

The Association between Serum Uric Acid Level and Dementia in Geriatric Population – A Case–Control Study

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Abstract

Importance: The increasing prevalence of dementia worldwide has reduced the quality of life in geriatric patients, thereby increasing the burden on the caregivers. As dementia evolves gradually, diagnosis of the disease is often delayed. Thus, the need for a sensitive biomarker for early diagnosis is instrumental.

Objective: The objective of the study was to study the association between serum uric acid levels and dementia in geriatric patients.

Design: This is a case–control study comparing the age-matched geriatric patients with and without dementia (cases – 50 and controls – 50).

Setting and Participants: A total of 100 geriatric patients from Government Villupuram Medical College and Hospital were included in this study for a study period of 4 months. Out of this, 50 were cases (with dementia) and 50 were controls (without dementia). Mini-mental state examination test was done to categorize the cases into mild, moderate, and severe subgroups (24–30 out of 30 as normal; 20–23 out of 30 as mild; 10–19 out of 30 as moderate; and score lesser than 10 out of 30 as severe). Serum uric acid levels were measured in the study population and compared between the cases and controls.

Results: The correlation of serum uric acid levels with cases and controls revealed 16% of the cases had hypouricemia, whereas none in the control group had hypouricemia. When serum uric acid levels were compared, it was found that 44% of the control group had normal serum uric acid levels and 82% of the cases had normal serum uric acid levels. Based on mini-mental state examination score, 10% of mild group and 21% of moderate group had hypouricemia and 4% of moderate group had hyperuricemia while the others had normal serum uric acid levels. All the data were statistically significant with “*P*” < 0.001.

Conclusion: The study identified the prevalence of hypouricemia in the study population. This study can pave the path for further multicentric research to delineate the role of uric acid level as potential biomarker for dementia.

Relevance: The information gained from this study will enable us to diagnose dementia in the early stages and improve the quality of life of the patients.

Key words: Dementia, Serum Uric acid level, Hypouricemia

INTRODUCTION

The World Health Organization (WHO) states that there is an increase in the dependence of geriatric population.^[1]

“Demographic Burden,” as it is known, occurs due to the limited regenerative abilities, decreased immunity, and hiked susceptibility to non-communicable diseases and other comorbidities that this population faces. Dementia – a syndrome, in which there is deterioration in memory, thinking, behavior, and the ability to perform everyday activities, affects 50 million people across the world with an increase of 10 million cases/year.^[2] The WHO estimates 4.1 million geriatric population with dementia in India and predicts the count would double every 20 years.^[3,4] The vast majority of dementias is due to Alzheimer’s disease

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(50–70%) with vascular dementia (25%), Lewy body dementia (15%), frontotemporal dementia, and alcohol-related dementia (10%) being the less common types.^[1,5] The clinical spectrum ranges from mild memory deficit to major cognitive impairments imposing dependency for activities of daily living (ADL).^[6] Dementia can lead to disability, reduced quality of life and also become a burden for the care takers.

The pathophysiology of dementia revolves around increased lipid content in neuronal tissues which is susceptible to free radical damage through lipid peroxidation compounded by reduced capacity of antioxidants.^[1] Antioxidants such as uric acid, Vitamin A, Vitamin C, Vitamin E, and scavenging enzymes control the oxidative damage.^[1]

Uric acid, an end product of purine nucleotides, is an endogenous aqueous antioxidant which traps free radicals and converts them into allantoin for urinary excretion.^[7] Elevated lipid peroxidation and insufficient enzymatic and non-enzymatic antioxidants were shown in the peripheral tissues of patients with Alzheimer's disease.^[8,9] After adjustment for several cardiovascular risk factors, higher serum uric acid levels were associated with a decreased risk of dementia and thereby a possible protective role.^[10] Uric acid also exhibits pro-oxidant properties which compounds the final pathway of neuronal damage.^[11] The contradicting effects of uric acid on dementia and cognitive function continue to perplex researchers in the field.^[11] Our research study aimed to ascertain the association between serum uric acid and dementia in geriatric population. The objectives of the study were as follows:

1. To compare the serum uric acid level among elderly patients with or without dementia.
2. To determine whether serum uric acid levels correlate with severity of dementia based on mini-mental state examination (MMSE) score.

