Cervical-Intracranial Atherosclerosis and Serum Uric Acid Level Association in Acute Stroke

Akut Inmede Servikal-Intrakraniyal Ateroskleroz ile Serum Ürik Asit Düzeyi arasındaki İlişki

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ABSTRACT

Objective: We aimed to identify whether high uric acid levels were associated with atherosclerotic intracranial/extracranial arterial stenosis and atrial fibrillation (AF) and to determine if serum uric acid (SUA) levels were an independent risk factor.
Methods: One hundred seventy-four patients who presented with acute stroke within 24 hours of onset and were admitted to our hospital between December 2016 and September 2017 were included in the study. Bamford classification was used for Stroke classification. The degree of vascular stenosis was classified as lumen contour irregularity, mild, moderate and severe stenosis using the The North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.
Results: The average age of 174 patients was 69 ± 12.7 years. Elevated serum uric acid levels were found in 66 patients. The mean SUA level was 7.33±1.02 mg/dL in these patients. Thirty-six patients were examined with AF and 14 of these patients had high SUA levels. It was found that high SUA levels were mostly related with lacunar infarct (LACI) and partial anterior circulation infarct (PACI), respectively. High SUA levels were seen more commonly in the anterior circulation, especially in the extracranial part of the carotid artery, but this was not statistically significant (p>0.05). We found a statistically significant relation between high SUA levels in moderate and severe stenosis of the extracranial portion of the posterior circulation in women (p=0.01). There was a relationship between atrial fibrillation and extracranial atherosclerosis of the anterior circulation as contour irregularity and moderate stenosis (p=0.05).
Conclusions: In our study, it was found that high SUA levels were related to LACI and PACI, respectively. Further studies with larger groups are needed.

Key Words: Stroke, Uric acid, Intracranial, Extracranial, Atherosclerosis, Atrial Fibrillation

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ÖZET

Amaç: Bu çalışmada amacımız, serum ürik asit düzeyleri ile aterosklerotik intrakranial/ekstrakranial arteriyel skleroz ve atriyal fibrilasyon (AF) arasındaki ilişkiyi belirlemek ve yüksek serum ürik asit (SUA) düzeyinin bağımsız bir risk faktörü olup olmadığını saptamaktır.
Yöntem: Çalışmaya, Aralık 2016 ve Kasım 2017 tarihleri arasında hastanemize akut inmenin ilk 24 saati içerisinde gelen 174 hasta dahil edildi. İnme sınıflandırması için Bamford sınıflandırması kullanıldı. Vaskuler stenozun derecesi, Kuzey Amerika Semptomatik Karotis Endarterektomi Çalışma kriterleri (NASCET) kullanılarak, lümen kontur düzensizliği, hafif, orta ve ağır olarak sınıflandırıldı.
Bulgular: Çalışmaya alınan 174 hastanın yaş ortalaması 69 ± 12.7 idi. Serum ürik asit düzeyi 66 hastada yüksek bulundu. Bu hastalarda ortalama serum ürik asit seviyesi 7.33 ± 1.02 mg / dL idi. AF 36 hastada belirlendi ve bu hastaların 14'ünde yüksek SUA düzeyleri vardı. Yüksek SUA düzeylerinin daha çok sırasıyla laküner infarkt (LACI) ve parsiyel anterior sirkülasyon infarktı (PACI) ile ilişkili olduğu bulundu. Yüksek SUA düzeyleri anterior dolaşımda, özellikle karotis arterin ekstrakranyal kısmında daha sık görüldü, ancak bu istatistiksel olarak anlamlı değildi (p> 0.05). Kadınlarda posterior dolaşımın ekstrakraniyal kısmında orta ve ciddi derecede darlık ile yüksek SUA düzeyleri arasında istatistiksel olarak anlamlı bir ilişki bulundu (p = 0.01). Anterior dolaşımın ekstrakranial kısmında kontur düzensizliği ve orta derecede darlık ile atrial fibrilasyon arasında anlamlı bir ilişki saptandı (p = 0.05).
Sonuç: Çalışmamızda yüksek SUA düzeylerinin sırasıyla LACI ve PACI ile ilişkili olduğu saptanmış olup, daha büyük gruplarla yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: İnme, Ürik asit, Intrakranial, Ekstrakranial, Ateroskleroz, Atrial Fibrilasyon

