

The Brain Ischemic Volume Correlation with the Ischemic Modified Albumin Level

İskemik Beyin Hacminin İskemik Modifiye Albümin Seviyesi ile Korelasyonu

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Abstract

Objective: Cerebrovascular disease is a frequent cause of emergency department visits, and early diagnosis can reduce mortality and morbidity. It was aimed to evaluate the relationship between diffusion-weighted-magnetic resonance imaging (DW-MRI) and blood ischemic modified albumin (IMA) levels of cerebrovascular diseases in terms of demographic characteristics, mortality, and morbidity.

Method: This prospective cohort study included 44 patients diagnosed with ischemic stroke in the emergency room between January and July 2014 and 44 people in the control group. Age, gender, vital signs, comorbid disease states, neurological deficit levels, IMA levels, DW-MRI involvement volumes, and mortality rates were analyzed in patients who were diagnosed with stroke and who had DW-MRI restrictions. Also, a control group of 44 volunteers who applied to our emergency department was added to compare the IMA level.

Results: The median age of the patients was 71 years (24 males, 20 females, range 47 to 83 years) and the median age of the control group was 68 (25 males, 19 females, range 52 to 79) years. The median age of the control group was close to that of the patient group, the two groups were also similar in terms of gender distribution. The most common comorbid disease was hypertension 28 (63.6%), atrial fibrillation (AF) 14 (31.8%), diabetes mellitus (DM) 10 (22.8%) and coronary artery disease 10 (22.8%). The median value of the IMA level was 13.84 in the patient group and 8.66 in the control group. While the patients' NIHSS stroke score was high, the area of involvement in MRI and also IMA levels increased.

Öz

Amaç: Serebrovasküler hastalık, acil servis başvurularının sık bir nedenidir, erken tanı mortalite ve morbiditeyi azaltabilir. Çalışmamızda serebrovasküler hastalıkların difüzyon ağırlıklı-manyetik rezonans görüntülemeleri (DA-MRG) ile kan iskemik modifiye albümin (İMA) düzeyleri arasındaki ilişkinin demografik özellikler, mortalite ve morbidite açısından değerlendirilmesi amaçlandı.

Yöntem: Bu prospektif kohort çalışmasına Ocak-Temmuz 2014 tarihleri arasında acil serviste iskemik inme tanısı almış 44 hasta ile 44 kontrol grubu dahil edildi. İmme tanısı konulan ve DA-MRG kısıtlaması olan hastalarda yaş, cinsiyet, yaşamsal belirtiler, yandaş hastalık durumları, nörolojik defisit düzeyleri, İMA düzeyleri, DA-MRG tutulum hacimleri ve mortalite oranları analiz edildi. Ayrıca, İMA düzeyini karşılaştırmak için acil servisimize başvuran 44 gönüllüden oluşan bir kontrol grubu eklenmiştir.

Bulgular: Hastaların ortalama yaşı 66,98±16,36 ve %54,5'i (n=24) erkekti. Kontrol grubu ile hasta grubunun yaşları benzerdi. En sık görülen komorbid hastalık hipertansiyon 28 (%63,6); atriyal fibrilasyon 14 (%31,8), diabetes mellitus 10 (%22,8) ve koroner arter hastalığı 10 (%22,8) idi. İMA düzeyinin ortanca değeri hasta grubunda 13,84, kontrol grubunda 8,66 idi. Hastaların NIHSS inme skoru yüksek iken, MRG'deki tutulum alanı ve ayrıca İMA seviyelerinin arttığı görüldü. Ayrıca difüzyon kısıtlama alanı ve İMA düzeyleri pozitif ve orta düzeyde ilişkiliydi.

Sonuç: İMA düzeyi, akut iskemik inmede kullanılabilen bir parametre ve DA-MRG'de kısıtlılık alanının bir göstergesi olarak değerlendirilebilir.



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Abstract

Besides, diffusion involvement area and IMA levels were positively and moderately correlated.

Conclusion: IMA level can be considered as a parameter that can be used in acute ischemic stroke and as an indicator of the diffusion restriction area in MRI.

