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Original Research Article.

Assessment of Low Serum Uric Acid Level in Patients with Amyotrophic Lateral Sclerosis Evidence for Oxidative Stress

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ABSTRACT

Background: The pathogenic mechanism of Amyotrophic Lateral Sclerosis (ALS) remains indistinct. However, increasing evidence has indicated that uric acid (UA) may play a protective role in the pathogenesis of ALS as well as in that of other neurodegenerative diseases. Low serum uric acid (UA) levels are found in many neurodegenerative diseases. It has been suggested that oxidative stress is one of the pathogenic mechanism for amyotrophic lateral sclerosis (ALS), and thus antioxidants such as UA that could reduce oxidative stress might be beneficial in the early detection of progression of the disease. The objective of this study was to prospectively investigate serum UA levels in ALS patients and to relate them to disease process and disease status.

Methods: ALS patients and healthy controls who were individually well-matched for age, sex, and body mass index (BMI) underwent blood testing for serum UA levels, and analyzed whether UA levels were correlated with the disease status of the patients, severity of the disease as defined by the ALS Functional Rating Scale-Revised (ALSFRS-R) and duration of illness.

Results: The study included 37 ALS patients and 37 matched controls. The serum UA level was lower in the ALS patients (4.29 mg/dl ±1.35 mg/dL, mean±SD) than in the controls (6.26 mg/dL±1.22 mg/dL; p<0.001). Female ALS patients had significantly lower (3.55 mg/dl± 0.89 mg/dL) than Male ALS patients (4.53 mg/dl±1.4 mg/dL; p<0.05). Among the ALS patients, the lower level of UA acid was strongly correlated with the rate of disease progression (decrease in ALSFRS-R score) p<0.001. Uric acid level is inversely correlated with the duration of the disease (r -0.32). Respondents with smoking history group showed more likely to develop ALS than the respondents with no smoking history.

Conclusion: ALS patients had lower serum UA levels than did healthy individuals and it is significantly lower in Female ALS patients than Male ALS patients. Uric acid levels in ALS were positively correlated with the ALSFRS-R (severity) and negatively associated with duration of illness. UA levels could be considered a biomarker of disease progression in the early phase in ALS patients.

Keywords: Amyotrophic Lateral Sclerosis, Serum Uric Acid, Oxidative Stress.

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INTRODUCTION

Motor neuron disease (MND) is a progressive degenerative disease of the motor neurons of motor cortex, brainstem, and spinal cord.[1] The prevalence of MND is 4-6 per 100,000 in most parts of the world, except the Western Pacific foci.[2] The annual incidence rate of the disease varies from 0.5 to 2.6 per100,000 populations.[3] The mean age of onset is 63 years and male to female ratio is about 1.3 to 1.5 for sporadic MND.[4]

People who develop ALS at young age are more likely to be male, less likely to have bulbar onset and more likely to have a slower disease course.[5] Incidence rates for ALS in Europe and North America range between 1.5 and 2.7 per 100,000/year, while prevalence rates range between 2.7 and 7.4 per 100,000.[6] In the US, rates of ALS are higher among whites compared with blacks, Hispanics, and other races.[7]

