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Serum Uric Acid Level as a Prognostic Factor in Benign Essential Tremor

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KA and HB designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors OM, VA and HB managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objective: Decreased serum uric acid has been associated with neurodegenerative diseases such as Parkinson's disease (PD) in the elderly. Several studies suggest that there may be a link between PD and Essential tremor (ET) which is thought to be a neurodegenerative disease. Serum uric acid level (UA) and its relationship with prognosis in ET patients have not been addressed.
Study Population: The current study was conducted in the outpatient neurology unit of Istanbul Medeniyet University Medical Faculty Göztepe Teaching Hospital between May 2011 and Sep 2013.
Methods: Subjects with ET were evaluated. We collected serum samples to determine biochemical indicators including UA, glucose, blood lipids, liver function, and renal function. All the patients with vascular risk factors, dementia, depression or other neurodegenerative disorders were excluded, as were the subjects on uric acid-lowering therapy or with serious illnesses such as severe anemia, chronic renal failure, hepatic disease or active or ongoing cardiovascular or cerebral vascular disease. One hundred and sixteen subjects (52 isolated ET patients and 64

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healthy controls well matched in comparison of age and sex) were enrolled.
Results: UA level was similar between the groups. Follow-up UA levels of the patients were similar to controls, too. UA level correlated to age, ET starting age, cholesterol level and creatinine level ($p<0.05$).
Conclusion: There were reasonable epidemiological evidences to support a link between ET and UA level, but we did not find any difference between serum UA levels of ET patients and controls in follow-up. Age was one of the factors contributing to the increased content of UA in the blood serum of especially the man with ET. These findings also supported the knowledge about isolated form of ET which was stable and benign.

Keywords: Essential tremor; Parkinson's disease; neurodegenerative disease; uric acid; age.

1. INTRODUCTION

Essential tremor (ET), characterized by postural and/or kinetic tremor, is one of the most common tremor disorders worldwide [1]. Although the exact pathogenesis of ET remains unknown, axonal swelling and loss of Purkinje cells in the cerebellum in ET patients have been identified [2-4]. Because Lewy body pathology is found in some ET patients and the Purkinje cell loss, it is thought that ET is a neurodegenerative disorder [5]. Moreover, several studies have suggested that there may be a link between Parkinson's disease (PD) and ET [6,7]. ET, especially in male patients, increases the risk of developing PD and rest tremor, which is commonly found in PD patients, also appears to occur in a subset of ET patients, for reasons that remain unknown [6,7]. Many studies have correlated higher urate levels with a lower risk of developing PD and with a favorable disease progression, indicating that urate could be a biomarker of the pathophysiology underlying PD [8]. Uric acid (UA) is, in fact, strongly linked to outcomes in neurodegenerative diseases and blood urate is a potential biomarker of a favorable prognosis not only in PD but also in Huntington's disease [9]. Another study showed that UA has neuroprotective effects in the progression from mild cognitive impairment to Alzheimer's disease [10]. Serum UA levels and their relationship with prognosis in ET patients has not been addressed previously. Given this background and the suspicion of a connection between ET and PD, we examined UA levels in ET patients. Furthermore, to test the connection, we examined follow-up measures of UA and the relationships between serum UA and other risk factors related to ET in the patients.

2. MATERIALS AND METHODS

2.1 Study Population

The current cross-sectional study was conducted in the outpatient neurology unit of Istanbul Medeniyet University Medical Faculty Göztepe Teaching Hospital between May 2011 and Sep 2013. The study was in accordance with the declaration of Helsinki, and informed consent was obtained from all patients before enrollment. The study protocol was approved by local Ethics Committee. The study population comprised patients with ET patients diagnosed clinically and electrophysiologically. Of 239 subjects that were screened for the study, 187 were excluded for the following prespecified reasons: unwillingness to participate in the study, Parkinson's disease, Parkinson plus syndrome, cerebellar syndrome, dementia and Alzheimer disease, use of antidepressants or depression, acute or chronic coronary syndrome, cerebrovascular disease, active peripheral arterial disease, hyper- or hypothyroidism, severe anemia (defined as hemoglobin <8 g/l), gout, use of hypouricemic drugs and dietary supplements, particularly antioxidants, alcohol abuse, smoking, diabetes, moderate or severe hypertension, hypercholesterolemia, active hepatic dysfunction, and of course nephropathy. Fifty-two samples were collected during follow-up period (2 nd measurements) and thus 52 subjects constituted the study population. Sixty-four healthy subjects were included for comparison.