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INTRODUCTION

Stroke is the second most common cause of death globally (1). Stroke has various etiologic factors, and recently uric acid was also listed among these factors (1,2). Uric acid is the final enzyme product of purine metabolism, which appears as a result of nuclear material catabolism. Pathologically high uric acid levels are found to be associated with gout, renal stones, hypertension (HT), visceral obesity, insulin resistance, dyslipidemia, cardiovascular, and cerebrovascular diseases (3-5). Our aim in this study was to investigate whether high uric acid levels were an independent risk factor in atherosclerotic intracranial and extracranial artery stenosis, and to determine if there was any relation with a history of atrial fibrillation (AF).

METHODS

One hundred seventy-four patients who were admitted to Marmara University Pendik Training and Research Hospital within the first 24 hours of acute stroke onset between December 2016 and September 2017 were included in this prospective study. The study was approved by the ethics committee of the coordinating center (No: 83045809/604/02-12333). Blood uric acid levels were measured using standard laboratory techniques. Neuroimaging of each patient was performed using diffusion magnetic resonance imaging (MRI), and cranial and cervical MR angiography (MRA).

Uric acid levels were considered high if ≥ 6.9 mg/dL in males and ≥5.9 mg/dL in females. Patients with bleeding diathesis, gout, polycythemia, chronic renal failure, current uric acid level-lowering drug use, malignancies, and liver disease were excluded from the study. The degree of vascular stenosis was classified as lumen contour irregularity, mild, moderate and severe stenosis using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Blood samples of patients were examined in the first 48 hours of acute stroke onset. All analyses of serum were studied in the Central Biochemistry Laboratory of Marmara University Pendik Training and Research Hospital using a Roche Diagnostics Cobas 8000 C 701 series auto-analyzer with spectrophotometry, and the serum uric acid levels are presented as mg/dL.

Statistical analysis

Statistical tests were performed by using the IBM SPSS Statistics Version 17 software. Statistical comparisons between the groups were performed using descriptive methods, the Chi-square test, and T-test. Pearson's correlation coefficient was used to measure the degree of linear relationship between quantitative variables. The statistical significance level was accepted as $p<0.05$.

RESULTS

This study was performed in Marmara University Pendik Training and Research Hospital. A number of total 315 patients were included. One-hundred forty one patients were excluded from the study because they did not meet the criteria. The mean age of 174 patients was 69 ± 12.7 (minimum-maximum: 33-94). Seventy (40%) of the patients were female and 104 (60%) were male. Sixty-six (38%) patients have elevated serum uric acid levels. The mean SUA level of these patients was 7.33±1.02 mg/dL. Thirty-six patients have AF and 14 of these patients (39 %) had high SUA levels.

An evaluation of co-morbid disease among the patients revealed that 71.8% of the patients had hypertension (HT), 37.9% had diabetes mellitus (DM), 64.4% of had hyperlipidemia, 20.6% had AF, and 20.11% had coronary artery disease (CAD). No significant relationship was found between serum uric acid levels and stroke risk factors ($p>0.05$).

Anterior/posterior system circulation and intracranial-extracranial atherosclerosis in patients with high uric acid levels were demonstrated in Table 1. Elevated SUA levels were mostly related with lacunar infarct (LACI) and partial anterior circulation infarct (PACI), respectively (Table 2). High SUA levels were seen more commonly in the anterior circulation, especially in the extracranial part of the carotid artery, but this was not statistically significant ($p>0.05$) (Table 3). We found a statistically significant relation between high SUA levels in moderate and severe stenosis of the extracranial portion of the posterior circulation in women ($p=0.01$) (Table 4). There was a relationship between atrial fibrillation and extracranial atherosclerosis of the anterior circulation as contour irregularity and moderate stenosis ($p=0.05$) (Table 5). No significant relationship between serum uric acid level and AF was found (Table 6).