Keywords: Acute ischemic stroke, biomarkers, diffusion-weighted magnetic resonance imaging, ischemic modified albumin

Öz

Anahtar kelimeler: Akut iskemik inme, biyobelirteçler, difüzyon ağırlıklı-manyetik rezonans görüntüleme, iskemik modifiye albümin

Introduction

In acute cerebrovascular events, definitive diagnosis and treatment processes should be started immediately as soon as the patient's clinic begins. The primary aim of the diagnostic procedure is to clarify whether the clinical condition is a result of ischemic disease or another neurologic or metabolic condition. The sensitivity of a good physical examination is 99% and the specificity is 85%, which cannot differentiate the ischemic and hemorrhagic causes of the stroke (1). Computed tomography (CT) is used as the first choice for the differentiation of ischemic and hemorrhagic stroke (2). The sensitivity and specificity of the CT for the ischemic cerebrovascular diseases (CVD) are 39.8% and 91.7%, respectively, in the first six hours; with repetition of CT between 6 and 24 hours, the sensitivity and specificity increases slightly but still not enough for exact diagnosis (3). In the first six hours, we use DW-MRI, which has a sensitivity of 58.3 to 97.3% and specificity of 100% (3).

The delay in the diagnosis and treatment of CVD is generally observed in transportation to the hospital and the evaluation of the diagnostic tests in the hospital (4). Despite the usage of all diagnostic methods, the etiologic reason cannot be specified in 20% of the CVD (5). Therefore, some new biomarkers that can be useful for an early diagnosis such as ischemic modified albumin (IMA) are investigated (6) in CVD patients. IMA is a sensitive biomarker that has shown the increase in some ischemic conditions such as myocardial ischemia, muscle ischemia, pulmonary embolism, mesentery ischemia, and cerebral ischemia (6).

The study aimed to investigate the relationship of IMA levels with DW-MRI findings and demographic characteristics in terms of morbidity and mortality in patients admitted to the emergency department due to cerebrovascular stroke.

Materials and Methods

Study Design and Population

After local ethics committee approval was received for this prospective study, 88 patients, (44 patients, and 44 controls) who were admitted to the emergency department between January and July 2014, were included. After informing the patients and controls voluntarily, the "information consent form" was signed and included in the study.

In addition to patients who did not have DW-MRI and whose IMA levels were not considered, patients with endocrine pathology, psychiatric drug use, chronic liver disease, need for dialysis, central nervous system infection, chronic inflammatory disease, malignancy, severe anemia, hematological disease, severe dietary history, radiotherapy in the head and neck region, and pregnancy were not included in the study.

The National Institutes of Health Stroke scale (NIHSS) score was used in the definition of cerebrovascular stroke in the patient group. NIHSS score was classified as no symptoms if 0, minor stroke if 1-4, moderate stroke if 5-15, moderate-heavy stroke if 16-20, and heavy stroke if 21-42 (7). Forty four healthy volunteers who did not have any ischemic disease were included in the study.

Laboratory Design

The venous samples of the patients taken to a plastic gel vacuum tube were kept for 20 minutes at room temperature to complete the coagulation. The samples were centrifuged at 4.000 cycles for 10 minutes, hemolyzed or icteric samples were excluded and repeated from the same patient. The IMA level was detected by Tweak original commercial kits by enzyme-linked immunosorbent assay (ELISA) method. The IMA level measurement was performed by putting the ELISA kit (Eastbiopharm, Hangzhou Eastbiopharm Co. Ltd. China, ref: CK-E90172, lot: 201402) on the BioTEK Plate reader. The blood serum samples were incubated in microplate wells that were covered by antibodies

identifying IMA antigen for 30 minutes at 37 °C. After the washing process, entrapped IMA antigens were incubated by adding the anti-human IMA antibodies that were conjugated with horseradish peroxidase for 30 minutes at 37 °C. Following this step, the chromogen A and B solutions were added and incubated for 15 minutes at 37 °C. The reaction was aborted by a stop solution. The absorbance of the yellow-colored product was measured by the spectrophotometric method at 450 nm wavelength. The absorbance was proportioned with IMA concentration. We obtained a standard calibration curve by marking the IMA standard concentration points. The unknown blood serum concentrations were determined by this obtained standard curve. The measurable concentration range of the ELISA kit was 1-60 U/mL, the lower limit of quantification was 1 U/mL.

Radiological Design

DW-MRI procedures were performed by 1.5T General Electric (GE®) MRI Machine. Hyperintense signal variances in apparent diffusion coefficient images were accepted as a diffusion restriction or a new infarct area. The infarct volume was calculated by ABC/2 formula, which is a fast method for estimating the affected volume of intracerebral area. This simple method provides a 3D analysis of the intracerebral area.

