The Cognitive Effect of Uric Acid in Idiopathic Parkinson’s Patients

İdyopatik Parkinson Hastalarında Ürik Asidin Kognitif Etkisi

Osman Korucu

Keçiören Training and Research Hospital, Department of Neurology, Ankara, Turkey

ABSTRACT

Objective: High serum uric acid level (sUA) has been associated with decreased Parkinson’s disease risk, slow disease progression, good cognitive performance and low dementia risk. In this study, the relation of dementia and uric acid levels was investigated in idiopathic Parkinson’s patients that are known to be associated with low sUA.

Methods: Patients files of patients, who were diagnosed with idiopathic Parkinson’s disease and have applied between dates 01.01.2009-31.01.2019, have been scanned retrospectively. Their age, gender, marital status, uric acid level and the presence of dementia were recorded. A total of 126 patients between ages 18-90 with creatinine levels below 1.25 mg/dl and no diagnosis of gout have been included in the study.

Results: Among 126 patients included in the study, 68 (54%) were male, 93 (73.81%) were married, and 37 (29.37%) patients were diagnosed with dementia. There was a statistically significant difference between groups with or without dementia diagnosis with regard to age (p:0.006) and marital status (p:0.007). Mean uric acid level was determined to be 4.6 mg/dl for the patients. There was no statistically significant difference between the two groups when this value was taken as reference (p:0.328). However, the number of patients diagnosed with dementia was relatively lower in the group with higher uric acid level.

Conclusion: The fact that median uric acid levels of our patients were within the interval recognized to be normal and the patients had relatively higher sUA levels in non-dementia group suggests that high sUA levels within normal interval may be protective.

Key Words: Cognition; Parkinson’s disease; Dementia; Uric acid

ÖZET

Amaç: Yüksek serum ürik asit düzeyi (sUA), azalmış Parkinson hastalığı riski, yavaş hastalık progressyonu, İyi bilişsel performans ve düşük demans riski ile ilişkilendirilmiştir. Bu çalışmada düşük sUA ile ilişkili bilinen İdyopatik Parkinson hastalarında demans ve ürik asit düzeyi ilişkisi araştırıldı.

Metod: İdyopatik Parkinson hastalığı tanılı, 01.01.2009-31.01.2019 arasında başvurmuş hasta dosyaları retrospektif tarandı. Yaşı, cinsiyet, medeni durum, ürik asit düzeyi ve demans olup olmadığı kaydedildi. Kreatinin düzeyi 1.25 mg/dl’in altında ve Güt tanısı olmayan 18-90 yaş arası 126 hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen 126 hastanın 68 (%54)’i erkek, 93 (%73.81)’ü evliydi ve 37 (%29.37) hastada demans tanısı vardı. Demans tanısı olan ve olmayan gruplar arasında yaş (p:0.006) ve medeni durum (p:0.007) arasında istatistiksel anlamlı fark saptandı. Hastaların ortalama ürik asit düzeyi 4.6 mg/dl bulundu. Bu değer referans alındığında 2 grup arasında istatistiksel anlamli fark yoktu (p:0.328). Ancak ürik asit düzeyi yüksek grupta nispi olarak demans tanısı daha az idi.

Sonuç: Hastalarnınıın median ürik asit değerlerinin normal kabul edilen aralığa olması ve demans olmayan gruptaki hastalarımızda nispi yüksek sUA seviyeleri, normal aralıklı yüksek sUA seviyelerinin koruyucu olabileceği aklı getiriktirdir.

Anahtar Sözcükler: Bilişsel; Parkinson hastalığı; Demans; Ürik asid

Received: 06.12.2019 Accepted: 08.29.2019

Address for Correspondence / Yazışma Adresi: Osman Korucu, MD, Keçiören Training and Research Hospital, Department of Neurology, Ankara, Turkey E-mail: osmankorucu@yahoo.com

©Copyright 2019 by Gazi University Medical Faculty - Available on-line at web site http://medicaljournal.gazi.edu.tr/ doi:http://dx.doi.org/10.12996/gmj.2019.97
INTRODUCTION

Parkinson’s disease (PD) and Alzheimer’s disease (AD) are neurodegenerative diseases that increase in prevalence with age (1,2). It has been suggested that oxidative stress plays a key role for the degeneration of nigrostriatal dopaminergic pathway in the development of PD (3). Neuronal damage mechanisms are not understood completely in the development of dementia, and potential risk factors are not known (2). Although two of previous studies did not determine any difference in serum uric acid (sUA) levels between PD patients and healthy subjects, high sUA level has been associated with decreased PD risk and slow disease progression in recent studies (4-9). The reason of this effect, which is only observed in men, could not be understood (8). Hyperuricemia is identified with sUA levels above 6.8-7 mg/dl, and it is associated with the development of gout, which is the most common inflammatory arthritis in developed countries (10).