Table 1: The numeric demonstration of anterior/ posterior system circulation and intracranial- extracranial atherosclerosis in patients with elevated serum uric acid levels

	Contour irregularity	Minimal stenosis	Moderate stenosis	Severe stenosis
Anterior system intracranial atherosclerosis	4	3	10	21
Elevated serum uric acid level	0	2	1	5
Anterior system extracranial atherosclerosis	80	14	25	33
Elevated serum uric acid level	31	2	6	9
Posterior system intracranial atherosclerosis	5	1	4	17
Elevated serum uric acid level	0	0	0	4
Posterior system extracranial atherosclerosis	11	3	4	16
Elevated serum uric acid level	3	0	0	3

The first line shows the number of patients with several degrees of atherosclerosis, the second line shows the number of patients with high uric acid levels.

Table 2: Serum uric acid levels and lesion localization association

Lesion localization	Mean ± SD (Min-Max)	Normal n	Abnormal n	%	*p*
TACI[1]	4.77±1.38 2.70±7.70	10	2	16.7	0.06*
PACI[2]	5.50±1.74 (2.30-10.7)	46	16	42	
POCI[3]	5.34±1.44 (2.70-9.00)	30	8	25.8	
LACI[4]	6.00±1.80 (0.80-9.40)	23	20	46.5	

[1]TACI: Total anterior circulation infarct; [2]PACI: Partial anterior circulation infarct; [3]POCI: Posterior circulation infarct; [4]LACI: Lacunar circulation infarct * Chi-square test

Table 3: Uric acid levels related to sex in the anterior circulation

	Anterior circulation	Female	Male
		p	*p*
Extracranial	Contour Irregularity	0.67	0.93
	Mild Stenosis	0.94	0.35
	Moderate Stenosis	0.77	0.19
	Severe Stenosis	0.28	0.88
	Total	0.88	0.51
Intracranial	Contour Irregularity	0.84	0.88
	Mild Stenosis	0.60	0.21
	Moderate Stenosis	0.12	0.82
	Severe Stenosis	0.76	0.24
	Total	0.13	0.49

*T-test

Table 4: Uric acid levels related to sex in the posterior circulation

	Posterior circulation	Female	Male
		p	*p*
Extracranial	Contour Irregularity	0.54	0.90
	Mild Stenosis	0.54	0.35
	Moderate Stenosis	0.01*	0.27
	Severe Stenosis	0.01*	0.07
	Total	0.01*	0.05
Intracranial	Contour Irregularity	0.21	0.99
	Mild Stenosis	0.01*	0.26
	Moderate Stenosis	0.34	0.89
	Severe Stenosis	0.96	0.98
	Total	0.67	0.95

*T-test

Table 5: The relationship between atrial fibrillation and intracranial-extracranial atherosclerosis in anterior/posterior circulation

		Posterior	Anterior
		p	***p***
Intracranial	Contour Irregularity	0.58	0.57
	Mild Stenosis	0.99	0.82
	Moderate Stenosis	0.57	0.69
	Severe Stenosis	0.37	0.96
	Total	0.26	0.48
		0.37*	
Extracranial	Contour Irregularity	0.46	0.05*
	Mild Stenosis	0.99	0.76
	Moderate Stenosis	0.87	0.05*
	Severe Stenosis	0.75	0.15
	Total	0.60	0.95
		0.64*	

*T-test

Table 6: Evaluation of serum uric acid levels with atrial fibrillation

	Normal	Abnormal	*p*
Atrial fibrillation (+)	22	14	0.84
Atrial fibrillation(-)	86	52	

* Chi-square test

DISCUSSION

Stroke is the most common neurologic disease and the second most common cause of death (1). Stroke has various etiologic factors such as, age, sex, HT, hyperlipidemia, DM, and AF, and recently uric acid was listed among these factors (2). Detecting risk factors is an important therapeutic strategy in the management of ischemic stroke.

An association between SUA levels and outcomes of ischemic stroke has been reported, but the results are controversial. Previous studies have shown that SUA levels are significantly correlated with cardiovascular and cerebrovascular diseases (6). The mechanisms through which uric acid induces cardiovascular and renal dysfunction as well as stroke have been documented in animal models and in vitro studies (7,8). Tissue hypoxia can induce purine catabolism, which then increases the production of SUA. This process contributes to the formation of reactive oxygen stress. Indeed, accumulating evidence supports a direct pathophysiologic role of uric acid in processing atherosclerosis because elevated SUA metabolism produces reactive oxygen species, which induce inflammatory responses in vascular endothelial cells and indirectly stimulate macrophage infiltration in atherosclerotic vessels (9). Furthermore, hyperuricemia promotes platelet adhesiveness and damage to vascular smooth muscle cell and endothelia, contributing to the pathology of cerebrovascular events (10). Our aim in this study was to investigate the effect of high uric acid levels on atherosclerotic intracranial/extracranial artery stenosis and AF, and to determine whether high serum uric acid levels were an independent risk factor in acute ischemic stroke.