Incidence of ALS may be lower among African, Asian, and Hispanic ethnic groups than among Caucasians.[8] The incidence of ALS increases with each decade, especially after age 40 years, and it peaks at age 74, decreasing thereafter.[6] 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.[6] It is now considered as the 3rd most common neurodegenerative disorder after AD & PD.[9] In the United States, MND is often referred to as Lou Gehrig's disease. In Europe the term Motor neurone disease is preferred, though this term can be used to designate the class of disorders of which MND is only one entity.Motor neuron disease is subdivided into several subtypes on the basis of the grouping of symptoms and signs, which include: Progressive bulbar palsy (PBP), Progressive muscular atrophy (PMA), Primary lateral sclerosis (PLS), Flail arm syndrome (Vulpian-Bernhardt syndrome), Flail leg syndrome (Pseudopolyneuritic form) and ALS plus syndrome (e.g., ALS with, front temporal dementia, autonomic insufficiency, parkinsonism, supranuclear gaze paresis, and/or sensory loss). Lord Russell Brain proposed the term Motor neuron disease (MND) to incorporate these conditions into a single spectrum of disorders.[10] Amyotrophic lateral sclerosis (ALS) is the most common and severe form of adult-onset MND. The first detailed description was by Jean Martin Charcot in 1869. ALS is a relentlessly progressive, presently incurable disorder with an incidence of about 1/100000.[11] 50% patients die within 30 months 20% of patients survive between 5 years and 10 years10% of patients with ALS survive for more than 10 years of symptoms.[12] Factors associated with reduced survival are older age at symptom onset, early respiratory muscle dysfunction, bulbar-onset disease. Independent predictors of prolonged survival are younger age at presentation, limb-onset disease, longer diagnostic delay.[12.] Factors contributing to the pathogenesis of ALS: Genetics, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, protein aggregation, inflammatory dysfunction & contribution of non-neuronal cells, deficits of neurotrophic factors & dysfunction of signaling pathways and apoptosis.[10] Familial ALS accounts for only 5–10% of all ALS cases, remaining are sporadic. Mutations in the familial cases: Cu/Zn superoxide dismutase gene (SOD1) for about 20%, TARDBP (TDP-43) gene for about 2–5%. Two percent of sporadic case, SOD1 and TARDBP mutations also occur.[10] The risk factors for sporadic ALS that have been identified are increasing age, male sex and smoking.[13] Other agents include agricultural work, exposure to lead or mercury, athletic activity, milk ingestion, work in the textile or plastic industries, mechanical trauma, and exposure to welding or soldering.[14] Motor neuron damage as a result of oxidative stress is a key hypothesis in ALS. Oxidative damage increases with age, so fits in with the middle-life onset of the disease. Several studies have confirmed the presence of elevated oxidative metabolism in ALS.[15] Oxidative stress might also link with other proposed disease mechanisms such as excitotoxicity and axonal transport defects. Glutamate excitotoxicity is another mechanism implicated in ALS pathogenesis, acts by disruption of intracellular calcium homeostasis and free radical production.

Under normal physiological conditions, glutamate is released from the presynaptic nerve terminal and diffuses into the synaptic cleft. It acts on several glutamate receptors on the postsynaptic neuron. The action of glutamate in the cleft is terminated by its rapid reuptake via glutamate transporter proteins. EAAT1 and EAAT2 are expressed on glial cells; EAAT3 is mainly on presynaptic motor neurons. EAAT2 is responsible for most glutamate reuptake in the human brain. Under normal physiological conditions postsynaptic activation of glutamate receptors results in a small rise in intracellular calcium that can be buffered in the cell. When excess glutamate is present, there is a greater elevation in intracellular calcium postsynaptically. This triggers mitochondrial production of reactive oxygen species (ROS), which then inhibit glial EAAT2 function. This leads to further increases in glutamate concentrations in the synapse and further rises in postsynaptic calcium levels.[14] UA is produced from purines by the enzyme xanthine oxidase via the purine metabolism pathway.[16] 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.[17] Removal of superoxide helps to prevent its reaction with NO, blocking the formation of peroxynitrite.[18] 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.[19] 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.[20] 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.[21',22] Elevated serum levels of uric acid are associated with slower disease progression in PD &and AD.[23] Reduced level of serum UA has been found and correlated with more rapid disease progression in patients with PD and AD.[24,25] Low UA have been reported in individuals who developed PD many years later, implicating high levels of UA might have a neuroprotective role.[26] In case of MS and PD, UA levels are low from the beginning of illness and do not change much through the course of disease. But in case of ALS, UA levels are higher in the early stage and decrease through the course. The UA levels reach the lowest point in the terminal stage of ALS and it is lower than in MS and PD.[27] A study in Israel among 86 ALS patients and 86 controls found, there was a correlation between the relative decrease of serum uric acid levels among patients & the rate of disease progression (ALSFRS-R decline) but not definitely concluded as causal relationship.[28]A prospective study for 10 years in Taiwan found that UA gradually declined as the disease progressed and eventually below normal limit at the terminal stage of the disease. In male patient group, they also found serum UA level was inversely correlated with the course factors (illness duration/terminal time) (R2: 0.677), but not with the illness duration (R2: 0.166) but found no correlation among female patients.[27] To see prognostic role of UA in ALS, a large study included 136 ALS patients and same number of control and they found the level of UA was inversely correlated with the rate of