UA has been shown to possess iron chelating characteristics. Iron is an important element in the metabolism of all cells. Iron loading in S. nigra especially plays an important role in the death of dopaminergic neurons (11,12). Also, toxic iron may increase synuclein misfolding and accumulation (13,14).

It was determined that 7119 patients have developed dementia (1214 gout patients and 5905 controls) in the 6-year monitoring that investigated the relation between gout and dementia in 28769 gout patients and 114742 control subjects. This study has shown gout patients have lower nonvascular dementia development risk after regulating related factors (15).

Conflicting results have been reported between gout and PD risk. Although a reverse relation was determined between gout and PD risk in 2 studies (16,17), there is a study that determined no relation between the use of antigout agents and PD risk (18), and also a meta-analysis study that did not determine an inverse relation between gout and PD risk (19).

While its mechanism is not known, it is assumed that uric acid may both recover oxidative stress, the pathogenic pathway in PD, and other neurodegenerative diseases such as dementia (20,21). A meta-analysis suggested that high sUA level may have possible neuroprotective effect in men (8), and another meta-analysis have suggested that some reversible effects can be obtained by modulating sUA levels due to neuroprotective effect (22).

However, results of studies investigating the relation of hyperuricemia and cognitive system are somewhat contradicting. While it was determined in a small study that Parkinson’s patients with dementia have similar sUA levels with subjects who had no cognitive disorder (23), it was shown in a recent study comparing uric acid levels and cognitive deterioration levels in patients diagnosed with PD that cognitive deterioration was associated with low sUA levels in de-novo PD patients (24).

Nevertheless, there are studies that have determined that high sUA levels are associated with better cognitive performance and low dementia risk in Alzheimer’s patients independent from cardiovascular risk (25), and there are studies that have determined lower nonvascular dementia risk in those with hyperuricemia after adjusting for age, gender and comorbidities (15). Similarly, a large meta-analysis has determined an inverse relation between sUA and AD (26). It was shown in a study performed in China that was comparing uric acid levels and cognition in idiopathic Parkinson’s patients with or without dementia.

RESULTS

Sixty eight patients (54%) were male among a total of 126 patients included in the study. Ninety-three of patients (73.81%) were married, and 33 (26.19%) were single or widowed. Among 89 patients that were not diagnosed with dementia, 48 were male. The difference between gender and uric acid (p:0.076). Creatinine (med(min-max)) value was 0.85(0.56-1.23) in the group with no dementia diagnosis, while it was determined as 0.82(0.37-1.22) in the group diagnosed with dementia, and there was no statistically significant difference between the two groups (p:0.394). There was a statistically significant difference between groups with or without dementia diagnosis with regard to age (p:0.006) and marital status (p:0.007), while no statistically significant difference was determined with gender (p:1) and uric acid level (p:0.79) (Table 1).

| Table 1. Group comparisons of sociodemographic data and uric acid levels |
|---------------------------|------------------|------------------|------------------|------------------|
| Dementia (n:126)          | Age (med(min-max)) | Gender (n %) | Marital status (n%) | Uric acid (med(min-max)) |
| Yes (n:37)                | 77(65-90)        | 17 (13.5%)    | 20 (15.9%)        | 21 (16.7%)       | 4.2 (1.8-10.6) |
| None (n:89)               | 73(49-89)        | 41 (32.5%)    | 48 (38.1%)        | 72 (57.1%)       | 4.74 (1.5-8.94) |
| p                        | 0.006            | 1              | 0.007             | 0.79             |

Mean uric acid level was determined to be 4.6 mg/dl for the patients. There was no statistically significant difference between the two groups when this value was taken as reference (p:0.328). However, the number of patients diagnosed with dementia was relatively lower in the group with higher uric acid level (Table 2).

