

A COMPARATIVE STUDY OF SERUM URIC ACID IN ALZHEIMER'S DISEASE PATIENTS WITH HEALTHY CONTROLS AT SMS HOSPITAL, JAIPUR

Dr Chaitanya Chattree¹, Dr Balveer Singh Gurjar^{2*}, Dr Ajay Saxena³, Dr SK Vardey⁴, Dr Vipul Garg⁵

1. Resident (Jr-3), 2. Assistant Professor, 3. Senior Demonstrator, 4. Senior Professor, 5. Senior Demonstrator, Biochemisrty, SMS Medical College, Jaipur

*Corresponding author – Dr Balveer Singh Gurjar

Email id – drbsdangas@gmail.com

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ABSTRACT

BACKGROUND: Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system, in which, there is brain atrophy and an accumulation of amyloid-plaques as well as neurofibrillary tangles throughout the cerebral cortex by the end of the disease. It has been suggested that oxidative stress might play an important role in the pathogenesis of AD. Uric acid is the end product of purine metabolism and it has been found that Uric acid has antioxidant properties. Evidences suggest that there might be a relation between uric acid and neurodegenerative diseases like AD. Therefore, this comparative study was done to find out an association between Serum uric acid levels in Alzheimer's disease patients and healthy controls. **Material & methods:** After taking necessary permissions, a comparative cross sectional study was conducted at Department of Biochemistry and Department of Psychiatry, SMS Hospital, Jaipur. Diagnosis of Alzheimer's disease was done by Psychiatrist on the basis of MMSE. Serum uric acid of 110 Alzheimer's disease patients and healthy controls was assessed spectrophotometrically in fully automated Beckmann Coulter AU680 .Uric acid levels thus obtained were compared using t test. **Results:** The mean uric acid levels in cases (3.96 ± 1.16) was less as compared to the controls (5.01 ± 0.725). The difference was statistically highly significant ($p < 0.001$). **Conclusion:** Uric acid may be used as a routine marker in diagnosis of Alzheimer's disease.

Keywords: Alzheimer's disease (AD), uric acid, MMSE.

INTRODUCTION

Alzheimer's disease (AD) is the most common and well-known form of dementia which affects the elderly population. It is the neurodegenerative dysfunction of the central nervous system, characterized by brain atrophy and accumulation of amyloid-plaques and neurofibrillary tangles throughout the cortex by the end of the disease.(1)

AD currently affects about 15 million people around the world and by 2040, it is expected to rise to 80 million.(2) About 10 percent of all people above 65 years and 50 percent above 85 years of age suffer

from AD.(3) The disease progresses at a slow pace,hence, the patient faces symptoms for many years.

The cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and progressing to language and visuospatial deficits.(4) Over time, patients become lost on walks or while driving.4 Finally, affected individuals may become incontinent, mute, and unable to walk.(5)

Pathologically, the disease involves a progressively increasing accumulation of amyloid plaques (β amyloid bodies) and neurofibrillary tangles (formed from hyperphosphorylation of tau protein) in the cerebral cortex.

It has been found that oxidative stress and impaired energy metabolism play an important role in the pathogenesis of Alzheimer's disease (AD).(6-14)

Oxidative stress on nervous tissue might seriously damage the brain via several mechanisms such as increase in intracellular free Ca^{2+} , release of excitatory amino acids, and direct neurotoxicity.(15,16)

Uric acid is the final product of purine nucleoside metabolism, synthesized by xanthine oxidase in humans.(17) Uric acid (UA) is also considered as a major natural antioxidant in plasma that reduces oxidative stress and protect against free radicals.(18)

Therefore, in this study, there was an effort to find out a relationship between the serum Uric acid levels in Alzheimer's disease patients and healthy controls.

Measuring serum UA is affordable, accurate, and also, it is minimally invasive, thus it might be useful as an appealing biological marker for the diagnosis of Alzheimer's disease (AD).

METHODOLOGY

After taking necessary permissions from the Institute ethics committee and the Department of Psychiatry, the study was conducted at the Central lab, Department of Biochemistry, S.M.S. Medical College and Geriatric OPD, Psychiatry hospital, SMS Medical College, Jaipur.

This study was a hospital based comparative cross sectional study and the sampling for study was done from the period of July 2019 to November 2019.

110 patients of Age > 50 years suffering from mild to moderate Alzheimer's disease on the basis of MMSE done by a qualified Psychiatrist in the

Department of Psychiatry were taken as case group. It was ensured that their attendants gave a written consent. 110 Age and sex matched healthy subjects who were willing to participate in the study and gave a written consent were taken as control groups. Patients with a history of Diabetes Mellitus, history of any renal disease, using any psychotropic drug, suffering from any other psychiatric illness, using drugs which modulate serum uric acid levels in body were excluded. For controls also, similar exclusion criteria was used.