disease progression. Kaplan-Meier analysis revealed a better survival rate among top-tertile levels of UA than with bottom-tertile levels.[29] 'Uric acid levels predicts survival in men with ALS' A large study conducted among 251 ALS patients found correlation among male patients as slower disease progression was associated with higher serum UA level. There was a 39% reduction of risk of death during that study with each 1 mg/dl increase in serum UA levels.[30,31] UA level among ALS was significantly lower than controls and Female ALS patients had significantly lower UA level than the Male cases.[31] They concluded that low UA may be associated with occurrence of ALS among Chinese population but they found no association between low UA level with disease progression and survival of the patients.[32] **S**erum UA level is lower in bulbar onset ALS patient and longer disease duration cases but concluded no casual relationship rather lower UA level due to malnutrition induced by ALS.[32] One study in Japan found no difference in UA between ALS patients and healthy controls.[33] But a more recent study in Japan showed relative reduction of serum uric acid levels was inversely correlated with ALS-FRS decline rate.[34] These all studies support the hypothesis that oxidative stress is an important mechanism in ALS and that uric acid protects neurons from oxidative stress and inhibits disease activity. There is some uncertainty whether low serum uric levels are a cause or a consequence of these neurodegenerative diseases, but most study found its causal relationship. The administration of UA or other agents to increase serum UA level could be a potential therapeutic or modulator agent for ALS patients. More studies are required to clarify the meaning and possible therapeutic implications of uric acid changes in neurodegenerative diseases including ALS. So this study was done to see the association of serum UA level among ALS patients in Bangladesh.

METHODS AND MATERIALS

Study Design: It was a Case control study.

Study Population: All patients diagnosed as ALS at Neuromuscular disorder clinic, outpatient and inpatient department of Neurology, BSMMU, Dhaka will be taken as study population.

Sampling Method: Convenient non-probability type of technique was followed to collect sample.

Inclusion Criteria (for case) are The Revised El Escorial diagnostic criteria fulfilling definite, probable, probable lab-supported and possible cases of ALS with no Family history of ALS Exclusion Criteria (for case) and also for controls are history of neck or spinal trauma, individual who had an advanced, severe or unstable medical conditions (Acute MI, Acute Respiratory failure, Heart failure, advanced malignancy), history of alcohol abuse, MS, Dementia, PD and other neurodegenerative disorders, systemic conditions which interfere with UA (Gout, DM, Hypertension, Dyslipidemia, Metabolic Syndrome, CKD, CLD; Hypothyroidism, Hyperthyroidism), use of Drugs which can increase serum UA (ascorbic acid, cisplatin, diazoxide, diuretics, epinephrine, ethambutol, levodopa, methyldopa, phenothiazines, and theophylline) and also drugs which can decrease UA (high-dose aspirin, azathioprine, clofibrate, corticosteroids, estrogens, glucose infusion, guaifenesin, mannitol, probenecid, and warfarin).Inclusions criteria (for Control) are age and sex matched healthy volunteers willingly participate in the study.

