The Relationship Between Serum Uric Acid Levels and Clinical Features in Essential Tremor

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ABSTRACT

Introduction: In this study, we aimed to investigate the effect of uric acid on the disease, its severity and progression in ET patients with partially co-clinical features with Parkinson's disease (PD).

Methods: Serum UA levels of 87 consecutive ET patients were measured and were matched according to age and sex with 87 healthy controls. Fahn-Tolosa-Marin scale was used for the severity of tremor. Sociodemographic characteristics, type of ET, duration of disease, and treatment modalities were evaluated.

Results: The mean uric acid level was calculated as 4.986 ± 2.1458 mg/dL and 6.004 ± 1.523 mg/dL in the patient and control groups, respectively ($p \leq 0.005$). The blood UA level of patients with sporadic (n: 61) ET was found to be lower than the familial ET (n: 26) ($p \leq 0.005$). The tremor severity of the family ET patients was lower than the sporadic ET. (n: 61)

($p \leq 0.005$). The mean blood UA level (4.429 ± 1.216 mg/dL) in the patients with high total tremor severity scores (n: 48) was found lower than in the patients with low total tremor severity scores (n: 39) (5.673 ± 2.106 mg/dL) ($P=0.000$). The serum UA level was significantly lower in the patients whose disease duration longer than 5 years than in patients whose duration of the disease was shorter than 5 years. 5.732 ± 1.240 for ≥ 5 years; $6.438 \pm 0.286 \leq 5$ years) ($P=0.001$).

Conclusion: We hypothesize that as a result of high antioxidant properties of high serum uric acid levels, it is a biomarker that can show disease risk and progression in patients with ET as well as PD.

Keywords: Essential tremor, uric acid, Fahn-Tolosa-Marin tremor scale, familial essential tremor, sporadic essential tremor, antioxidant effect

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INTRODUCTION

Essential tremor (ET) is one of the most common neurological disorder occurring twice as frequent as Parkinson's disease. The most important feature of ET is the postural and kinetic tremor of the upper extremities (90–95%) The head (30%), lower limbs (10–15%) and voice (20%) can also be affected. (1). The prevalence of ET gradually increases with age. So that, age and family history are the most important risk factors for ET (2). Families with an autosomal dominant inheritance pattern are common. Progression is usually close to the age of 65, slow until late in life (3, 4). ET affects both hands, but can be asymmetric or even unilateral; it may occur over a wide, non-specific frequency range (4–12 Hz). Tremor may exceed its postural amplitude at rest (as in parkinsonian tremor) or on action (as in cerebellar outflow tremor); and it may affect handwriting but not exclusively at onset (as in primary writing tremor) (5). Despite a known autosomal dominant inheritance, a neurophysiological marker of ET is not known yet. Essential tremor is clearly a polygenic disorder, much like hereditary ataxia and Parkinson's disease. Thus, diagnosis of ET is based on exclusion of other causes of tremor (5–9)

Uric acid is the final product of the catabolism of guanylic acid, inosinic acid, adenylic acid and adenosine triphosphate, which are purine

nucleotides and endogenous plus exogenous source for human bodies. There is also an antioxidant and pro-inflammatory mechanism for uric acid cycles (10). Studies have demonstrated that it eliminates the toxic reactants and protects the tissue against oxidative stress when it is within normal limits. However, the increase in serum uric acid levels indicate the state of the uric acid balance when there is an oxidative stress in human body (9–11). On the other hand, hyperuricemia has been associated with metabolic syndrome, stroke, preeclampsia, hypertension, renal and cardiovascular diseases (12, 13). In contrast to the association of chronic uric acid elevation with the diseases described above, it is suggested that the acute increase of serum uric acid levels may have beneficial effects. Recent studies showed that, the addition of uric acid to patients with normal uric acid levels increases the plasma antioxidant capacity and restores endothelial function in patients with type 1 diabetes and regular smokers. Uric acid neutralizes oxidative damage related to aging and atherosclerosis. As a result of these studies, uric acid can play a beneficial role in maintaining vascular function under both physiological and pathological conditions (10, 14, 15). Thus, serum uric acid levels have been reported to be inversely related to disease duration, progression or L-Dopa administration in patients with Parkinson's Disease by Vieru et al.