2.2 Diagnosis of ET

ET is a clinical diagnosis, and there are currently no lab tests or radiological scans to aid in the diagnosis. The patients with bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that was visible and persistent, and with duration greater than 5 years were included in the present study [11]. Neither hereditary nor senile ET patients was included in the present study. Sporadic ET diagnosis was made according to the following definition proposed by Deuschl and Elble; the patients who fulfilled the consensus criteria for definite or classic ET, but did not have an immediate family member with ET, and whose age at onset of ET

was younger than 65 years [12]. Other exclusion criterias were the presence of other abnormal neurological signs (except Froment's sign), presence of known causes of increased physiological tremor, concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state, the presence of direct or indirect trauma to the nervous system within 3 months before the onset of tremor, historical or clinical evidence of psychogenic origins, and convincing evidence of sudden onset or evidence of stepwise deterioration. In suspicion, the patients also had neurophysiologic diagnosis and criteria required the presence of all of the following: rhythmic burst of postural tremor on EMG, tremor frequency greater than or equal to 4 Hz, absence of rest tremor or, if present, frequency 1.5 Hz lower than the postural tremor, absence of tremor latency from rest to postural position, changes of the dominant frequency peak less or equal to 1 Hz after the weight load test, and no changes in tremor amplitude after mental concentration [13].

2.3 Additional Assessments and Laboratory Analysis

Subjects with ET and controls also underwent the following assessments: medical history, physical examination, cognitive assessment by mini mental status exam (MMSE) and office BP measurements. Sociodemographic and clinical assessment included age, gender and current medications. Fasting blood samples were measured with Cobas 8000 Biochemical Analyzer (USA) for UA, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, thyroid-stimulating hormone, and total cholesterol. After at least 2 year, blood samples were redrawn from the patients. It was recorded as follow-up measure. Hyperuricemia was defined as a blood UA concentration greater than 7.0 mg/dL in men and 6.0 mg/dL in women similar to literature [14].

2.4 Vascular risk factor assessment

Hypertension was considered to be present if at the time of diagnosis the participants had a systolic blood pressure >140 mmHg or a diastolic pressure >90 mmHg, and if treatment for high blood pressure was administered previously. Previous coronary artery disease and a related history of ischemia were considered to be present if the subjects had previously been treated for these. Hypercholesterolemia was considered to be present in subjects with serum cholesterol >200 mg/dL. Hyperglycemia was considered to be present in subjects with a serum level of >100 mg/dL, or if treatment for diabetes had previously been started. Smoking was considered to be present in subjects with cigarette smoking ≥ 20 pack years. Alcohol was considered to be present in subjects with alcohol consumption ≥24 g/day. All these patients with vascular risk factors were excluded from the study, but the patients who smoked <20 packs per year or who presented with alcohol consumption <24 g/day were included in the study.

2.5 Statistical Analysis

Statistical analysis was performed by using SPSS 11.0 statistical software (SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normally distributed. Parametric tests were applied with normal distribution, whereas nonparametric tests were used without normal distribution (i.e age, MMSE score, creatinine, cholesterol, duration of disease, date the disease started). Normally distributed variables were given as mean-/+ standard deviation, while those variables featured by non-normal distribution were given as medians with interquartile ranges. Chi-square test was used for categorical variables to test the differences among the patients. A P value <.05 was accepted to be statistically significant.