A; is the greatest hemorrhage diameter.

B; is affected area's diameter 90 degrees to A in the axial plane.

C; is the approximate number of CT slices with hemorrhage multiplied by the slice thickness.

The multiplication of A, B, and C were divided by 2 and the final result was accepted as the volume of the infarct region (8). Besides, measurements were made in centimeters (cm), then the formula gave the results as cubic centimeters (cm³).

Statistical Analysis

All statistical analyses were calculated with SPSS 18.0 for Windows (New York, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as n (%). Median and minimum-maximum limits were given for age. Normal distribution was determined by the Kolmogorov-Smirnov test advertising histogram. Differences of continuous variables between the groups were calculated by the Mann-Whitney U test and Kruskal-Wallis test for non-normally distributed variables; student's t-test was used for normally distributed data; chi-square

test was used for categorical variables. Correlations of continuous variables were calculated with the Pearson's correlation. P<0.05 was considered significant at 95% confidence interval.

Results

The median age of the patients was 71 years (24 males, 20 females, range 47 to 83 years) and the median age of the control group was 68 (25 males, 19 females, range 52 to 79) years. The median age of the control group was close to that of the patient group; The gender distributions of the two groups were similar (p=0.830, Table 1).

The most frequently observed co-morbidity in the patient group was hypertension with a rate of 63.6% (n=28); followed by AF, 31.8% (n=14), DM, 22.8% (n=10), and coronary artery disease, 22.8% (n=10) (Table 2).

When the vital signs of the patients we included in the study were examined, the mean systolic blood pressure value of the patients was 177.14±18.28 mmHg, the mean diastolic blood pressure value was 97.68±14.46 mmHg and the heart rate was 89.02±9.1 beats/minute as seen (Table 3).

The median IMA level was 13.84 U/mL (range 6.25-209.72 U/mL) in the patient group and 8.66 U/mL (range 1.79-49.58 U/mL) in the control group (Table 4).

IMA level was significantly higher in the patient group (p<0.001). While the NIHSS score was increasing the ischemic volume in DW-MRI, IMA level showed the increase

Table 1. Age and gender characteristics of patient and control groups

	Patient Median (min-max)/n (%)	Control Median (min-max)/n (%)	p
Age	71 (47-83)	68 (52-79)	-
Gender			0.830*
Male	24 (54.5)	25 (56.8)	
Female	20 (45.5)	19 (43.2)	

*: Chi-square, n: Number of patients, p<0.05

Table 2. Comorbid properties of the patient group

	n (%)
Hypertension	28 (63.6)
Atrial fibrillation	14 (31.8)
Diabetes mellitus	10 (22.8)
Coronary artery disease	10 (22.8)
Cerebrovascular disease	4 (9)
Other diseases	4 (9)

n: Patients number, p<0.05

(Table 5); also, there was a moderate positive correlation with ischemic volume in DW-MRI and IMA level ($p < 0.001$, $r = 0.641$).

The mortality rate was 6.8% ($n = 3$). The IMA level and the ischemic volume in DW-MRI were similar in the dead and alive patients ($p = 0.172$ and $p = 0.239$, respectively).

Discussion

The early diagnosis of CVD is important for reducing mortality and morbidity. According to previous study reports, there is not a significant gender difference in CVD but most of the cases are reported over the age of 65 years (9,10). In our study, the median age of the patients was 71 years, males constituted 54.5% of all cases and it was found to be compatible with similar studies.

Hypertension can be observed before or after the CVD diagnosis (11-13). Only by regulating the blood pressure

Table 3. Patient's blood pressure status and pulse numbers

	Mean \pm SD	Min-max
Systolic arterial pressure (mmHg)	177.14 \pm 18.28	130-210
Diastolic arterial pressure (mmHg)	97.68 \pm 14.46	70-130
Heart rate (beats/min)	89.02 \pm 9.1	62-104

SD: Standard deviation, $p < 0.05$

Table 4. Comparison of IMA levels of patient and control groups

	Patient level (min-max)	Control level (min-max)	p
IMA	13.84 (6.25-209.72)	8.66 (1.79-49.58)	0.001

$p < 0.05$, IMA: Ischemic modified albumin

Table 5. The ischemic volume in DW-MRI and median IMA level according to NIHSS score

