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Physiology

ASSESSMENT OF COGNITIVE FUNCTIONS OF NON DIABETIC CHRONIC KIDNEY DISEASE PATIENTS (STAGE 5D) AND ITS CORRELATION WITH SERUM URIC ACID LEVELS

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ABSTRACT

Background: In recent years, Chronic Kidney Disease (CKD) is becoming more prevalent in developing countries like India because of poor control of diabetes and hypertension. Cognitive deterioration progresses as disease increase in its severity. Many studies proved diabetes as an importatnt risk factor for cognitive deterioration. This study focuses mainly over the role of uremic toxins, mainly uric acid in cognitive deterioration in non diabetic CKD patients.

Methods: After getting informed consent, cognitive function of 30 non diabetic CKD and age and sex matched controls was assessed by NIMHANS Neuropsychology battery 2004 and comparison between these 2 groups by student t tests. Later using Pearson's correlation, relationship between each and every cognitive domain & serum uric acid level were analysed.

Results: Cognitive function scores of non diabetic CKD patients was less than their age and sex matched controls. These results were statistically significant with P value less than 0.001. As serum uric acid level goes high, cognitive function test scores reduces as well as they take more time to perform the test and commit more errors. So Time based scores & error based scores were more & Hit based scores were less in non diabetic CKD patients compared to their controls.

Conclusion: In this study it is found out that uremic toxins causes cognitive deterioration in non diabetic CKD patients. Early identification and correcting these factors may improve the cognitive function, which in turn enhances quality of living and life expectancy of CKD patient

KEYWORDS : Cognitive deterioration, Non diabetic Chronic Kidney Disease (CKD), Uremic toxins, Uric acid.

INTRODUCTION

Nearly 80 % of CKD patients were affected with cognitive decline and this advances as the disease progresses in its severity[1]. The affected individuals find difficult to carry out their daily activities and also do not turn up for regular check ups which ultimately reduces their quality of life as well as life span. Its prevalence in older generations living in South India was estimated to be around 11.5 % [2]. Most common etiology of CKD is diabetes, which in recent studies found to be an independent risk factor for cognitive dysfunction as it affects the endothelial function of cerebral vasculature resulting in cognitive deterioration[1,3,4,5]. This study aims to know whether uremic toxins play any role in cognitive decline in nondiabetic CKD patients.

MATERIALS AND METHODS

A case control study was conducted in the department of Physiology, in association with department of Nephrology and Biochemistry in Coimbatore Medical College and Hospital, Coimbatore. After getting written consent 30 non diabetic CKD patients of both gender with age group between 18 and 60 years, with eGFR less than 15 ml /min /1.73 m2, for more than 3 months of duration were selected for this study. Age, gender, BMI and education matched normal individuals were used as controls. Cognition was assessed by **NIMHANS Neuropsychology Battery 2004** for both groups.

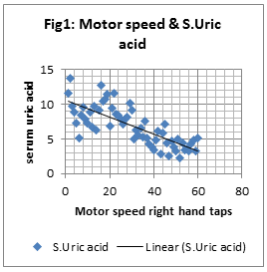
Domains	Sub – Categories	Tests
Speed	Motor Speed	Finger Tapping Test
	Mental Speed	Digital Symbol Substitution Test
Attention	Focussed Attention	Color Trails Test 1 and 2
	Sustained Attention	Digital Vigilance Test
	Divided Attention	Triads Test
Executive Functions	Phonemic Fluency	Controlled Oral Word Association Test
	Category Fluency	Animal Name Test
	Visual Fluency	Design Fluency Test
	Verbal Working Memory	Verbal N Back Tests – 1 and 2 version
	Visual Working memory	Visual N Back - 1 and 2 versions
	Internally guided Verbal and Visual Memory	Self Ordered Pointing Tests
	Planning	Tower Of London Test
	Response Inhibition	Stroop Test
Comprehension	Verbal comprehension	Token Test
Learning and memory	Verbal	Rey's Auditory Verbal Learning Test
	Logical	Passage - Recall Test
	Visuo Spatial	Complex Figure Test
	Visual Learning and Memory	Complex Figure - Recall
		Design Learning Test

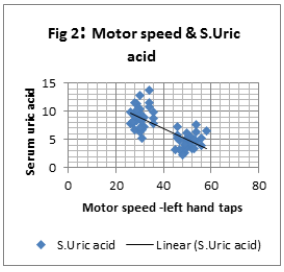
Table 1: Comparison of Cognitive tests between 2 Groups (Student's t Test)