METHODOLOGY

This is a case–control study involving elderly South Indian population conducted in a public sector tertiary care hospital for a period of 1 year. Fifty cases and 50 age-matched controls were recruited using simple random sampling method. Eligible patients attending neurology outpatient clinic were screened for recruitment. The diagnosis of dementia was as per diagnostic and statistical manual of mental disorder (DSM-5), National Institute of Neurological and Communicative disorders and Stroke (NINCDS), and the Alzheimer's Disease and Related Disorders Association (ADRDA) recommendation. We employed the MMSE scoring system for patient enrolment. The inclusion and exclusion criteria are as per Table 1.

MMSE SCORING SYSTEM

The MMSE is a cognitive test which measures:

- Language abilities
- Visuospatial skills
- Attention and calculation
- Orientation to time and place
- Word recall

The MMSE is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function. The MMSE takes only 5–10 min to administer and is, therefore, practical to use repeatedly and routinely.

The National Institute for Health and Care Excellence (NICE) classifies

- 24–30 out of 30 are considered normal,
- 20–23 as mild cognitive impairment (MCI),
- 10–19 as moderate cognitive impairment, and
- <10 as severe cognitive impairment.

The enrolment process was based on self-interest of the participants and written informed consent was obtained from them or their legal guardian as the case may be. IEC approval was obtained. The recruited participants underwent the MMSE and their scores were recorded. Furthermore, 3 ml venous blood samples were collected, centrifuged and serum uric acid levels were analyzed by Beckman coulter fully auto-analyzer using uricase method. The collected data were analyzed statistically by SPSS version 25.

RESULTS

The sex distribution was 56% of males and 44% of females. The mean age of the cases was 69.68 ± 4.1 and that of controls 70.04 ± 4.3 . The mean serum uric acid level of cases was observed to be 4.02 ± 0.01 and that of control group was 6.32 ± 0.01 [Table 2]. The mean values

Table 1: Criteria for the selection of the cases and controls

Inclusion criteria	Exclusion criteria
Geriatric patients with dementia based on MMSE score	People affected with dementia even before they reach the age of 65
	Patients with secondary causes for dementia like head injury, brain tumor, vitamin deficiency, and thyroid disorders.
	Patients with hyperuricemia such as gout, psoriasis, malignancies, and renal disorders.
	Patients consuming alcohol and drugs.

MMSE: Mini-mental state examination

of serum uric acid levels were subjected to two-tailed “*t*” test and very significant with $P < 0.0001$. Normal serum uric acid level is 3.4–7.0 mg/dl for males and 2.4–5.7 mg/dl for females. The variables were subjected to univariate and multivariate analyses to ascertain the association with cases and controls. Data revealed that 16% of the cases had hypouricemia, whereas none of the controls had hypouricemia. About 44% of the control

group and 82% of the cases had normal serum uric acid levels which had statistical significance with $P < 0.001$. However, 2% of the cases had hyperuricemia when compared with 56% controls. The data showed statistical significance with $P < 0.001$ [Table 3].

In the cases based on MMSE score, 28% (14 cases), 66% (33 cases), and 6% (3 cases) of the patients belonged to the mild, moderate, and severe category, respectively [Table 4]. In this category, 7% ($n = 1$) mild and 21.2% (7 of 33 in moderate group had hypouricemia, whereas 2% of moderate group were hyperuricemic [Figure 2]. Correlation of MMSE score and serum uric acid level shows that 7% (1 out of 14) of mild group has hypouricemia and 85% (12 out of 14) has normal level of uric acid level. In the moderate group, 30% (10 out of 33)

Table 2: Mean serum uric acid level in cases and controls

	Cases	Control	“ <i>P</i> ” value
Mean serum uric acid level	4.02±0.01	6.32±0.01	<0.0001
Mean age of the study participants	69.68±4.1	70.04±4.3	