Method of Data Collection: All subjects were selected according to the revised El Escorial criteria, and fulfilled the criteria for definite, probable, probable—laboratory-supported or possible ALS. None of the patients had family history of ALS. The ALS Functional Rating Scale-Revised (ALSFRS-R) was used to assess the patients' functional status. Non fasting serum uric acid was done by using photo-spectrometry technique by auto analyzer Backman Coulter Synchron CX9, and Clinical System ALX in department of Biochemistry, BSMMU, Shahbag, Dhaka, other necessary investigations were also done and prescribed data collection forms were filled up. Between All patients were included following the inclusion and exclusion criteria. A semi-structured questionnaire was developed in English. The questionnaire was developed using the selected variables according to the specific objectives. A check list section was also developed for data collection. Necessary modification was done before finalizing the questionnaire. Before proceeding to data collection, the detail of the study was explained to each patient and informed written consent from the respondents obtained. The researcher collected data through face-to-face interview with the patient. Physical examination was done properly. Medical records, demographic profiles, clinical and laboratory records of the patients were recorded in the data collection sheet. All the data were checked after collection

Data Analysis: Continuous variables (e.g., age, BMI, and serum uric acid level) were presented as mean ± SD values. Comparisons between ALS patients and control subjects regarding demographic and laboratory characteristics was performed using Student's *t*-test and chi-square tests. The correlations between serum uric acid levels and the variables were calculated using Pearson's correlation. Multiple regression analyses were used to examine the association between serum levels of uric acid and the other variables (age, sex, BMI, and ALSFRS-R score). The cutoff for statistical significance was set at $p<0.05$ for all of the data analyses. Statistical analyses carried out using SPSS (version 21; SPSS Inc., Chicago, IL, USA).

Ethical Considerations: Approval from the Institutional Review Board (IRB) of BSMMU was obtained prior to the commencement of this study. Informed written consent was obtained from the participants.

RESULTS

This Case-control study was carried out at neuromuscular disorder clinic, inpatient and outpatient department of Neurology, BSMMU, Dhaka. A total 37 adult patients and same number of age and sex matched control group were selected. They were interviewed by specific questionnaire to find out the Association of serum uric acid level with Amyotrophic lateral sclerosis. This chapter presents findings of those data. Data were presented through tables and figures. Table 1 showing the mean age of Patients is 41.95±16.42; among them male are 28 and female 9, mean BMI is 20.73±3.44. Most of the patient (76%) has spinal onset ALS. Mean ALS functional rating scale is 35.41 and duration of illness 9.38±13.22 months. Table 2 showing Smoking is associated with ALS. Table 3 showing Mean serum uric acid level is lower than the control group. Table 4 showing Mean serum uric acid is lower among female Patients. Table 5 showing serum uric acid level is inversely correlated with duration of illness and positively correlated with ALS functional rating scale.

Table 1: Comparison of baseline characteristics of patients and controls

Variable	Patient n=37	Control n=37	p
Age years (mean ±SD)	41.95±16.42	44.76±12.96	0.416^{ns}
Sex Male/ Female (Number)	28/9	26/11	
BMI, kg/m^2 (Mean±SD)	20.73±3.44	20.08±2.14	0.331^{ns}
Involved site at onset	Spinal 76%		
	Bulbar 24%		
ALS-FRS (Mean)	35.41		
Duration of Illness in months (Mean ±SD)	9.38±13.22		

Table 2: Association of Smoking with ALS

History of smoking	Presence of ALS		χ^2	P
	Cases (n=37)	Controls (n=37)		
	No. (%)	No. (%)		
Present	17(68)	8(32)	4.89	<0.05*
Absent	20(40.8)	29(59.2)		

Chi-square test; *The association is significant at the level of 0.05

Table 3: Comparison of uric acid between case and control (N=74)

Uric acid	ALS Case (n=37)	Control (n=37)	p-value
	Mean ±SD	Mean ±SD	
Mean ±SD	4.29±1.35	6.26±1.39	<0.001*

Data were expressed as Mean ±SD; p-value reached from Unpaired student t-test, * significant

Table 4: Association of Uric acid with sex of cases

Sex	Uric Acid level		P value
	Frequency	Mean (SD)	
Male	28	4.53 (1.4)	0.05
Female	9	3.55 (0.89)	

*The mean difference is significant at the level of 0.05

Table 5: Correlation of Serum uric acid with different variables (n=37)