Cognitive test	Non diabetic CKD	Control	T Value	P value
Motor speed Right hand taps	32.67 ± 3.021	53.23 ± 3.501	24.352	.000
Motor speed Left hand taps	30.43 ± 2.812	50.43 ± 3.266	25.417	.000
Mental Speed (Time)	498.97 ± 88.839	172.77 ± 27.575	19.207	.000
Color Trail 1 (Time)	142.67 ± 15.493	44.80 ± 12.455	26.966	.000
Color Trail 2 (Time)	346.97 ± 46.464	95.90 ± 18.391	27.519	.000
Digital Vigilance (Time)	924.03 ± 92.040	354.27 ± 44.265	30.555	.000
Digital Vigilance Error	3.63 ± 1.629	0.13 ± 0.346	11.511	.000
Divided attention Error	9.53 ± 1.042	0.47 ± 0.681	39.864	.000
Verbal fluency	3.37 ± 0.999	11.10 ± 2.155	17.824	.000
Category fluency	7.70 ± 1.022	15.90 ± 2.171	18.717	.000
Design – Free	4.10 ± 1.125	16.40 ± 4.223	15.415	.000
Design - Fixed	1.73 ± 0.868	11.57 ± 2.269	22.185	.000
Verbal 1 back Hit	6.93 ± 0.828	9.00 ± 0.000	13.693	.000
Verbal 1 back Error	3.67 ± 1.213	0.00 ± 0.000	16.571	.000
Verbal 2 back Hit	4.27 ± 0.907	8.67 ± 0.661	21.473	.000
Verbal 2 back Error	7.03 ± 2.042	0.47 ± 0.860	16.216	.000
Visual 1 back Hit	7.07 ± 0.944	8.9 ± 0.355	9.938	.000

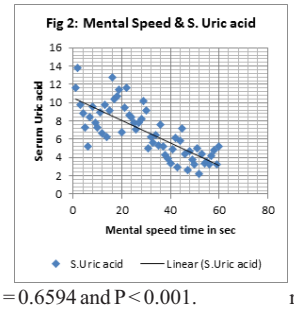
Visual 1 back Error	3.00 ± 1.232	0.13 ± 0.434	12.034	.000
Visual 2 back Hit	4.33 ± 1.093	8.63 ± 0.718	18.009	.000
Visual 2 back Error	5.23 ± 1.251	0.47 ± 0.937	16.680	.000
SOPT – Word Error	3.80 ± 0.761	0.37 ± 0.615	19.200	.000
SOPT – Picture Error	3.97 ± 0.890	0.17 ± 0.379	21.516	.000
Tower Of London - Minimum Moves	5.13 ± 0.776	11.50 ± 1.075	26.315	.000
Response Inhibition	265.80 ± 35.161	83.90 ± 18.773	24.995	.000
Token Test	27.43 ± 2.012	35.67 ± 0.711	21.149	.000
AVLT - LTPR	65.10 ± 8.323	93.57 ± 6.735	14.564	.000
Passage - Immediate Recall	6.33 ± 1.348	19.07 ± 2.273	26.405	.000
Passage – Delyed Recall	4.97 ± 1.629	18.00 ± 2.792	22.078	.000
Visuo Spatial Memory	28.95 ± 31.11	31.50 ± 3.869	0.4455	0.657
Figure - Immediate Recall	10.93 ± 2.753	31.93 ± 4.258	22.684	.000
Figure – Delayed Recall	7.23 ± 2.542	28.37 ± 3.819	25.239	.000
Design - Delayed Recall	8.30 ± 1.950	44.03 ± 7.757	24.467	.000