For estimation of Serum Uric acid, 5ml venous blood sample was taken in a plain vial and after centrifugation, the serum was analyzed spectrophotometrically in fully automated Beckmann Coulter AU 680 machine. All the relevant Demographic, clinical and laboratory data was entered into Microsoft office excel sheet, and thereafter, the data was collected on primer software for Statistical analysis. The association between continuous and categorical variables was assessed by comparisons of means using student t-test and p value less than 0.05 was set as statistically significant.

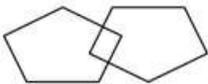
MMSE: The Mini Mental State Examination or MMSE is a set of questions of a total of 30 points which helps in determination of cognitive impairment and thus helps in diagnosing AD. The test involves a set of questions. For each question which is answered correctly, scoring is given. Maximum score of the test is 30. On the basis of the scores out of 30, interpretation is done as follows-

- Score of 25 and above-Normal cognition.
- Score of 20 to 25-Mild AD.
- Score 10 to 20-Moderate AD.
- Score 0 to 10-Severe AD.

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) <div style="text-align: center;">  </div>
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Proforma of MMSE. Source: www.medicine.uiowa.edu/igec/tools/cognitive/MMSE.pdf

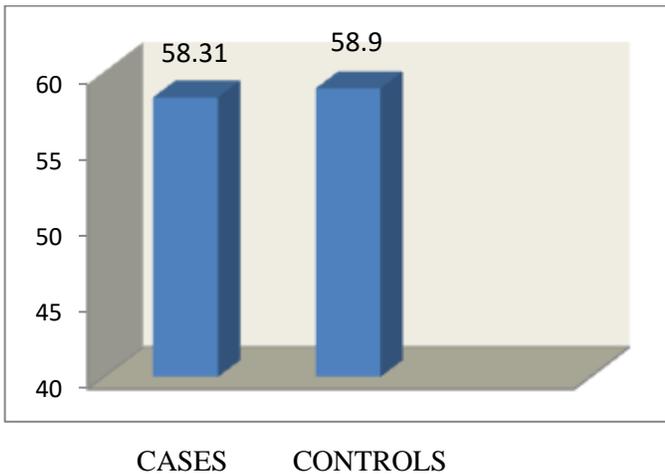
RESULTS

AGE:- Table 1 : Comparison of Age

	Groups	N	Mean	Std. Deviation	P value
Age (Years)	Cases	110	58.31	5.38	0.509(NS)
	Controls	110	58.90	6.19	

*Student t test

In the above table, it is shown that mean age group of cases (58.31± 5.38 years) was slightly less than the controls group (58.90±6.19 years), p value was non-significant (p=0.509) as the cases and controls were matched for age.



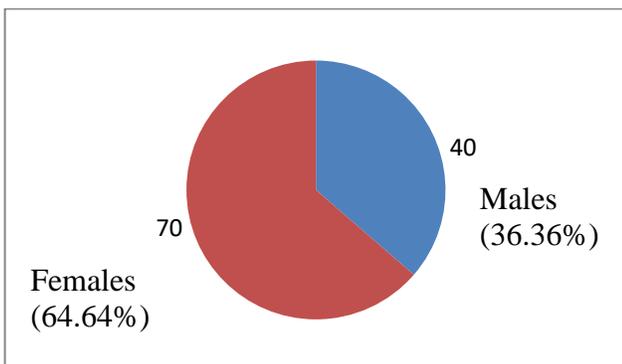
Graph 1: Comparison of mean age group of cases and controls

GENDER:-

Table 2: Gender Distribution

Gender	Cases		Controls	
	No.	%	No.	%
Male	40	36.36	40	36.36
Female	70	64.64	70	64.64
Total	110	100	110	100

Above table reveals that there is a female dominance of the disease. Female cases were 64.64% as compared to 36.36% of males. Controls were matched in this regard.



Graph 2: Gender Distribution among patients Suffering from Alzheimer’s Disease

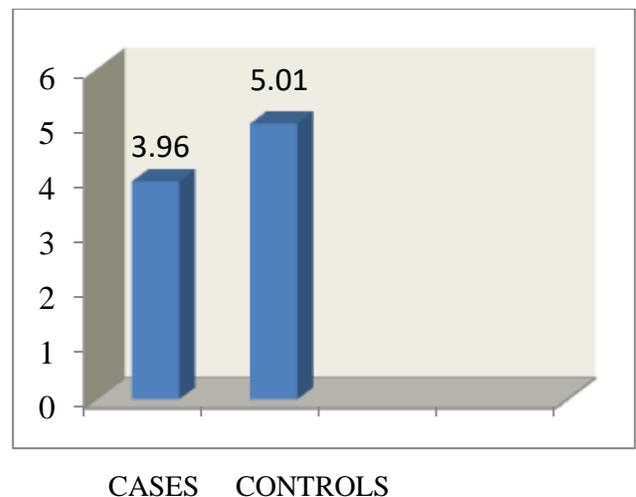
URIC ACID:-

Table 3: Comparison of Uric Acid

	Groups	N	Mean	Std. Deviation	P value
URIC ACID (mg/dl)	Cases	110	3.96	1.16	<0.001
	Controls	110	5.01	0.725	

*Student t test

As shown in the above table, the mean uric acid levels in cases (3.96±1.16 mg/dl) was found to be less as compared to the controls (5.01±0.725 mg/dl). The difference is statistically highly significant (p <0.001).