Table 3: Correlation of serum uric acid level with cases and controls

	Cases (%)	Control (%)	OR (95% CI)	“ <i>P</i> ” value
Below normal (hypouricemia)	16	0		
Normal range	82	44	0.36 (0.1619,0.8167)	<0.001
Above normal (hyperuricemia)	2	56	22 (4.094,458.8)	<0.001

Table 4: Cognitive function using mini-mental state examination score in cases and controls

Interpretation	Score	Cases	Controls	OR (95% CI)	<i>P</i> value
Normal	24–30	0 (0%)	50 (100%)	Reference	
Mild	20–23	14 (28%)	0 (0%)	4.2 (2.272, 8.617)	<0.001
Moderate	10–19	33 (66%)	0 (0%)	1.4 (0.9136, 2.24)	0.11
Severe	0–9	3 (6%)	0 (0%)	15.6 (5.467, 63.57)	<0.001

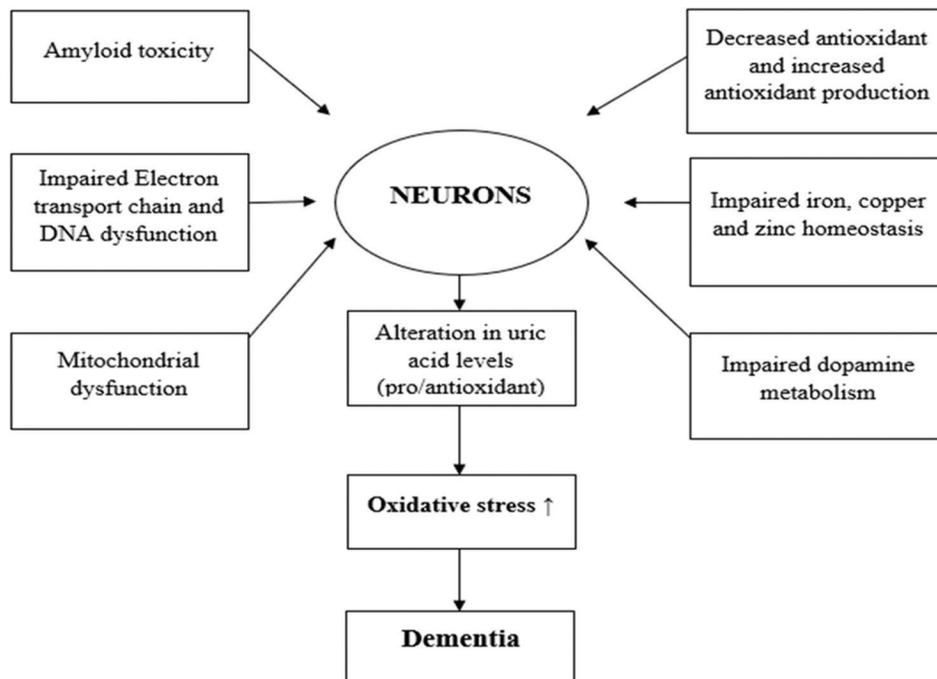


Figure 1: Pathophysiology of dementia

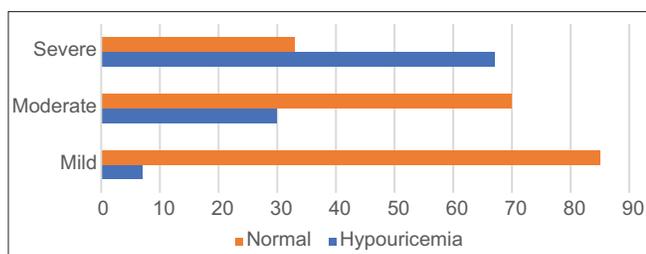


Figure 2: Correlation of mini-mental state examination score and serum uric acid levels

Table 5: Correlation between MMSE score and uric acid levels in cases

MMSE score	Hypouricemia	Normal	"P" value
Mild	1 (3.45) [1.74]	12 (9.55) [0.63]	<0.1
Moderate	10 (8.76) [0.18]	23 (24.24) [0.06]	<0.1
Severe	2 (0.80) [1.82]	1 (2.20) [0.66]	<0.1

MMSE: Mini-mental state examination

were hypouricemic and 70% has normal levels of serum uric acid levels. About 67% (2 out of 3) and 33% (1 out of 3) in the severe group had hypouricemia and normal uric acid levels, respectively. Correlation had statistical significance with " P " < 0.1 [Table 5].

