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SERUM URIC ACID LEVEL IS AN IMPORTANT PROGNOSTIC MARKER IN NEURODEGENERATIVE DISEASES

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ABSTRACT

Background: Neurodegenerative disease is a feature of many debilitating, incurable diseases that are rapidly rising in prevalence, such Alzheimer's, Parkinson's, prion, Huntington's, as amyotrophic lateral sclerosis (ALS) spinocerebellar ataxia(SCA), spinal muscular atrophy(SMA) and some other diseases or disorders. In contrast to many other disease states, low serum uric acid (UA) levels are found in many neurodegenerative diseases. **Aim of the Study:** The aim of this study was to evaluate the Serum Uric Acid Level as a prognostic marker in several neurodegenerative diseases. **Materials and Methods:** This study was carried out at neuromuscular disorder clinic, inpatient and outpatient Department of Neurology, Bangabandhu Sheik Mujib Medical University (BSMMU) Dhaka, Bangladesh. The duration of the study was from January 2018 to December 2018. This case-control cross-sectional study included 37 patients with several neurodegenerative diseases such as Alzheimer's disease (n=9), Parkinson's disease (n=8), prion disease (n=8), Huntington's disease (n=7) and finally amyotrophic lateral sclerosis (ALS) (n=5) were finalized as the case. On the other hand, 37 healthy people without any type of neurodegenerative or cerebrovascular disease met the proper exclusion criteria were recruited as the control group participants from stable outpatients and medical staff of the mentioned hospital. **Results:** In analyzing the Serum UA level we found the mean (±SD) Serum UA level of case and control groups were 4.66 ± 1.15 and 5.42 ± 1.20 respectively where the p-value was 0.0069 which indicated a significant correlation between both the groups. Besides this, in a specific analysis of the Serum UA level of only Alzheimer's patients, we found it was 4.58 ± 1.02. Although the number of Alzheimer's patients was 9, the p-value was 0.0377. So there was also significant. So Serum Uric Acid Level played an important role as a prognostic marker in several neurodegenerative diseases. **Conclusions:** Serum Uric Acid levels played an important role as a prognostic marker in several neurodegenerative diseases. The findings may be helpful in the diagnostic system of several neurodegenerative diseases.

KEYWORDS: Serum Uric Acid Level, Neurodegenerative diseases, Alzheimer's.

INTRODUCTION

Uric acid (UA) is a kind of endogenous, water-soluble anti-oxidant and a by-product of purine metabolism as well as a major natural antioxidant in plasma that reduces oxidative stress and protects against free radicals. Many studies showed that UA is associated with an increased risk of myocardial infarction, stroke, and cardiovascular mortality.[1] There is a well-recognized epidemiological link between higher levels of UA and the increased risk of AD.[2] Noted that here AD indicates Alzheimer's disease, one of the neurodegenerative diseases. Recently, a meta-analysis of 11 studies including 2708 participants conducted by Chen et al suggested that serum UA levels do not differ significantly in patients with AD,[3] which was the same as the conclusions of some large studies,[4,5] but many studies also indicated that serum UA levels are significantly lower in patients with AD in comparison to control participants, supporting the purported potential neuroprotective role of UA.[6] Serum uric acid (UA) levels have been reported to be lower in patients with Parkinson's disease (PD) and multiple system atrophy (MSA) than in control subjects.[7] Reactive oxygen species and oxidative stress may contribute to the pathogenesis of PD.[8] Postmortem analyses of the brains of PD patients have reported increased iron levels as well as altered levels of other metal ions (Dexter et al., 1989). UA exerts antioxidant effects in neurons by acting as a scavenger of free