The ischemic volume			
	n	DWMRI median (min-max)	IMA level median (min-max)
Minor stroke (NIHSS 1-4)	16	3.91 (1-78.14)	14.42 (6.25-209.72)
Moderate stroke (NIHSS 5-15)	15	9.7 (1.92-24.35)	8.93 (6.25-25.63)
Moderate-severe stroke (NIHSS 16-20)	9	54.88 (4.3-88.2)	28.75 (8.93-196.30)
Severe stroke (NIHSS 21-42)	4	49.82 (5.65-131.83)	16.07 (10.72-159.89)
p	-	0.002	0.017

DWMRI: Diffusion weighted magnetic resonance imaging, IMA: Ischemic modified albumin, $p < 0.05$

and controlling hypertension, we can decrease the CVD risk by up to 40% (14). Previous studies reported the mean systolic pressure on admission as around 155 mmHg (9,15). We know that CVD frequency increases with AF and DM (16) as we observed their frequency as 31.8% and 22.8%, respectively, in our study. Blood pressure values were found to be slightly higher than the values indicated in similar studies. The mean systolic blood pressure value was determined as 177.14 \pm 18.28 mmHg. Also, the most common co-morbid disease was hypertension, followed by AF and DM. We think that the average systolic pressure values are slightly higher, depending on the socioeconomic level and eating habits.

Free oxygen radicals produced in the process of ischemia, reperfusion, acidosis, and hypoxia lead to a structural change of transition metals like cobalt, copper, and nickel on N-terminal end, which causes a decrease in binding of albumin to these points (17-19). The IMA level is in the normal range in healthy people but smoking, age, race or gender do not also influence the level of IMA (20). The IMA level increases in CVD, acute mesentery ischemia, acute pulmonary embolism, and acute coronary syndromes (21-23). Abboud et al. (19) reported that the IMA level increased in ischemic stroke but did not increase in hemorrhagic stroke. Gunduz et al. (21) reported that the IMA level was higher in ischemic stroke than in hemorrhagic ones and suggested to use it in differential diagnosis. IMA level was found to be high as in similar studies. We think that the reason for this is that due to increased free radicals, the protein cannot be attached to the cell, it remains free in the blood and the IMA level increases accordingly.

DW-MRI is generally used for the diagnosis of ischemic stroke in the case of CT but suspicion of ischemic CVD is still present. In ischemic CVD, while the ischemic volume increases, the clinical condition gets worse (24,25). In SVO cases; as diffusion involvement became more common in DW-MRI, it was found that the NIHSS score and IMA levels increased and the patient's clinic worsened as a result. In similar studies, Can et al. (26) reported that the IMA level increased while the ischemic volume in DW-MRI increased. Additionally, Ahn et al. (27) reported that the IMA index [serum albumin concentration (g/dL) $\times 23 + \text{IMA (U/mL)} - 100$] was more sensitive than the IMA level in ischemic CVD. Also, some studies reported that the clinical condition of the patients with ischemic stroke was positively correlated with the IMA level (17,19). Consuegra-Sanchez et al. (23) reported that the IMA level

was higher in one-month and one-year mortality. In our study, there were not enough mortal cases and also the study population was low. Further studies with large patient sizes can give better results, especially about mortality.

Study Limitations

Our most important restrictive reason was that the study was single-centered. Also, late admissions were not included in the study. Moreover, the patients who came with the SVO clinic, patients who did not give consent to be included in the study, and other patients with comorbid diseases were excluded from the study.

Conclusion

The IMA level can be used in the differential diagnosis of CVD and also positively correlated with ischemic volume. The IMA level may be useful as a new biomarker for the patients who have normal CT results but show clinical symptoms of ischemic CVD.

Ethics

Ethics Committee Approval: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Project identification code: 2013-703-04/12/2013.

Informed Consent: It is a prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D., M.E.K., Ç.Ç., S.A.U., S.İ., Design: B.D., M.E.K., Ç.Ç., İ.B., S.A.U., S.İ., Data Collection or Processing: B.D., M.E.K., İ.B., C.Y., S.A.U., S.İ., Analysis or Interpretation: B.D., M.E.K., C.Y., K.Ü., İ.B., Literature Search: B.D., A.C., Ç.Ç., K.Ü., C.Y., Writing: B.D., A.C., Ç.Ç., K.Ü., C.Y., S.İ.

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