HT: Systemic hypertension; CKD: Chronic kidney disease; NT: native thiol; TT: total thiol; D: disulfide; Index 1: D/NT; Index 2: D/TT; Index 3: NT/TT; IMA: Ischemia Modified Albumin; ABSU: Absorbance units
*Mann Whitney-U test (Median; IQR; min-max)   †Pearson Chi-Square test   ‡Fisher's Exact test   §Independent Samples-t test

Table 2. Multivariate logistic regression analysis for differential diagnosis of central and peripheral vertigo (all patients and age group over 50 years old)

		All patients (n = 153)					Over 52-year of age patient group (n = 80)			
Variables		B	Wald	Sig.	Exp(B)	Variables		B	Wald	Sig.	Exp(B)
Step 3ᵃ	Age	0.059	15.364	<0.001	1.061 (1.030-1.093)	Step 2ᵃ	Index-1 (x 10)	0.937	2.894	0.089	2.553 (0.867-7.515)
	Index-1 (x 10)	0.885	6.042	0.014	2.423 (1.196-4.906)						
	IMA	0.058	4.200	0.040	1.060 (1.003-1.121)		IMA	0.051	3.171	0.075	1.053 (0.995-1.114)
	Constant	-9.688	16.488	<0.001	0.000062		Constant	-5.151	5.264	0.022	0.006

a. Variable(s) entered on step 1: Age, native thiol, Index-1, ischemia modified albumin (IMA).
Equation: logit (p) = -9.688 + (0.059 x age) + (0.885 x 10 x Index-1) + (0.058 x IMA)
Reference: Peripheral vertigo

a. Variable(s) entered on step 1: Native thiol, Index-1, IMA.
Reference: Peripheral vertigo

Table 3. Diagnostic statistics of age, Index-1 and IMA cut-off levels for central vertigo diagnosis (total group)

Parameters	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC analysis	
						AUC (95% CI)	p-value
Age (year) ≥	52	86.21	58.87	32.89	94.81	0.758 (0.668-0.849)	<0.001
Index-1 ≥	0.038	82.76	45.16	26.09	91.80	0.665 (0,562-0,769)	0.006
	0.046	75.86	54.84	28.21	90.67		
IMA ≥	72.4	72.41	58.87	29.17	90.12	0.642 (0,529-0,756)	0.017
	73.3	68.97	62.10	29.85	89.53		

NT: native thiol; D: disulfide; Index 1: D/NT; IMA: Ischemia modified albumin NT: native thiol; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC: area under the curve; CI: confidence interval
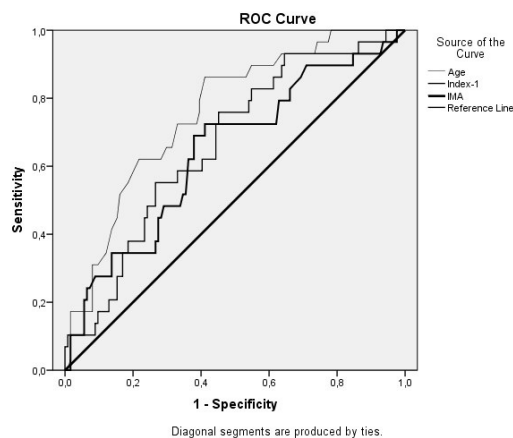

Figure 1. ROC curve for age, Index-1 and IMA

ROC analysis is performed for the differential diagnosis of central and peripheral vertigo; AUC values for age, Index-1 and IMA are shown in Table-3; ROC curves were presented in Figure 1. As it can be seen from Table 3, there is no common coordinate with both high sensitivity and high specificity rates. For the age variable, the maximum Youden index on the ROC analysis was calculated at the level of ≥52 years old. We repeated the analysis for the subgroup aged ≥52 (Tables 1 and 2). In this analysis, while IMA, index-1 and index-2 were found to be significantly higher in the central vertigo group, the index-3 was found to be lower in the peripheral vertigo group. There was no significant difference in other variables (Table 1). Among these age-homogeneous groups, no parameters were found valuable in the differential diagnosis of vertigo in multivariate logistic regression analysis (Table 2).

Discussion

Differential diagnosis of central and peripheral vertigo can be challenging when patients present with isolated acute vertigo in ED. MRI is the most commonly used diagnostic tool. No useful biomarker suitable for clinical practice has been found for this differentiation. In this study, we found that there was a significant difference in IMA and TDH parameters between these two patient groups. According to the results of this study, it is possible to say that IMA and TDH parameters can be used in the differential diagnosis of vertigo, if evaluated with the age of the patient. However, it is not possible to declare clearly that these parameters can be used instead of MRI in the differential diagnosis of central and peripheral vertigo.