DISCUSSION

The association between serum uric acid levels and dementia has been controversial for more than a decade. The MMSE is used to help diagnose dementia and rate its severity; however, it might not be an appropriate assessment tool if the patient has learning, linguistic/communication, or other disabilities.^[12] Therefore, the need for a diagnostic biomarker is most felt for this disorder.

Most of the hypotheses explain that uric acid is a natural antioxidant, which might reduce oxidative stress and protect against the detrimental effects of free radicals in the brain. Historically, low serum uric acid level has been often reported in neurodegenerative diseases. We found in our study 16% (8 out of 50) of cases had hypouricemia, 82% (41 out of 50) had normal uric acid levels, and 2% (1 out of 50) had hyperuricemia. Comparatively, none of the control group subjects had hypouricemia, which was statistically significant (P < 0.001). Based on MMSE scores, the cases were divided into three categories such as mild (22%), moderate (66%), and severe (12%).

The correlation between uric acid levels and various stages of MMSE score in dementia patients showed that 7% [1 out of 14 patients] of subjects had hypouricemia in mild category. The data showed significant P < 0.001 and 21% had hypouricemia

in moderate cases. At the same time, 4% hyperuricemia individuals were found in moderate group. However, most of the subjects had normal serum uric acid in both the groups.

A more recent meta-analysis by Tana *et al.*^[13] included 46 papers (n = 16,688 participants) dealing with the causes of dementia and 22 papers dealing with Alzheimer's dementia (AD) diagnosis. They found lower serum uric acid levels in patients with a diagnosis of dementia with a stronger association between serum uric acid (SUA) and Alzheimer's dementia, as compared to Parkinson's dementia (PD) patients. These data could suggest a neuroprotective role of UA on cognitive function, showing its best influence on patients with the AD rather than other dementia types. However, there is no correlation that was found between the MMSE test score and SUA levels except for the subset of patients with Parkinson's disease.

The mechanisms of uric acid in neurodegenerative diseases of cognitive function are still controversial. One plausible model for neuronal damage is depicted in [Figure 1]. Uric acid is an antioxidant and also pro-oxidant, a double-edged weapon. Cervellati *et al.*^[14] study says that oxidative stress seems to play a key role in the pathogenesis of the most of causes of dementia, in particular AD and PD. A meta-analysis by Schrag *et al.* found a significant reduction of total antioxidant capacity and sUA levels in AD patients than controls.^[15] Only about 10% of persons affected with dementia are correctly diagnosed. Hence, it is of critical importance to carry out early identification and control methods in the diagnosis of dementia.

Zarry *et al.* analyzed the relationship between Alzheimer's dementia and serum uric acid based on disease progression. It was revealed that low plasma urate was associated with faster cognitive decline (P = 0.008).

Shen *et al.*^[16] found that patients with Parkinson's dementia had lower serum levels of uric acid than healthy controls and this association was more significant in men than in women. Gregory *et al.*^[17] did a French population-based cohort study that included 1598 adults >65 years of age, wherein low serum uric acid correlated with dementia. Chen *et al.*^[16] in a meta-analysis of case-control studies (n =2708 participants), found no significant difference between patients with AD and healthy controls in SUA level. Our study population had low serum uric acid levels among cases which was associated with severity of cognitive impairment.

CONCLUSION

The diagnosis of dementia is a clinical exercise. This study shows low serum uric acid levels more common in

dementia patients when compared with controls groups. SUA level could be a potential cost-effective agent to enable early diagnosis of dementia in geriatric population and plan timely intervention.

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Limitations

- Since it was a time bound study, the formula-based sample size could not be achieved.
- MMSE is a screening test even though it has high reliability and validity. MMSEs have subjective variability which may be very high in older age of the study population. This may be due to the potential survival bias.

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