radicals and as an iron chelator.[9] In a study[10] they found a relation between serum UA and dopamine transporter availability in drug-naïve PD patients: serum UA levels were positively correlated with averaged, ipsilateral and contralateral dopamine transporter binding in the striatum, specifically in the caudate and putamen. In PD patients, low serum UA levels have been associated with cognitive dysfunction.[11] PD patients with the lowest quartiles of serum UA levels showed higher scores on the Unified PD Rating Scale part III (motor part), higher total nonmotor symptom (NMS) scores, and higher domain scores relating to sleep, mood, and gastrointestinal function.[12] A study10 reported that early- stage, drug-naïve PD patients with lower serum UA levels had higher scores in the attention/memory, cardiovascular, and sleep domains, as evaluated by NMSQuest. In MSA patients, no correlation has been found between serum UA levels at the initial visit and the mean rate of annual changes in the Unified MSA Rating Scale.[13] However, few studies have compared serum UA levels among patients with PD-related disorders, including PD, MSA, and progressive supranuclear palsy.[14] Recently, a study[15] have reported significantly reduced levels of serum UA in patients with PSP and PD compared with those in healthy controls. In their study, there was no correlation between disease duration and serum UA level in either PD or PSP patients. On the other hand, the incidence of ALS increases with each decade, especially after age 40 years, and it peaks at age 74, decreasing thereafter. In a systematic review, the mean age of ALS onset was 62 years and the incidence and mortality rates of ALS have been slowly increasing over decades.[16] It is now considered as the 3rd most common neurodegenerative disorder after AD & PD.[17] On the other hand, UA is produced from purines by the enzyme xanthine oxidase via the purine metabolism pathway.[18] Uric acid is a natural antioxidant, accounting for up to 60% of the free radical scavenging activity in human blood and can scavenge superoxide, the hydroxyl radical, and singlet oxygen.[19] Removal of superoxide helps to prevent its reaction with NO, blocking the formation of peroxynitrite.[20] Uric acid is also very effective at preventing peroxynitrite from nitrating the tyrosine residues of proteins, thereby preventing the inactivation of cellular enzymes and modification of the cytoskeleton.[21] Uric acid also has the ability to bind iron and inhibit iron-dependent ascorbate oxidation, preventing an increased production of free radicals that can further contribute to oxidative damage.[22] Uric acid acts upon astroglia and up-regulates protein levels of EAAT-1, a glutamate transporter, to protect neurons from glutamate-induced toxicity. The protective effect of UA on neurodegeneration has been widely studied. Due to its antioxidant effects, higher concentrations of UA might protect against the development of neurodegenerative diseases and modulate their natural history. Some studies demonstrated a correlation between serum UA level and certain disorders of CNS, including MS and PD and they strongly suggest the antioxidant effect of UA is very essential in protecting against MS and PD.[23, 24] Elevated serum levels of uric acid are associated with slower disease progression in PD & and AD.[25] Reduced level of serum UA has been found and correlated with more rapid disease progression in patients with PD and AD.[26, 27] Low UA has been reported in individuals who developed PD many years later, implicating high levels of UA might have a neuro-protective role.[28]

OBJECTIVES

a) General objective

- To evaluate the Serum Uric Acid Level as a prognostic marker in several neurodegenerative diseases.

b) Specific Objectives

- To evaluate the Serum Uric Acid Level as a prognostic marker specifically in Alzheimer's disease.

METHODOLOGY AND MATERIALS

The present study was approved by the institutional review board of Bangabandhu Sheik Mujib Medical University (BSMMU) Dhaka, Bangladesh. All subjects provided written informed consent. This cross-sectional study included 37 patients with several neurodegenerative diseases such as Alzheimer's disease (n=9), Parkinson's disease (n=8), prion disease (n=8), Huntington's disease (n=7) and amyotrophic lateral sclerosis-ALS (n=5) were finalized as the case. On the other hand, 37 healthy people without any type of neurodegenerative or cerebrovascular disease met the proper exclusion criteria were recruited as the control group participants from stable outpatients and medical staff of the mentioned hospital. The study was conducted during the period from January 2018 to December 2018. The 37 participants of the case group were selected by first come first register basis during the first six months of the study. According to the exclusion criteria of the study, patients with renal dysfunction (estimated glomerular filtration rate <50 ml/min/1.73 m2), patients with thyroid disease, patients receiving treatment with anti-hyperuricemic drugs, and patients who were taking diuretics were excluded from this study. No patient had diabetic ketoacidosis, a body mass index (BMI) ≥30, and cancer or a hematological malignancy (e.g., leukemia or myeloproliferative disease). A diagnosis of PD was made based on the UK PD Society Brain Bank clinical diagnostic criteria.[29] The Unified PD Rating Scale (UPDRS) part III was used to assess motor symptoms. UPDRS part III has been reported to be a reliable assessment of motor symptoms in PSP (Cubo et al., 2000)30. A general linear model was used to compare the estimated mean serum UA levels between the patient and control groups after adjusting for age and BMI. Correlations between the serum UA levels and other clinical parameters were analyzed using Spearman's rank correlation coefficients. Statistical significance was defined as a two-tailed $p < .05$. On the other hand,