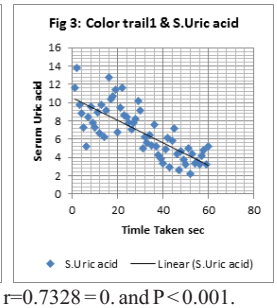
CORRELATION OF COGNITIVE FUNCTIONS WITH SERUM URIC ACID:





r = - 0.729 and P < 0.001 r = - 0.737 and P < 0.001





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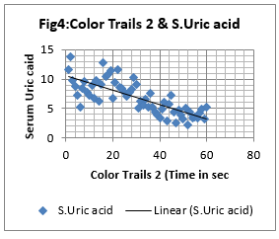
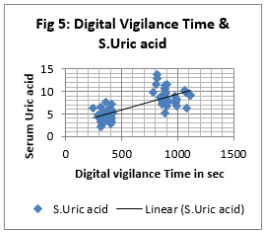
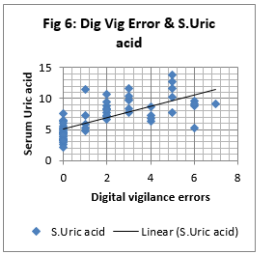
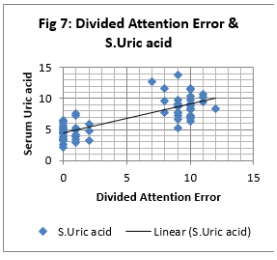


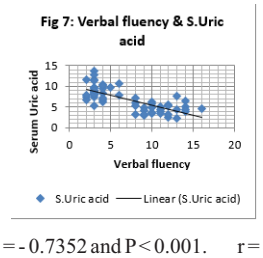


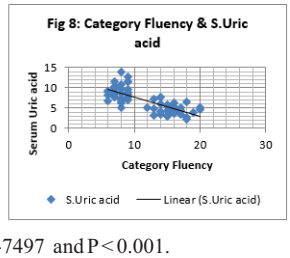
r = 0.7228 and P < 0.001. r = 0.7465 and P < 0.001.



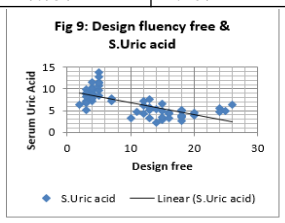


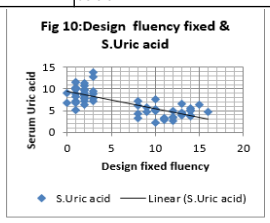
r = 0.7024 and P < 0.001. R = 0.7797 and P < 0.001.



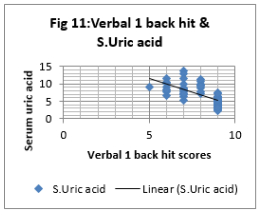


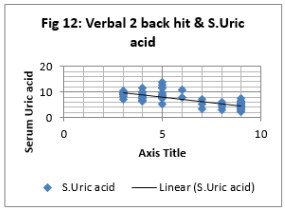
r = - 0.7352 and P < 0.001. r = -7497 and P < 0.001.



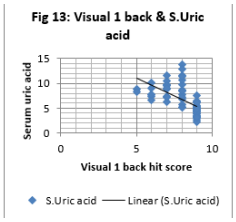


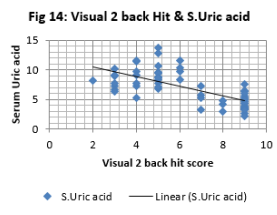
r = - 0.6957 and P < 0.001. r = - 0. 7531 and P < 0.001



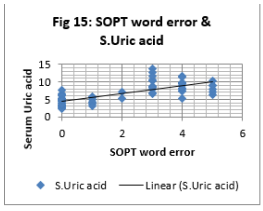


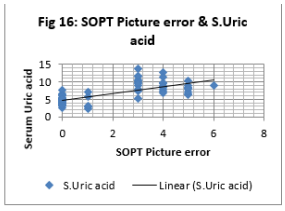
r = - 0. 6877 and P < 0.001. r = -0.7444 and P < 0.001



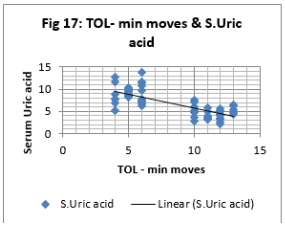


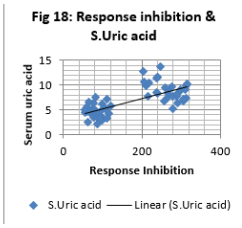
r = -0.5886 & p<0.001 r = -0.6931 & P<0.001



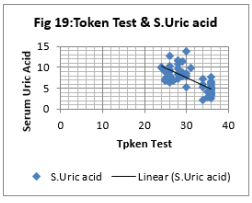


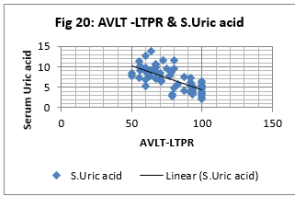
r = 0.7268 and P < 0.001. r = 0.7033 and P < 0.001



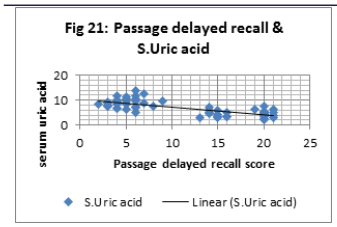


r = - 0.7677 and P < 0.001. r = 0.7044 and P < 0.001.