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This beneficial efficacy proved to be explained by the antioxidant effect of uric acid (16).

There have been several studies demonstrating an association between ET and PD greater than expected (15–18). A prospective, case-control study in Singapore found a higher prevalence of ET in PD patients. On the other hand, Leon et al showed that ET patients were 4 times more likely to develop PD compared to controls (15). Thus, PD patients, particularly those with tremor-dominant PD, have a greater frequency of a family history of ET compared to controls (16). According to the literature, compared to ET patients, ET-PD patients had less widespread postural and kinetic tremor, had less evidence of cerebellar dysfunction (nystagmus, intention tremor or dysmetria) and were on fewer ET medications additionally (17). In this study, we aimed to investigate the function of uric acid levels in ET and determine the protective effect of uric acid and prognosis in patients with ET.

METHODS

From August 2018 to January 2019, 87 patients followed from our hospital (Department of Neurology, Bakirkoy Research and Training Hospital for Neurologic and Psychiatric Diseases) with the diagnosis of essential tremor (familial, sporadic) who were clinically diagnosed according to Tremor Task Force of the International Parkinson and Movement Disorder Society 2018 Criteria (19) and 87 age-sex matched healthy controls were included in the study prospectively. Each patient attending in this study provided written informed consent. The patients were enrolled on a random basis, i. e., on random weekdays. Patients with comorbid diseases and patients who are on pharmacological therapies that may affect uric acid levels were excluded. Sociodemographic characteristics, type of ET, duration of disease, and treatment modalities were recorded. Fahn-Tolosa-Marin scale was used for the severity of tremor. Tremor severity was calculated by dividing total score to maximum score. Values below 50% were considered low (including no functional disability and mild/moderate disability score) and values above 50% as high (including marked and severe disability score). The blood uric acid levels of all patients and control group were compared. Patients with a history of disease (Gout disease, preeclampsia and eclampsia, pneumonia, leukaemia, Haemolytic anaemia, Pernicious anaemia, renal failure, polycythaemias, Lymphomas, Hypoparathyroidism, Ischemic heart disease, Lead poisoning, Down syndrome, Glycogen storage disease, A-alpha lipoproteinemia Type III hyperlipoproteinemia, Acute hepatitis, Improper ADH syndrome, Wilson's disease, Acromegaly Fanconi syndrome, Neoplastic diseases) and drug usage that may affect uric acid levels (losartan, various diuretics; hydrochlorothiazide furosemide, ethacrynic acid, corticosteroid drug) were excluded. In order to investigate the effects of the agents used for the treatment of ET on uric acid blood level and to understand its importance

in the prognosis, the patients were divided into two groups as receiving or not receiving treatment. Statistical analyses were conducted using SPSS software (version 21.0). Means and standard deviations were calculated for baseline characteristics. The Student's t-test (two-tailed) and Pearson's correlation analysis were used for normally distributed variables, while the Mann-Whitney U test and Spearman's rank correlation test were used for nonparametric variables. P values lower than 0.05 were considered to be statistically significant. The required written permission was obtained from the ethics committee of our hospital for this study.

RESULTS

87 patients and 87 healthy subjects were included in the study. The mean age of the patients was 62.21 ± 11.08 years ($58.34 \pm 9.24 \pm 10.12$ years); mean duration of disease was 13 ± 6.2 years. (min: 4 months, max: 26 years). Twenty-six patients had diagnosed with familial ET and 61 of 87 were diagnosed with sporadic ET (Table 1).

The mean uric acid level was calculated as 4.986 ± 2.1458 mg/dL and 6.004 ± 1.523 mg/dL in both patient and control groups, respectively. In the context of this result, uric acid levels of ET patients were statistically lower than those of the control group with the same demographic characteristics ($p \leq 0.005$) (Table 2).