Variables	Uric acid	
	Correlation coefficient (r)	P value
Age	-.041	0.809
ALS functional rating scale	+.396	0.015*
Duration of disease	-.324	0.050*
BMI	+.103	0.542

Table 6: Multi-variable regression with Uric Acid level

Variables	Uric Acid		P value
	B	Std. Error	
Presence of ALS	.713	.541	.192
ALS functional rating scale	.063	.032	.056
Weakness duration	-.026	.017	.126
Sex	.859	.364	.021
Smoking	-.058	.359	.872

Multi-variable regression with Uric Acid level showing when Presence of ALS, ALS-FR score, Weakness duration and Smoking variable were fixed or controlled, Sex had significant effect (At 5% significant level).

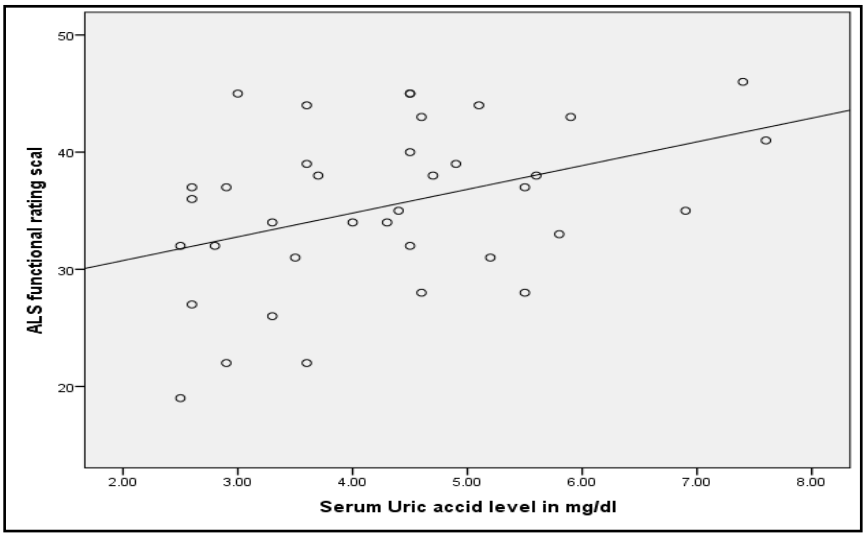

Fig 1: Scatter diagram showing the Positive correlation between ALS functional rating scale and serum Uric acid of the study subjects

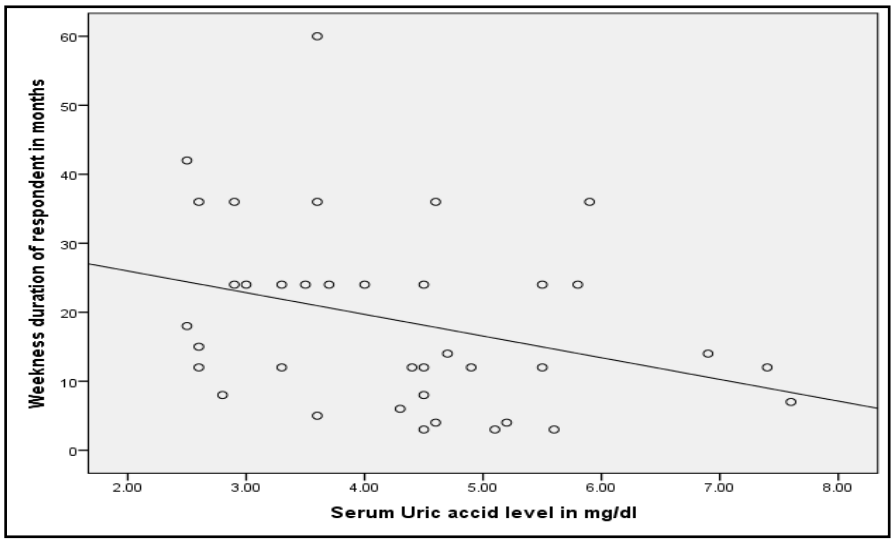

Fig 2: Scatter diagram showing the inverse correlation between duration of illness (in months) and serum uric acid of the study subjects