Weir et al. found an association between poor prognosis and moderate-severe disability and hyperuricemia in their study conducted on 2498 patients with acute stroke who were evaluated within the first 24 hours after stroke and the 90th day of stroke.

In addition, hyperuricemia was found to be a risk factor for developing major vascular events in the same study (11). Neogi et al. found a significant relationship between higher serum uric acid levels and carotid atherosclerotic plaques in males. In that study, the authors also suggested that hyperuricemia accelerated the pro-inflammatory process, existed in large amount within the vascular atherosclerotic plaques, and induced pro-inflammatory processes in smooth muscle cells (12-15). In recent experimental studies, hyperuricemia was found to induce endothelial dysfunction and increase local oxidant formation, monocyte chemoattractant protein-1, interleukin (IL)-1-beta, IL-6, and systemic inflammatory mediators such as tumor necrosis factor (TNF)-alpha in the blood circulation (16-21). In our study, high SUA levels were found in atherosclerosis of the extracranial portion of the anterior circulation. Patients with higher uric acid levels had severe stenosis both in the anterior and posterior circulation.

In a study conducted in 237 patients in 2013, serum uric acid levels were found to be high in all types of stroke, but were the highest in the PACI group (22). In our study, SUA levels were highest in the LACI and PACI groups, respectively.

The relationship between serum uric acid and the effect of sex after acute ischemic stroke has yet to be explored. The biologic mechanisms underlying such sex specificity remains unclear. It is known that there is a sex difference in uric acid levels; women usually have lower uric acid levels than men (23). Several previous studies demonstrated that higher uric acid levels were significantly related with the development of HT and metabolic syndrome in women than in men. In the China Antihypertensive Trail in Acute Ischemic Stroke (CATIS) trial, Chen et al. found that elevated serum UA was positively associated with better prognosis in men, but not in women (24-26). In our study we found a relation between high uric acid levels in moderate and severe stenosis of the extracranial portion of the posterior circulation in women.

Tamariz et al. examined the relationship between SUA levels with AF in the Atherosclerosis Risk in Communities Study (ARIC) study, the hypothesis was that high SUA levels would be indicative of AF (27). Animal studies have also shown

that atrial electrical remodeling is enabled with oxidative stress (28,29). The hypothesis of the Kuwabara et al. was that hyperuricemia induced the electrical remodeling process by affecting ion channel expression in atrial myocytes, and the authors thus examined whether it caused AF. In their study, uric acid levels above 8 mg/dL were shown to be independent predictors of AF. In the study group, the prevalence of AF was significantly lower in individuals using uric acid-lowering agents (30). In our study, AF was detected in 36 of 174 patients and elevation of uric acid was observed in 14 of these patients. There was no statistically significant difference between serum uric acid levels and AF; no statistically significant correlation was found between AF and atherosclerotic intracranial artery stenosis. We only found a correlation between AF and extracranial atherosclerosis of the anterior circulation as contour irregularity and moderate stenosis (p=0.05).

The current literature does not support the treatment of asymptomatic hyperuricemia, even among subjects at high cardiovascular risk. The usefulness of reducing SUA with xanthine oxidase inhibitors in the setting of ischemic stroke and other acute illnesses still requires further evaluation with appropriately designed randomized controlled trials (31).

Our study is one of the few studies that is mostly based on SUA levels and intracranial-extracranial arteriostenosis location. As a conclusion, in the present study, we found that LACI and PACI were the most frequent lesion locations for patients with high uric acid levels. According to our results, female patients have elevated uric acid levels in moderate and severe stenosis of extracranial portion of posterior circulation. So it has to be taken in consideration for woman with extracranial posterior circulation stenosis who has a high serum uric acid level.

The limitation of our study is the small number of patients. It is possible that a significant relationship between high uric acid levels and atherosclerotic intracranial- extracranial artery stenosis and AF could have been shown with larger groups.

Conflict of interest

No conflict of interest was declared by the authors.

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