Windows 10 was used for the figures, and SPSS Statics 23 was used for the statistical analyses.

RESULTS

In this case-control cross sectional study in analyzing gender of case group participants we found among 37 participants 17 were male which was 45.95% and 20 were female which was 54.05%. The mean age of them was 71.50 ± 6.25 years. On the other hand, the mean age of control group participants was 66.25 ± 6.20 years. Here p value was 0.0005. So significance value (P-value) and 95% confidence interval (CI) of the difference is reported. Besides these, in diseases distribution among case group it was found that, the highest 24% (n=9) patients were with Alzheimer's disease whereas 22% (n=8) were with parkinson's disease, 22% were with prion disease, 19% (n=7) were with huntinton's disease and 13% (n=5) were with amyotrophic lateral sclerosis (ALS).In this current study age and BMI were significantly different among the groups. Case group patients received higher levodopa-equivalent doses (LEDs) than patients in the other group. In BMI analysis we found a significant correlation between the groups where p=0.0034 ($p<0.05$). Moreover, a significant correlation was found between the groups in UPDRS III scores whereas the p value was less than 0.0001. Finally in analyzing the Serum UA level we found the mean (±SD) Serum UA level of case and control groups were 4.66 ± 1.15 and 5.42 ± 1.20 respectively where the p value was 0.0069 which indicated a significant correlation between both the groups. Besides this in specific analyzing of Serum UA level of only Alzheimer's patients we found it was 4.58 ± 1.02. Although the number of Alzheimer's patients was 9, the p value was 0.0377. So there was also significance. So Serum Uric Acid Level played an important role as a prognostic marker in several neurodegenerative diseases.

Table 1: Gender distribution among case group.

Gender	Frequency(n)	Percentage (%)
Male	17	45.95
Female	20	54.05
Base	37	100

In table-1 shown: Among 37 patients of case group, 54% were female & 46% were male.

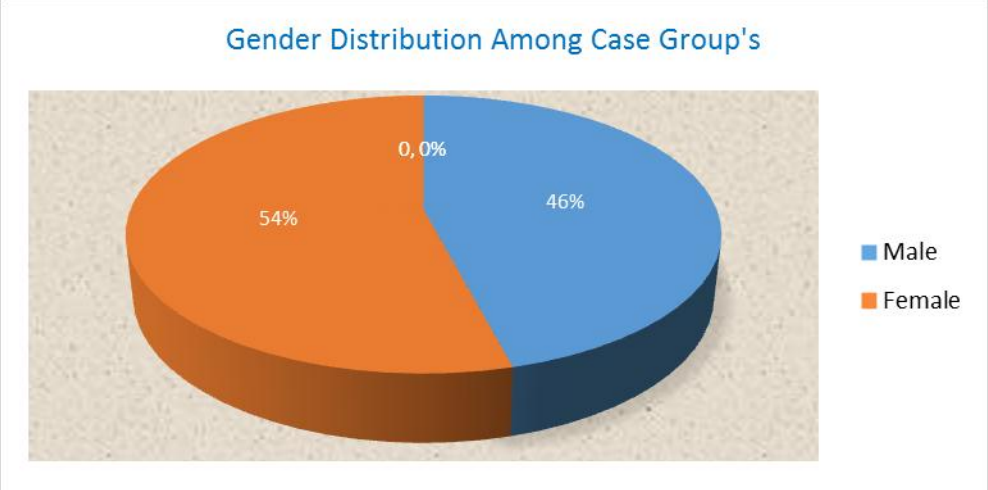

Figure 1: Gender Distribution among Case Group's.