3. RESULTS

The study consisted of 52 newly diagnosed ET patients (17 female, 35 male) and 64 (15 female, 48 male) healthy control patients. Table 1 summarizes the demographic and clinical data of the study groups. The patients were older and their UA levels were greater than those in the control groups, but the difference did not reach statistical significance. There were also no significant differences between the groups in terms of sex distribution and levels of FBG, Total Cholesterol, AST, ALT, Sodium, Urea, Creatinine and BMI. Duration of disease was 4 years (Min-Max: 1-30) and starting age of the disease was 53.5 years (Min-Max: 36-64) in ET patients. Smoking consumption rate was higher in the patients group. UA level was correlated with age (r:0.34, p:0.02), ET starting age (r:0.29, p:0.04), cholesterol level (r:-0.33, p:0.04) and creatinine level (r:0.54, p<0.001) in the patients with ET. It reached a significant low level in the age group of 50-59 years if compared to the age group of 60-69 and 70-79 years (p values were 0.032 and 0.025 respectively). Maximum increase of the

uric acid content in men was revealed in the age group of 70–79 years and it presented a significant difference if compared to other age groups (p=0.001). In women, there was not any significant difference between age groups although higher UA level was seen in the age group of 60-69 years. Incidence of hyperuricemia among the women totaled 17.6% (n=3), among the men –16.6% (n=6). In comparison, baseline and follow-up uric acid values of patients, and uric acid levels of controls were similar (*p*=0.64, ANOVA test, Table 1 & Fig. 1).

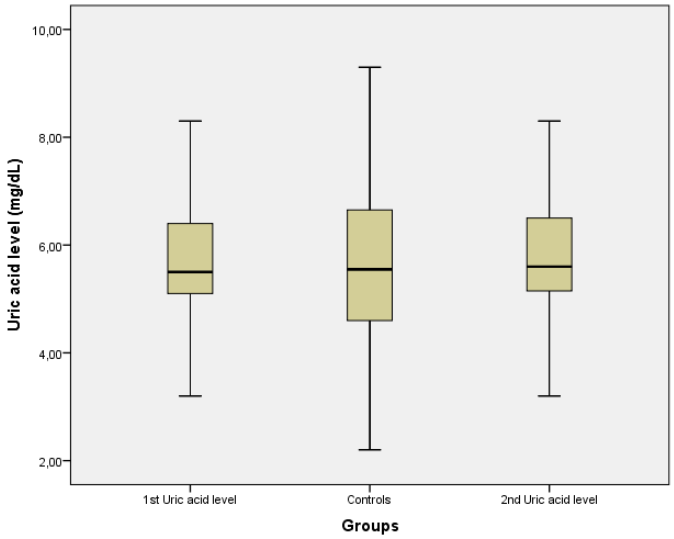

Fig. 1. Comparison of UA levels among three measurements

Table 1. Clinical and laboratory findings in comparison of study groups

Variable	Group	n	Mean	SD	Median	Min.-Max.	*p* value
Age (year)	Patient	52	60.90	8.03	63.5	43-72	.06
	Control	64	59.41	4.23	59	49-71	
Uric acid (mg/dL)	Patient*	52	5.61	1.55			.64$^{\mu}$
	Patient$^{\alpha}$	52	5.98	1.44			
	Control	64	5.56	1.36			
FBG (mg/dL)	Patient	52	96.41	10.59			.77
	Control	64	97.18	12.68			
Cholesterol level (mg/dL)	Patient	52	182.53	19.96			.35
	Control	64	178.43	20.05			
Na level (mg/dL)	Patient	52	141.33	2.40			.06
	Control	64	141.13	2.34			
Creatinine level (mg/dL)	Patient	52	1.037	0.17	1.1	0.80-1.50	.32
	Control	64	0.99	0.18	1.0	0.60-1.50	
Urea level (mg/dL)	Patient	52	34.94	8.65			.48
	Control	64	33.56	10.27			
ALT level (U/L)	Patient	52	23.19	9.49			.52
	Control	64	24.46	10.18			
AST level (U/L)	Patient	52	22.54	7.21			.72
	Control	64	23.11	8.17			
MMSE score	Patient	52	28.64	1.53	29	24-30	.52
	Control	64	29.03	0.89	29	27-30	

*Abbreviations: *1st record, α2 year follow-up record (2nd record), μ p value (ANOVA), FBG (Fasting blood glucose), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), BMI (Body mass index), MMSE (Mini mental state exam)*

4. DISCUSSION

Essential tremor was known previously as "benign essential tremor," but the adjective benign has been dropped in recognition of the sometimes disabling nature of the disorder [15,16]. ET may be progressive (sometimes rapidly, sometimes very slowly) and associated with a variety of features, such as gait abnormalities, parkinsonism, cognitive impairment, and dementia. ET is now accepted as a family of diseases that are aging-associated, progressive, and associated with cell loss and other types of changes (e.g., Lewy body formation) that occur traditionally in neurodegenerative disorders [17]. Today, the presence of heterogeneity in etiological, clinical, including pharmacological response profiles, and post-mortem findings is well known, although ET is still unified by tremor during voluntary movements [18].