DISCUSSION

Motor neuron disease (MND) is a progressive degenerative disease of the motor neurons of motor cortex, brainstem, and spinal cord. The present Case-control study was targeted to find out the association of serum uric acid level with Amyotrophic lateral sclerosis. For the research, total 37 patients (ALS cases) were selected of all age group along with control group. They were interviewed by specific questionnaire to find out the association. The mean age of the cases was 41.95±16.42 years. The mean age of onset of ALS varies from 50 to 65 years.[35] Only 5% of the cases have an onset <30 years of age with the median age of onset was 64 years. In our study mean age of ALS was found low in comparison to other studies. Out of 37 cases 28(76%) were male and 9(24%) were female. The age-adjusted incidences of 1.27 per 100 000 person-years in males and 1.03 per 100 000 person-years in females were lower than recent rates in the northern US, Canadian, and northern European studies but higher than rates in southern European studies. Mean BMI of the respondents were 20.73 kg/m^2 with SD (3.44). The respondents were measured by the BMI (categorized in body build), where majority of them had was healthy level of BMI (Cases 22 and control 26). But it is observed that Underweight (BMI) is more likely in ALS cases (11). In this study the involvement of anatomical sites at onset was identified by interviewing the cases. Among the cases majority 28(76%) had the onset of ALS by spinal involvement and Bulbar onset 9(24%) were prominent. According to the study result about 24% of cases, muscles of the bulbar region are affected first. In approximately 25% of patients, weakness begins in bulbar-innervated muscles (bulbar-onset ALS).[36] Mean duration of illness presented to us was 9.38±13.22 months. Among them 20 cases (54.1%) were more than 12 months duration. Following the ALS functional rating scale score interpreted by Carmel Armonin Medscape wed page, ALS cases were categorized to mild (>40), moderate (39-30), severe (<30) and advanced (<20). One case was in advanced state and 6 were

in severe state, others (30) were in mild to moderate state of the disease among the ALS cases. Respondents with smoking history group showed more likely to develop ALS than the respondents with no smoking history. Among the respondents with smoking history group ALS cases was 68% and where as in respondents with no smoking history was 40.8%.The association between smoking and ALS status showed statistically significant [p = <0.05]. Smoking is possibly associated with ALS. A 2009 review concluded that smoking was an established risk factor for ALS. According to the research of Armon C Twenty-eight titles were identified, but only 7 articles met inclusion criteria. Of these, 1 provided class II evidence, and 1 class III evidence: both showed increased risk of ALS with smoking. The class II study showed a dose-response effect, and risk decreasing with number of years since quitting smoking.[13] In our study, variable analysis revealed that the mean of Uric Acid in ALS cases is lower 4.29 mg/dl with SD 1.35 than in control 6.26 mg/dl with SD 1.39. Where the P value is <0.001 which explains Uric acid level declines significantly in ALS. Various studies support these findings except few. Association analysis of ALS functional rating scale with Uric Acid level revealed that UA is significantly related with ALS functional rating scale (p value <0.001). That indicates decrease in Uric Acid level with the decline of ALS-FR scale (severity). On the other hand Uric acid declines with the duration of the disease onset (P value 0.05). Various studies showed consistently with the above result. Study variable analysis revealed that the mean of Uric Acid in female is significantly lower than Male ALS cases (p value is <0.001). Where mean of UA in female are 3.55. Similar report was found in another study.[30] For this; disease progression rate is higher among female ALS due to their lower serum UA level than male. In our study we have found no significant difference of mean of UA between bulbar and spinal onset ALS which is in contrast to the result of a study done in Italy.[33]When controlling other variables, no significant effect of Presence of ALS, ALS-FRS score, Weakness duration and Smoking were found on Uric Acid level. But, there was a significant effect of sex was found on Uric Acid. Compared to female, Uric acid in male is 0.85 times higher. Generally in bivariate analysis the association is seen between two variables without controlled or fixed confounding variables. Whereas, in multi variant regression, relation / effect is seen by controlling other variable (confound variables). According to regression result no adjusted effect of explanatory or independent variables was found except Sex. That means when Presence of ALS, ALS-FR score, Weakness duration and Smoking variable were fixed or controlled, Sex had significant effect (at 5% significant level).Like 'Sex' no similar type of effect was found for the other factors, though those variable showed adjusted association in bivariate analysis. But, ALSFR score showed significant effect at 10% significant level. It may be significant at 5% level for large sample size. The current study design does not allow us to conclude the causal relationship between low uric acid level and ALS. But decreased serum levels of UA in ALS patients compared to control might be the outcome of an oxidative stress-related process in the CNS, meaning that this decrease is resulting from the direct reaction between UA and oxidizing agents with the metabolism of UA.[37] If the low UA concentration is a secondary event, a pharmacological increase in the UA level might contribute to the diminishing of the oxidative stress, and thus slow down disease progression.