| Table 2. Dementia and uric acid level |
|---------------------------------------|
| Dementia (n:126)          | Age (med(min-max)) | Gender (n %) | Marital status (n%)  |
| 4.6 mg/dl and above       | 22 (17.5%)        | 43 (34.1%)  | 65 (51.6%) |
| 4.61 mg/dl and above      | 15 (11.9%)        | 46 (36.5%)  | 61 (48.4%) |

Cognitive effect of uric acid level (225001)
In this study, the relation of dementia and uric acid levels was investigated in idiopathic Parkinson’s patients that are known to be associated with low sUA. No statistically significant relation was determined in our study between dementia and uric acid level, however, sUA level was found to be relatively higher in patients who were not diagnosed with dementia. Furthermore, a statistically significant difference was determined between the prevalence of dementia and advanced age and marital status. The advanced age and marital status results are in compliance with literature, where normal older adults from a cognitive aspect are gradually decreased with advanced age (30) and where dementia is higher in unmarried people, especially in widows (31).

High sUA level has been associated with decreased PD risk and slow disease progression recent studies, and while this effect is only observed in men (4-9), we could not determine this effect due to our study design. The relation between all dementia symptoms including Alzheimer’s disease, and cardiovascular risk factors such as hypertension and hypercholesterolemia has been shown in many studies in the literature (32,33). While two studies performed in AD and non-AD dementia patients have determined that high sUA level decreases dementia risk after adjusting for age, gender and comorbidity (15,25), this positive correlation may not be detected in our patient group since they were all Parkinson’s patients and mostly had sUA levels at low and normal limits.

There is evidence in literature showing high sUA level may be protective for PD (16,17) and cognitive deterioration in de novo PD patients are associated with low sUA levels (24). A meta-analysis comparing healthy controls and PD patients has determined a linear relation in PD patients between low sUA level, and global cognitive and functional decrease (29). These studies were performed on early stage Parkinson’s patients or by controlling with healthy controls. In our study, all patients diagnosed with idiopathic PD have been included and classified according to the presence of dementia. Upon including healthy controls in the study, detection of a significant difference seems possible with regard to sUA level especially in dementia group. However, the clinical importance of the significant difference in the comparisons between gout patients and healthy controls is still unclear in early stage PD.

It was determined in this 3-year follow-up study comparing urine UA level and follow-up neuropsychological tests that the correlation is decreased within years, and it was suggested this may mean possible neuroprotective effect of UA will be decreased throughout the progression of PD. This study has argued that UA may be a secondary marker for PD, rather than an etiological factor (34).

Similar to this follow-up study, it seems possible that we could not determine the cognitive effect correlation of uric acid due to our limitations which are our patient population consisting of only early stage idiopathic PD, not being a follow-up study, and not excluding cardiovascular risk factors such as hypertension and hypercholesterolemia. However, the fact that median uric acid levels of our patients were within the interval recognized to be normal and the patients had relatively higher sUA levels in non-dementia group compared to other group suggests that high sUA levels within normal interval may be protective.

Upon considering UA may have a neuroprotective effect in dementia and Parkinson’s patients, the protection or increase of uric acid levels may be an option (5,22). Ascherio and colleagues have suggested diet or medical treatments in order to achieve this (5).

Since the relation between hyperuricemia and cognition in PD patients is still unclear, follow-up studies with a longer period are required in order to clarify this relation.

Conflict of interest
No conflict of interest was declared by the authors.

REFERENCES
1-de Lau LM, Breteler MM. Epidemiology of Parkinson’s disease. Lancet Neurol. 2006;5:525-35.
2-Alzheimer’s Association. 2016 Alzheimer’s disease facts and figures. Alzheimers Dement. 2016;12:459-509.
3-Jiang T, Sun Q, Chen S. Oxidative stress: a major pathogenesis and potential therapeutic target of antioxidative agents in Parkinson’s disease and Alzheimer’s disease. Progr Neurobiol 2016;147: 1–9.
4-Jesus S, Pérez I, Cáceres-Redondo MT, Carrillo F, Carballo M, Gómez-Garre P, et al. Low serum uric acid concentration in Parkinson’s disease in southern Spain. J Neurol. 2013;20:208-10.
5-Ascherio A, LeWitt PA, Xu K, Eberly S, Watts A, Matson WR, et al. Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol. 2009;66:1460–8.