The blood UA levels of patients with sporadic (n: 61) ET was found to be lower than the familial ET (n: 26) significantly (3.95 ± 2.274 mg/dL 4.62 ± 1.216 mg/dL) ($p \leq 0.005$). However, no significant difference was found between age and gender of patients ($p = 0.021$) (Table 2).

The severity of tremor was evaluated according to Fahn-Tolosa-Marin Staging (FTMS); total score and subgroup scores were calculated. As the duration of the disease prolonged, the total tremor severity score

Table 1. Demographic and clinical features of patients

Patients (n: 87)	Features
Women/Men (n) (%)	52/35 (59.7%; 40.2%)
The mean age (years) (min-max)	62.21 ± 11.08 (18–71)
ET* types (n) (%)	familial (26) (29.8%)
	sporadic (61) (70%)
The mean disease duration (years)	13 ± 6.2 (min 4 month, max: 26 years)

*essential tremor.

Table 2. The comparison uric acid levels between patients, control group and other properties

Variables		The mean age (year) $\pm$ SD	p value	Uric acid level (mg/dL) $\pm$ SD	p value
Control (n: 87)		59.87 ± 10.49	0.0341	6.004 ± 1.5233	<0.005
Total ET patients (n: 87)		62.21 ± 11.08		58.34 ± 9.2	
ET patients (n: 87)	Familial ET (n: 26)	58 ± 11.54	0.0067	4.62 ± 1.216	<0.005
	Sporadic ET (n: 61)	63 ± 10.09		3.95 ± 2.274	
The mean FTM tremor score	High level (marked and severe) (n: 48)	59.94 ± 9.43	0.0135	4.429 ± 1.216	0.000
	Low level (none, mild, moderate) (n: 39)	63.08 ± 11.20		5.673 ± 2.106 mg	
The disease duration	<5 years (n: 38)	61 ± 10.50	0.028	6.438 ± 0.286	0.001
	≥ 5 years (n: 49)	57 ± 12.89		5.732 ± 1.240	

ET: essential tremor, SD: standard deviation, FTM: Fahn Tolosa Marin

increased as expected (Mean difference (MD): -7.96% 95 CI: -14.82 to -2.74). Thus, the mean blood uric acid levels (4.429 ± 1.216 mg/dL) in the patients with high total tremor severity scores (n: 48) was found lower than in the patients with low total tremor severity scores (n: 39) (5.673 ± 2.106 mg/dL) significantly ($p=0.000$). This is particularly evident in the motor function tremor severity scores subgroup which is part of FTMS (MD -5.07 -2.35 95% CI: -7784). Thus, the mean score of FTM subgroups as follows kinetic, postural and rest were 2.33 ± 0.88 ; 2.13 ± 0.66 ; 0.22 ± 0.77 in ET group respectively. Also, we obtained that the serum uric acid level was significantly lower in the patients whose disease duration was longer than 5 years than in patients whose duration of the disease was shorter than 5 years (5.732 ± 1.240 for ≥ 5 years; $6.438 \pm 0.286 \leq 5$ years) ($p=0.001$). In addition, when the severity of tremor according to ET type was evaluated; the tremor severity of the familial ET patients (n: 26) was lower than the sporadic ET group (n: 61) significantly. (MD: -4.99% 95 CI: -6.67 vs -3.13) ($p \leq 0.005$). For postural and kinetic subscores came through high level for sporadic ET patients with the significance in comparison with familial ET patients also ($p=0.002$).

Patients were divided into two groups: no treatment (n: 30) and treatment with primidone and/or propranolol hcl (n: 57). In comparison of treated and untreated patient groups; the uric acid levels did not reveal any differences ($5.3968 (\pm 1.3418)$ mg/dL vs. $5.4035 (\pm 1.3152)$ mg/dL respectively)

DISCUSSION

This study is the unique research investigating the relationship between ET and uric acid levels. The levels of uric acid were detected low in ET patients compared to the control group. Serum UA levels in patients with short disease duration and low tremor severity were significantly higher than patients with high tremor severity and long duration of disease. According to ET types, the results of familial ET cases, which shows lower score of tremor severity and higher serum uric acid level in comparison with sporadic ET cases, strengthens this hypothesis too.

