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Original Research Article

PREVALENCE OF COGNITIVE FUNCTION IMPAIRMENT IN CKD PATIENTS IN INDIA & TO STUDY EFFECT ON COGNITIVE FUNCTION AFTER HEMODIALYSIS INITIATION IN CKD STAGE V PATIENTS

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ABSTRACT
BACKGROUND & METHOD: The aim of this study is to study prevalence of cognitive function impairment in ckd patients in india & to study effect on cognitive function after hemodialysis initiation in ckd stage v patients.
65 patients from department of Nephrology Pushpawati Singhania Research Institute, New Delhi , who were CKD Stage III – V (eGFR < 60 ml/min/1.73m^2), & were not on Hemodialysis and those End Stage Renal Disease patients in whom hemodialysis was initiated.
RESULT: Result of both the group was statically significant, showing improvement in cognitive dysfunction after hemodialysis initiation. P vaue by both HMMSE and HMOCA score was less than 0.05.
CONCLUSION: Our study also emphasizes on the fact that with the increasing CKD population there are more chances of cognitive dysfunction. Early evaluation of cognitive impairment in these patients is important because it affects the quality of life and adding life to years is adding years to life.
KEYWORDS: prevalence, cognitive, ckd patients & hemodialysis,

STUDY DESIGNED: Cross sectional Prospective Observational Cohort.

1. INTRODUCTION

A major determinant of quality of life in CKD patients is the level of cognitive function. Various studies had demonstrated higher prevalence of cognitive impairment in CKD patients. The mechanisms involved in this process have not been completely elucidated, but research indicates that, in addition to neuronal damage induced by uremic toxins, the risk of cognitive involvement and dementia in these patients may be due to the high prevalence of symptomatic and asymptomatic brain ischemia. Neuropsychological performance tends to improve after the introduction of dialysis, and patients on dialysis have lesser cognitive deficits than untreated individuals and patients with uremia. The present study was to evaluate prevalence of cognitive dysfunction in CKD stage 3-5 patients and changes seen after hemodialysis intiation in advanced disease.

2. MATERIAL AND METHODS

Study Population - 65 patients from department of Nephrology Pushpawati Singhania Research Institute, New Delhi , who were CKD Stage III – V (eGFR < 60 ml/min/1.73m^2), &

were not on Hemodialysis and those End Stage Renal Disease patients in whom hemodialysis was initiated.

Study Design-Cross sectional Prospective Observational Cohort
Study **Sample size**
On the basis of previous studies[1,2], prevalence of cognitive function impairment in advance chronic kidney disease patients (GFR less than 60ml/min/1.73 m^2) was 13% to 25%. Taking this value as reference, the minimum required sample size with 10% margin of error and 5% level of significance is 57patients.So total sample size of minimum 57 was planned. Formula used is:-

$N \geq ((p(1-p))/(ME/z\alpha)^2$

Where Zαis value of Z at two sided alpha error of 5%, ME is margin of error and p is prevalence rate.

Statistical analysis
Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Statistical tests were applied as follows-

1. Quantitative variables were compared using paired t test/Wilcoxon signed rank test (when the data sets were not normally distributed) between pre and post MMSE and MOCA score.

2. Qualitative variables were correlated using Chi-Square test/Fisher's Exact test.

3. Univariate and multivariate logistic regression was performed to find out significant factors affecting cognitive impairment (MOCA and MMSE).

A p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Inclusion Criteria

1. Patients of Chronic Kidney Disease having eGFR less than 60 ml/min/m^2 who are not on hemodialyisis and out of these, End Stage Renal disease patients in whom hemodialysis would be initiated .
2. Patients having age between 19-80 years
3. Patients having minimal primary level education (8th).

Exclusion Criteria

1. Patients not knowing Hindi language
2. Patients with
    a. Psychiatric disorders / drug dependence
    b. Neurological disorders (CVA, Parkinson's disease, Alzheimer's, Epilepsy e.t.c).
    c. Pregnant and lactating patients
    d. Blind patients
    e. Patients below 18 years and above 80 years

f. Renal transplant patients
g. Patients with acute kidney disease
h. Thyroid disorder
i. Vitamin B12 deficiency
j. Chronic liver disease/chronic alcohol intake.
k. Obstructive sleep apnoea
l. Hepatitis B,C or HIV positive
m. H/o vasculitis /joint pain/rash/oral ulcer/ANA positive.