CONCLUSION

UA is one of the most important antioxidant of human body. Our result demonstrated that UA levels are lower in the serum of ALS patients compared to well-matched controls and female ALS patients had significantly lower UA than male ALS patients. UA was inversely correlated with their functional decline and negatively associated with duration of illness. Among the other factors, smoking history signified an association as the prior factor for ALS. Since most of the ALS cases reveal delayed symptoms; therefore, UA levels could be considered a biomarker of disease progression in the early phase in ALS patients. It also supports the hypothesis that oxidative stress is involved in the pathogenesis of ALS, and UA might reduce disease activity via antioxidant properties. This pathogenetic pathway could lead to new directions for future therapeutic interventions.

REFERENCES

1. Imam I, Ball S, Wright D, Hanemann CO, ZajicekJJJon. The epidemiology of motor neurone disease in two counties in the southwest of England. 2010; 257(6):977-81.
2. Leigh P, Whitwell H, Garofalo O, Buller J, Swash M, Martin J, et al. Ubiquitin-immunoreactive intraneuronal inclusions in amyotrophic lateral sclerosis: morphology, distribution, and specificity. 1991; 114(2):775-88.
3. Bracco L, Antuono P, Amaducci LJANS. Study of epidemiological and etiological factors of amyotrophic lateral sclerosis in the province of Florence, Italy. 1979; 60(2):112-24.
4. Ringel S, Murphy J, Alderson M, Bryan W, England J, Miller R, et al. The natural history of amyotrophic lateral sclerosis. 1993; 43(7):1316-.
5. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LHJTLN. Amyotrophic lateral sclerosis: moving towards a new classification system. 2016;15(11):1182-94.
6. Worms PMJJotns. The epidemiology of motor neuron diseases: a review of recent studies. 2001; 191(1-2):3-9.
7. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MGJN. Race/ ethnicity, socioeconomic status, and ALS mortality in the United States. 2016:10.1212/WNL. 0000000000003298
8. Cronin S, Hardiman O, Traynor BJJN. Ethnic variation in the incidence of ALS A systematic review. 2007;68(13):1002-7.
9. Talbot, K. (2002) 'Motor neurone disease', Postgrad Med J, 78 pp.513-519.
10. Wijesekera LC, Leigh PNJOjord. Amyotrophic lateral sclerosis. 2009; 4(1):3.
11. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, et al. A comprehensive review of amyotrophic lateral sclerosis. 2015; 6.
12. Turner MR, Kiernan MC, Leigh PN, Talbot KJTLN. Biomarkers in amyotrophic lat-eral sclerosis. 2009;8(1):94-109.
13. Armon CJJotns. Sports and trauma in amyotrophic lateral sclerosis revisited. 2007; 262(1-2):45-53.
14. Goodall EF, Morrison KEJErimm. Amyotrophic lateral sclerosis (motor neuron dis-ease): proposed mechanisms and pathways to treatment. 2006;8(11):1-22.
15. Simpson ERJTJosb, biology m. Sources of estrogen and their importance. 2003; 86(3-5):225-30.
16. Kushiyama A, Nakatsu Y, Matsunaga Y, Yamamotoya T, Mori K, Ueda K, et al. Role of uric acid metabolism-related inflammation in the pathogenesis of metabolic syndrome