Vertigo and dizziness are complaints that affect more than 90 million people in the United States only [1,16]. The differential diagnosis of vertigo is very important because of the effects on morbidity, mortality, and of course, financial costs [1,17]. Central nervous system pathologies that present with isolated acute vertigo can cause permanent neurological deficits, as well as death [1]. Patients with central vertigo etiologies present with imbalance and ataxia rather than acute vertigo. In contrast to peripheral lesions, in central pathologies, nystagmus is not affected by fixed gaze, changes direction with gaze, and may be completely torsional or vertical [16]. But often central pathologies are misdiagnosed as peripheral vertigo [3]. Central etiology may mimic peripheral vertigo, and peripheral lesions may mimic central etiology [16].

Nowadays, MRI is the preferred diagnostic tool for the differential diagnosis of patients with acute vertigo [17,18]. In recent years, the frequency of using MRI and CT in this regard has increased significantly. However, there was no significant increase in the rate of central pathologies diagnosed with this increased use [1]. This fact reminds the issue of the financial cost. In this manner, patient selection for MRI is important in the differential diagnosis of vertigo.

In the literature, we identified two biomarker studies on the differential diagnosis of central and peripheral vertigo. Akıncı et al reported that C-reactive protein, fibrinogen and D-dimer levels did not show a statistically significant difference in patients with central and peripheral vertigo [19]. Kartal et al also studied s100B protein for the same purpose and found that s100B level was significantly higher in the central group;

however, the authors finally stated that it was not possible to conclude that s100B could be used instead of MRI [1].

It has been shown a decrease in thiol levels is due to oxidative stress in a wide spectrum of diseases such as a cerebrovascular event, benign paroxysmal positional vertigo, pneumonia, and myocardial infarction [9,13,20-23]. Additionally, IMA levels were found to be higher in many diseases in which ischemic processes were more prominent [11,15,24,25]. Based on these data, it can be predicted that central vertigo cases can be differentiated from peripheral vertigo cases by using TDH and IMA parameters. Thus, in this study, for the first time in the literature, TDH parameters and IMA were investigated in the differential diagnosis of vertigo.

Bektaş et al stated that oxidative stress plays an important role in ischemic stroke [9]. In this study, NT and TT levels were found to be lower in the stroke group than in the control group. In our study, similar results were found. In a study of Şahin et al on benign paroxysmal positional vertigo (BPPV), the mean values of NT and TT were statistically significantly lower than in the control group; the authors stated that oxidative stress was important in the pathogenesis of BPPV in light of these results [13]. In our study, while determining the peripheral vertigo patient group, all central causes were excluded using MRI; also, all other ischemic and metabolic causes were excluded by laboratory analysis. Additionally, in this study, contrary to the study by Şahin et al, TDH and IMA blood samples were analyzed simultaneously with all routine laboratory analyzes. These differences in methodology may have affected the results. In our study, significant differences in TDH parameters between central and peripheral vertigo groups showed a more severe oxidative stress pathogenesis in stroke (central vertigo) group. However, in order to make a comment based on the specificity and sensitivity values in Table 3, no clear data are available in this study that all TDH parameters can be used instead of MRI in the differential diagnosis of vertigo.

It is known that the risk of stroke increases with age [1,2]. Therefore, higher age in the stroke group is expected in this study. When interpreting the results of the analysis, it should be considered that this situation (although it disrupts the homogenization of the groups) is in accordance with the usual distribution in the population. However, according to the level determined in the ROC analysis for age, the analyzes were repeated in the age group of 52 years and above (Tables 1 and 2). In the analyzes performed in this subgroup, it was observed that age and gender were homogeneously distributed, and there was no difference between the central and peripheral vertigo groups in terms of NT and TT parameters (Table 1); but Index-1 and Index-2 were found to be higher in the central vertigo group. However, it is clear that this subgroup analysis does not reflect the universe. The results of the logistic regression analysis show that it would be reasonable to include the age parameter in the analysis anyway.

In the literature, studies on ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage have shown that IMA levels are increased in patients compared to healthy volunteers [10,11,15]. To the best of our knowledge, this study is the first to analyze the IMA parameter in the differential diagnosis of central and peripheral vertigo; in addition, IMA has not been

analyzed previously in the peripheral vertigo patients. The results of this study on stroke disease are consistent with the fact of ischemic pathogenesis of stroke and the literature. IMA levels were significantly higher in the central vertigo group compared to the peripheral vertigo group.

Limitations

Being a single-center study and the small number of patients in the study groups are important limitations. However, the fact that the inclusion criteria were quite strict was effective in a small number of subjects. Since this is the first study on this subject in the literature, sample size analysis should have been conducted using similar studies as much as possible. Whether the difference in age distribution between groups is a limitation is an issue open to interpretation. False negative results may occur in the first 48 hours with MRI; in this respect, the lack of a new MRI for follow-up should be considered as another limitation.

Conclusions

Although the value of many biomarkers has been studied in both central and peripheral vertigo, there is no marker included in clinical practice. In this study, it was observed that TDH indices and IMA were higher in the central vertigo group compared with the peripheral vertigo group. However, with these results, it is not correct to say that adequate sensitivity and specificity rates have been reached in terms of differential diagnosis of vertigo and using these markers instead of MRI. Nevertheless, we can say that these parameters can be useful in the differential diagnosis of vertigo when considering the age of the patient.

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