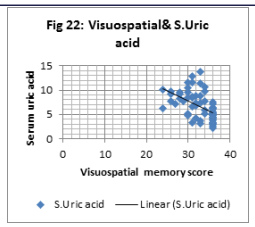




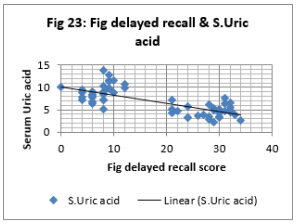
r = - 0.752 and P < 0.001. r = 0.6991 and P < 0.001.



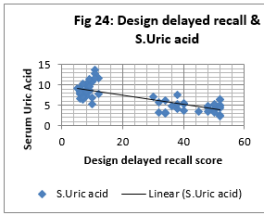
r = - 0.7455 and P < 0.001.



r = - 0.5162 and P < 0.001.



r= - 0.7422 and P < 0.001.



r = - 0.7701 and P < 0.001.

DISCUSSION:

In this study it was found out there was statistically significant decline of cognitive functions in CKD patients compared to their controls in almost all cognitive domains including Motor Speed, Mental Speed, Attention (Focused, Sustained and Divided Attention), Executive Functions (Phonemic Fluency, Category Fluency, Visual Fluency, Verbal and Visual Working memory, Planning, Response Inhibition, Verbal comprehension, Learning and Memory (Verbal, Logical, Visuo Spatial, Visual). Also a statistically significant correlation exists between uric acid and cognitive scores. As uric acid level increases the patients took more time to complete the task, number of errors increased and number of correct responses decreased. So in hyperuricemia, time based and error based scores were high and correct response based scores were low.

When serum Uric acid > 7 mg / dl in men and > 5.7 mg / dl in women it is referred as hyperuricemia[6]. Despite being an anti oxidant, uric acid is capable to transform into a pro oxidant even when it is mildly elevated or in high normal range. Intracellularly, uric acid reacts with peroxy nitrite leading to the formation of more free radicals like triuretcarbonyl and amino carbonyl which oxidisstion of lipids. Uric acid also suppresses nitric oxide synthase enzyme, which ultimately damages the endothelium through oxidative stress[7]. Endothelial damage in cerebral and coronary vaculature might be the possible mechanism through which hyperuricemia affects cognition and cardio vascular health of general population as well as diabetic and hypertensive patients[7,8,9].

Etgen T, Chonchol M, Förstl H, Sander D similarly confirmed an independent relationship between renal disease and decline in cognition and proposed the traditional endothelial risk factors like oxidative stress and hyper homocystinemia as pathological mechanism behind it [10]. Schretlen DJ, et al study confirmed even mildly elevated serum uric acid affects verbal and working memory of 96 healthy elderly adults and found mild hyperuricemia[7].

Yu MA, Sanchez – Lozada LG, Johnson RJ, Kang DH study stated that hyperuricemia damages endothelium via free radical generation and enhancement of mRNA expression of angiotensinogen and angiotensin converting enzyme[11].

Khosla UM, et al found out reduced levels of serum nitrites and nitrates were seen in hyperuricemia induced rats and also studied that allopurinol was able to reverse it. Hence they concluded hyperuricemia causes endothelial dysfunction by suppressing nitric oxide synthase enzyme[12].

CONCLUSION: In this study it is found out that hyperuricemia leads to cognitive deterioration in non diabetic CKD (stage 5D) patients. Early identification and controlling hyperuricemia may improve the cognitive function, which inturn enhances the life span and quality of living of CKD patients.

FUTURE SCOPE OF THE STUDY: Pharmacological trials can be done by providing medicines to control hyperuricemia in CKD patients (Stage5D) and repeating the cognitive function tests to analyse any improvement is present.

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