Table 2: Types of neurodegenerative diseases of case group.

Disease Types	Frequency(n)	Percentage (%)
Alzheimer's disease	9	24.32
Parkinson's disease	8	21.62
Prion disease	8	21.62
Huntington's disease	7	18.91
Amyotrophic lateral sclerosis-ALS disease	5	13.51
Base	37	10.00

In table-2 shown: Among 37 neurodegenerative diseases patients, Alzheimer's disease were 9(24.32%), Parkinson's disease 8(22.62%), Prion disease 8(22.62%), Huntington's disease 7(18.91%) and Amyotrophic lateral sclerosis-ALS disease were 5(13.51%)

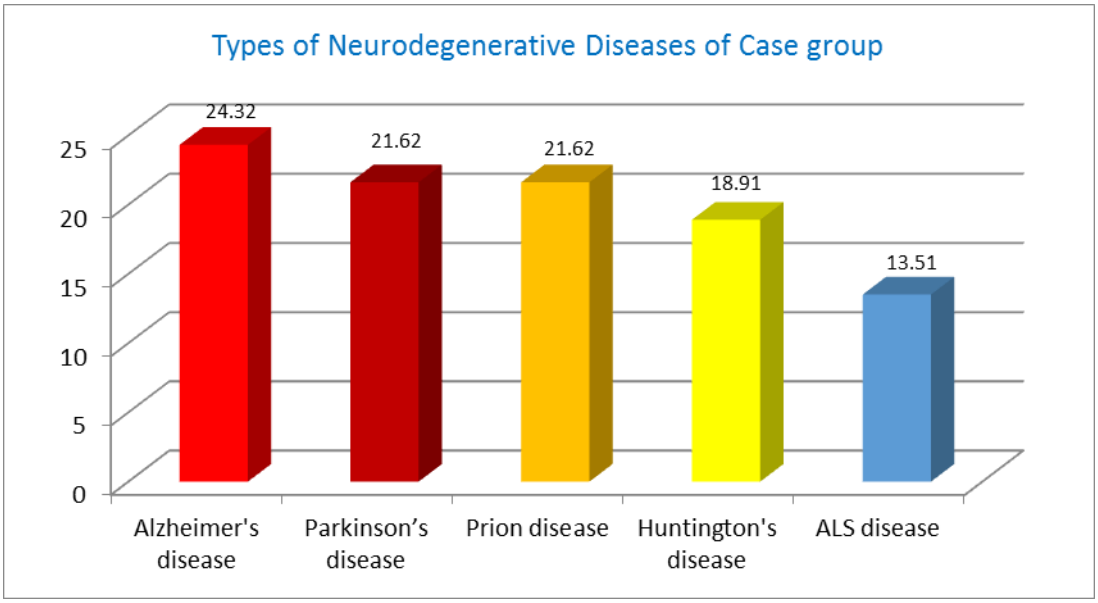

Figure-2: Types of Neurodegenerative Diseases of Case groups./

Table 3: Variables comparison between case & control groups (N=74).

Variables	Case(37)	Control(37)	p-Value
Age (Yrs.)	71.50 ± 6.25	71.50 ± 6.25	0.0005
BMI (kg/m2)	22.62 ± 3.75	24.80 ± 2.25	0.0034
Sufferings Years	2.95 ± 2.6	-	-
HY Stage	3.74± 1.3	-	-
UPDRS III	35.75 ± 25.20	2.12 ± 1.56	< 0.0001
LED (mg/day)	112.67 ± 197.35	-	-

In table-3 shown: Mean and standard deviation (±SD) of case & control group were 71.50 ± 6.25 and p-value was 0.0005, BMI (kg/m2) case were 22.62 ± 3.75 & 24.80 ± 2.25 and p-value 0.0034, UPDRS III case were 2.12 ± 1.56 control 2.12 ± 1.56 and < 0.0001.