It's thought that uric acid cleans high levels of toxic reactants and protects against oxidative stress (endogenous anti-oxidant). The argument supports this hypothesis due to the low levels found in patients with various neurological disorders (19, 20). Recently, uric acid has been shown to play a role in innate immune responses for infection and other injuries (17, 21). However, uric acid loses its antioxidant properties in a hydrophobic environment. It may also be prooxidant alone or in combination with peroxynitrite to form free radicals. Different mechanisms have been proposed to explain the paradoxical associations of uric acid, but the role of uric acid as a causal, compensatory or random risk factor is still unclear. In recent publications, it has been shown that high uric acid levels play an important role in preventing the pathogenesis of dopaminergic cells in the pathophysiology of PD by the endogenous antioxidant role and decreasing the risk of developing PD and causing a positive effect on PD progression (16, 22–24).

In the literature, the levels of uric acid were lower in PD patients than healthy subjects (16, 25). A recent research showed that, serum uric acid levels have been reported to be inversely related to disease duration, progression or L-Dopa administration (26), similar findings were published in the study by Sun et al. A in 2012 (27). The relationship between serum uric acid levels and disease progression was investigated in 411 patients with PD. Serum uric acid levels were found to be lower in PD-patients with higher Hoehn and Yahr Scale scores (27). In the PRECEPT study, 804 patients with PD were followed-up prospectively and an adverse association was found between the PD progression and serum uric acid levels, already as same as recent published study by Vieru including 80 PD patients (16, 28). Cipriani et al. also reported that serum uric acid level

is an important biomarker for development and prognosis of PD (29). In line with these articles, the authors conclude that as uric acid eliminates free radicals and decreased oxidative stress, it will have an impact on the risk and progression of PD when uric acid levels are low. In our study, we have found out that as the duration of the disease and the severity of tremor increases, patients have decreased serum uric acid levels. There are also several studies pointing a relationship between ET and PD (15, 18). In a study evaluating 130 patients with ET, 25 (19%) patients with parkinsonism were observed. (18) Similar parkinsonism findings were found in 6.1% of the 678 ET patients and in 8.7% of 357 ET patients, and clinically these two disease similarities were supported. (20). According to these findings and possible relationship of the diseases, we consider that serum uric acid levels will have an effect on disease progression with the same antioxidant mechanism in ET patients.

Another hypothesis about uric acid is that higher uric acid levels may provide incomplete dopaminergic effect. Therefore, there are studies defining a relationship between dopaminergic treatment and uric acid in PD (16, 26, 29). Because the pathophysiology of ET patients was not explained by the dominant dopaminergic deficiency as in PD and the drugs used (propranolol and primidone) do not affect this system, there was no clear relationship between propranolol/primidone treatments and serum uric acid levels in ET patients. Also, there is not any publication in the literature comparing sporadic ET and familial ET according to uric acid levels.

In conclusion, we hypothesize that as a result of high antioxidant properties of high serum uric acid levels, uric acid is a biomarker that can show disease risk and progression in patients with ET as well as other neurological diseases. To support this hypothesis, we think that a greater number of ET patients and longer follow-up studies are needed.

Compliance with Ethical Standards Clinical Implications or Article Highlights:

High level UA has a protective effect on essential tremor patients due to endogenous antioxidant effect as same as Parkinson's disease patients. This study is the first research to investigate the relationship between ET and UA levels.

Ethics Committee Approval: The required written permission was obtained from the ethics committee of our hospital (Department of Neurology, Bakirkoy Research and Training Hospital for Neurologic and Psychiatric Diseases) for this study.

Informed Consent: Each patient attending in this study provided written informed consent.

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