Graph 3: Comparison of mean uric acid levels of cases and controls.

DISCUSSION

Age and Gender:-

The mean age in this study in cases was 58.31±5.38 years and in the controls, the mean age group was 58.90±6.19 years. As control and cases were matched for age, so there was no correlation and the p value was non-significant (p=0.509). In the present study, the number of females suffering from Alzheimer’s disease were more as compared to males. There were 70 females (63.64%) and 40 males (36.36%) out of total 110 cases of Alzheimer’s disease. This shows female dominance in this study.

A possible explanation of this was given in a review study conducted by Melissa K Andrew¹⁹ and Mary C Tierney¹⁹ at Canada in which, they concluded that women live longer than men, there is a drop in the levels of estrogen which is neuroprotective in nature in post-menopausal women, and there is increased APOE4 gene allele in females and all these factors might increase chances of Alzheimer's disease in females.

Uric Acid:-

In this study, the mean serum uric acid in patients was 3.96 ± 1.16 mg/dl which was lower as compared to the control group (5.01 ± 0.725 mg/dl). This difference was statistically highly significant ($p < 0.001$).

Similar results were seen in some previous studies. In a study conducted by Rinaldi P et al⁽²⁰⁾ in the year 2003 at Italy, peripheral levels and activities of antioxidants like vitamin C, vitamin A, vitamin E and uric acid were found to be lower in MCI and AD patients as compared to controls.

Similarly, when a study was conducted by Tae-Suk Kim et al ⁽²¹⁾ in the year 2006 at South Korea, it was found that plasma antioxidants including uric acid were decreased in patients suffering from Alzheimer's disease as compared to healthy controls.

SM Euser et al ⁽²²⁾ finished a prospective cohort study in the year 2009 at Netherlands. Serum uric acid levels were divided in four quartiles and it was found that there was a significant trend in the four quartiles of serum uric acid for cognition and memory function, which indicated a better cognition for participants with higher levels of serum uric acid.

In year 2014-15, a study was conducted by Eman Al Khateeb et al ⁽²³⁾ at Jordan. It was found that Serum Uric acid levels were significantly lower in the AD patients than in the healthy controls.

Uric acid has been found to have a concentration dependent effect on reducing hydroxyl and superoxide radicals such that increasing the concentration of uric acid increases scavenging of these radicals.⁽²⁴⁾ Cerebral tissue is affected by oxidative damage because of its high oxygen consumption, low content of antioxidants, and high

content of polyunsaturated fatty acids of neuronal membranes.⁽²⁵⁾ Thus, higher levels of uric acid might be neuroprotective and might play a preventive role in Alzheimer's disease.

However, there are also a few contrasting studies. In a study conducted by JE Ahlskog et al ⁽²⁶⁾ in the year 1995 at USA, no significant changes were seen in the level of substances associated with oxidative stress such as Serum uric acid, alpha tocopherol, malondialdehyde and 5-S-cysteinyl dopa in the patients suffering from either Parkinson's disease or Alzheimer's disease. Another contrast study done by David J Schretlen et al ⁽²⁷⁾ in year 2007 at USA, concluded that even mild elevations in serum uric acid levels might increase the risk of decline in cognition in older people.

Our study is the first study of its kind in Northern India and the highly significant result of our study further support the hypothesis that uric acid, being antioxidant in nature might prevent the risk of developing Alzheimer's disease.

CONCLUSION

In our study, the mean uric acid level of AD patients was notably low as compared to healthy controls. Thus, it can be concluded that uric acid levels decrease in Alzheimer's disease and in near future, serum uric acid can be used as a routine marker for diagnosis of AD.

LIMITATIONS

There were a few limitations in this study:

- 1) Sample size was limited. Studies with larger sample would draw a better conclusion.
- 2) This study was a cross sectional study which is not an ideal study. A cohort study or a meta-analysis can be a better study to find a correlation.

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ABBREVIATIONS

- AD** : Alzheimer's disease
- UA** : Uric acid
- MCI** : Mild Cognitive Impairment
- MMSE** : Mini Mental State Examination
- APOE4 /Apo ε4** : Apolipoprotein E4

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