Table 4: Serum UA level comparison between case & control groups (N=74)

Serum UA level	Case(37)	Control(37)	p-Value
Total participants	4.66 ± 1.15	5.42 ± 1.20	0.0069
Only Alzheimer's patients	4.58 ± 1.02	5.42 ± 1.20	0.0377

NB: Number of Alzheimer's patients is 9 in total

In table-4 shown: Comparison serum UA level between total patients and only Alzheimer's patients, for case group it were 4.66 ± 1.15 and for control group it were 4.58 ± 1.02 & 5.42 ± 1.20. And the p-values were 0.0069 & 0.0377

DISCUSSION

In this study, we found that serum UA levels were lower in male patients than in male control subjects, but this relationship wasn't observed in females. This difference between men and ladies could also be associated with the various influence of estrogen on UA metabolism in women[31] and gender differences within the renal handling of UA, no matter the influence of estradiol.[32] Serum UA levels are usually higher in men comparing the women. Similarly, previous studies have found reduced serum UA levels in male PD and MSA patients compared with male control subjects[13,14], but these studies didn't include PSP patients. Constantinescu et al. (2013)[14] classified parkinsonian patients into synucleinopathy and tauopathy groups and not only observed lower serum UA levels in patients with synucleinopathy than in those with tauopathy but also observed no difference in spinal fluid UA levels. Against this, in our study, the serum UA levels were significantly decreased within the tauopathy group (PSP) compared with the synucleinopathy group (PD and MSA). In accordance with our results, a recent study including 47 PSP patients and 225 PD patients showed that serum UA levels attended is lower in PSP than in PD.[15] Decreased glutathione has been observed within the nucleus niger and other brain regions of PD and PSP patients, which could end in abnormal UA utilization and should have a task within the decreased serum UA levels in these disorders. No significant correlation between UA levels and disease severity in PD patients were found in our study. In another study[33] observed positive but statistically insignificant correlations of serum UA levels

with HY stage and UPDRS part III in PD patients using regression models. In our study, a big correlation was found between the groups in UPDRS III scores whereas the p-value was but 0.0001. Supported a prospective population study, higher levels of serum UA were also related to a decreased risk of PD.[34] Low serum UA levels are related to an increased risk for developing PD, but it's unclear whether the UA levels are generally low among individuals who are susceptible to PD or whether the UA levels decrease during the long preclinical stages of PD.[11] Several studies suggest that variants or polymorphisms of the UA transporter gene may delay the event of PD. Dysfunctional variants of ATP-binding cassette transporter, sub-family G, member 2 (ABCG2) causing elevated serum UA levels are reported to be associated not only with the first onset of gout but also with a later onset of PD.[35] Neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and the spinocerebellar ataxias represent a serious threat to human health. These age-dependent disorders are getting increasingly prevalent, partially because the elderly population has increased in recent years.[36] These diseases are diverse in their pathophysiology–with some causing memory and cognitive impairments et al. affecting a person's ability to maneuver, speak and breathe.[37] Effective treatments are desperately needed but will only accompany a deep understanding of the causes and mechanisms of every disease. In our study, in analyzing the Serum UA level we found the mean (±SD) Serum UA level of case and control groups were 4.66 ± 1.15 and 5.42 ± 1.20 respectively where the p-value was 0.0069 which indicated a big correlation between both the groups. Besides this, in specific analyzing of Serum UA level of only Alzheimer's patients, we found it had been 4.58 ± 1.02. Although the number of Alzheimer's patients was 9, the p-value was 0.0377. So there was also significant. So Serum acid Level played a crucial role as a prognostic marker in several neurodegenerative diseases.

LIMITATIONS OF THE STUDY

This was a single centered study with a limited sample. So the findings of this study may not reflect the exact scenario of the whole country.

CONCLUSION AND RECOMMENDATIONS

Serum Uric Acid levels played an important role as a prognostic marker in several neurodegenerative diseases. The findings may be helpful in the diagnostic system of several neurodegenerative diseases. For getting more specific findings we would like to recommend conducting similar more studies with the larger sized samples in several places.

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