The association between serum UA levels and various neurodegenerative disorders has been of particular interest in recent years. UA reduces oxidative stress, mitochondrial dysfunction, and cell death occurring spontaneously in culture or induced by pesticides, glutamate, and iron ions [19,20]. Increased oxidative stress, mitochondrial dysfunction, DNA damage, lipid peroxidation, and protein aggregation are common in the brain tissues of PD patients [21]. Substantia nigra pars compacta dopaminergic neurons are initially more vulnerable to oxidative stress; one explanation for this suggests that dopamine itself may confer neurotoxicicity and can be auto-oxidized to neuromelanin, which, in turn, promotes the generation of oxyradicals [22]. UA has also been demonstrated to reduce oxidation of dopamine in the caudate and substantia nigra of PD patients [22]. That is, the protective effects of urate may be meditated by its antioxidant activity. Reduced serum levels of UA have been associated with PD, and individuals with a history of gout have a significantly lower risk of developing PD than those with no such history [23-25]. Purkinje cell loss and Lewy bodies have been observed in the brains of individuals with ET and Purkinje cell loss is characteristic of the ET brain, in comparison with normal aging. These changes are not uniform but are similar to those seen in degenerative diseases [26]. Although ET and PD are considered distinct disorders, a long-standing postural tremor in the hands may precede the onset of PD features by several years. The most robust evidence, from case-control, prospective, and familial aggregation studies, indicates that ET is associated with increased risks of both PD and AD [27]. In short, there is much reasonable epidemiological evidence supporting a link between ET and these neurodegenerative diseases, so we examined UA levels in ET. As described in the Results, UA levels were similar between patients and controls and correlated independently with age, ET starting age, cholesterol levels, and creatinine levels, but not with duration of disease or severity of tremor in the patient group. Age is one factor contributing to the increased content of UA in the serum of both females and males [28]. Similar to previous reports, a higher uric acid content after the age of 60 in the patient group was seen in our study [28,29]. Additionally, we found that males had a higher incidence of hyperuricemia than females, as reported previously [28,29]. Additionally, many studies have shown that higher total cholesterol and creatinine serum levels are positively associated with serum uric acid [30]. Consistent with these reports, we found that higher total cholesterol and creatinine levels were correlated with higher serum UA levels in the current study.

We particularly excluded the patients with concomitant diseases and none of the study subjects were using medication affecting UA level in order to minimize the effect of confounding factors on UA level in the present study. Because of this strict but valuable criteri the small number of patients should be kept in mind as the limitation of this measure. In other words, our sample represented benign essential tremor. Its 2 year follow-up nature was another limitation of the present study. Despite these limitations, we believe in that the findings of this study especially follow-up period records will improve the understanding of the inflammation's effect on prognosis of ET.

5. CONCLUSION

In this study, we showed that UA levels were independently correlated with ET starting age but not with duration of disease or severity of tremor in benign ET patients. To the best of our knowledge, these findings have not been reported previously. Despite our results, the exact inflammatory components in ET pathology versus that in PD remain still unknown. Long term follow up and serial serum uric acid evaluation from a large prospective study may illuminate the clinical impact of uric acid levels in ET patients.

CONSENT

The study was in accordance with the declaration of Helsinki, and informed consent was obtained from all patients before enrollment as it was written in method section.

ETHICAL APPROVAL

The study protocol was approved by local Ethics Committee as mentioned in method section.

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On behalf of all authors, the corresponding author states that there is no conflict of interest. The study has been accepted for poster presentation in AD/PD 2015.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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