components such as atherosclerosis and nonalcoholic steatohepatitis. 2016; 2016.
17. Ames BN, Cathcart R, Schwiers E, Hochstein PJPotNAoS. Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: a hypothesis. 1981; 78(11):6858-62.
18. Van der Veen RC, Hinton DR, Incardonna F, HofmanFMJJon. Extensive peroxynitrite activity during progressive stages of central nervous system inflammation. 1997; 77(1):1-7.
19. Pacher P, Beckman JS, LiaudetLJPr. Nitric oxide and peroxynitrite in health and disease. 2007; 87(1):315-424.
20. Davis J, Grandinetti A, Waslien C, Ross G, White L, MorensDJAjoe. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. 1996; 144(5):480-4.
21. Sato M, Wakayama T, Mamada H et al. Identification and functional characterization of uric acid transporter Urat1 (Slc22a12) in rats. 2011; 1808(6): 1441-7.
22. Schwarzschild MA, Schwid SR et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease.2008;65(6):716-23.
23. Abraham A, DroryVEJJon. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. 2014; 261(6):1133-8.
24. Annanmaki T, Muuronen A, Murros KJMD. Low plasma uric acid level in Parkinson's disease. 2007; 22(8):1133-7.
25. Kim TS, Pae CU, Yoon SJ, Jang WY, Lee NJ, Kim JJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. 2006;21(4):344-8.
26. Weisskopf M, O'reilly E, Chen H, Schwarzschild M, AscherioAJAjoe. Plasma urate and risk of Parkinson's disease. 2007; 166(5):561-7.
27. Lin Y-W, Lin T-S, Lai M-LJAJCMR. The correlation between uric acid levels and amyotrophic lateral sclerosis. 2011; 1(3):35-9.
28. Keizman D et al. Low uric acid levels in serum of patients with ALS: further evidence for oxidative stress? 2009; 285(1-2):95-9.
29. Oh S-i, Baek S, Park J-S, Piao L, Oh K-W, Kim SHJJocn. Prognostic role of serum levels of uric acid in amyotrophic lateral sclerosis. 2015; 11(4):376-82.
30. Paganoni S, Zhang M et al. Uric acid levels predict survival in men with amyotrophic lateral sclerosis. 2012; 259(9):1923-8.
31. Zheng Z, Guo X, Wei Q, Song W, Cao B, Huang R, et al. Serum uric acid level is associated with the prevalence but not with survival of amyotrophic lateral sclerosis in a Chinese population. 2014; 29(3):771-5.
32. Zoccolella S, Simone IL, Capozzo R, Tortelli R, Leo A, D'Errico E, et al. An exploratory study of serum urate levels in patients with amyotrophic lateral sclerosis. 2011; 258(2):238-43.
33. Sohmiya M, Tanaka M, Suzuki Y, Tanino Y, Okamoto K, Yamamoto YJJotns. An increase of oxidized coenzyme Q-10 occurs in the plasma of sporadic ALS patients. 2005; 228(1):49-53.
34. Ikeda K, Hirayama T, Takazawa T, Kawabe K, Iwasaki YJIm. Relationships between disease progression and serum levels of lipid, urate, creatinine and ferritin in Japanese patients with amyotrophic lateral sclerosis: a cross-sectional study. 2012; 51(12):1501-8.
35. Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. Journal of Neurology, Neurosurgery & Psychiatry. 2010; 81(4):385-90.
36. Daroff, R. B., Jankovic, J., Mazziotta, J. C. & Pomeroy, S. L. (2015) Bradley's neurology in clinical practice, 7th edition, Elsevier Health Sciences, pp.1508.
37. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. 2000; 376(2):333-7.

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