Evaluation of cognitive function by:-

1. The Hindi Mini-Mental Status Examination.- 30-point questionnaire, On the basis of Orientation to time & Place, Registration, Attention and calculation, Recall, Language ,Repetition ,Complex commands.
2. Hindi Montreal Cognitive Assessment (MOCA)
   - ➢ It is a 30-point test, on the basis of short-term memory recall, Visuospatial abilities, Executive functions ,Attention, concentration ,working ,Language, repetition and Orientation to time and place is evaluated.
   - ➢ Time of administration for test was between 10-15 minutes
   - ➢ Score ≤25 was taken as cutoff point for a diagnosis of cognitive impairment.

3. RESULTS

Table 1: Sociodemographic, clinical, and laboratory characteristics of the study participants

Variable	CKD Patients
Mean Age ± SD	55.8 ± 14.04
Sex Male Female	66.15% 33.85%
Occupation Buiseness Farmer Housewife Job Lawyer Retired Student	 7.69% 7.69% 33.85% 29.23% 1.54% 16.92% 3.08%
Level of education $_8$th 10th 10+2th Graduate Post Graduate	 10.77% 12.31% 16.92% 49..23% 10.77%
DM Present	 64.62%

Absent	35.38%
HTN Present Absent	 84.62% 15.38%
Primary kidney disease CGN CIN DN Others	 15.39% 27.69% 53.85% 3.07%
CKD prevalence according to stage Stage 3 Stage 4 Stage 5	 16.92% 18.46% 64.62%

TABLE 2: MMSE INTERPRETATION UNIVARIATE LOGISTIC REGRESSION (HMMSE)

	BASE COEFFICIENT	STANDARD ERROR	P VALUE	ODDS RATIO	95% confidence interval for Odds ratio	
					Lower	upper
AGE	.056	.022	**.011**	1.058	1.013	1.104
S. CREATININE	.039	.051	.446	1.039	.941	1.147
e GFR (ML/MIN/1.73 M2)	-.060	.026	**.022**	.942	.895	.991
Hb	-.482	.159	**.002**	.617	.452	.844
SERUM IRON	-.029	.011	**.007**	.972	.951	.992
TRANSFERRIN SATURATION	-.103	.032	**.001**	.902	.847	.961
FOLIC ACID	.022	.044	.613	1.023	.938	1.115
VIT B12	.000	.000	.477	1.000	.999	1.000

BLD UREA	.019	.005	**.0001**	1.019	1.009	1.030
U. ACID	.006	.101	.954	1.006	.826	1.225
S.CALCIUM	-.015	.246	.952	.985	.609	1.595
S.SODIUM	-.016	.062	.798	.984	.872	1.111
S.POTTASIUM	-.165	.349	.637	.848	.428	1.680
S.PHOSPHORUS	.063	.105	.550	1.065	.867	1.308
Mg	-.719	.511	.160	.487	.179	1.327
PTH	.000	.001	.790	1.000	.999	1.002
S.BILRUBIN	.655	1.268	.605	1.926	.160	23.126
vit D	.001	.012	.931	1.001	.978	1.025
TSH	0.673	0.244	**.006**	1.960	1.216	3.160
S.ALBUMIN	-3.709	.916	**.0001**	.024	.004	.147
SEX						
Female				1.00		
Male	-.706	.532	.185	.494	.174	1.401
OCCUPATION						
BUISENESS				1.00		
FARMER	1.792	1.443	.214	6.000	.354	101.568
HOUSEWIFE	.588	1.008	.560	1.800	.249	12.988
JOB	-.624	1.051	.553	.536	.068	4.204
LAWYER	-	-	-	-	-	-
RETIRED	-.154	1.107	.889	.857	.098	7.510
STUDENT	-	-	-	-	-	-
EDUCATIONAL STATUS						

1) 8th				1.00		
2) 10th	-1.281	1.304	.326	.278	.022	3.577
3) 10+2th	-1.974	1.238	.111	.139	.012	1.573
4) GRADUATE	-2.890	1.155	**.012**	.056	.006	.534
5) POST GRADUATE	-1.504	1.323	.256	.222	.017	2.970
DM	-.251	.528	.635	.778	.277	2.190
HTN	.811	.702	.248	2.250	.569	8.902
H/O SMOKING	.306	.591	.605	1.358	.427	4.324
PRIMARY DIS OF CKD						
DN				1.00		
Non DN	-.489	.508	.335	.613	.227	1.659
CKD STAGE						
3				1.00		
4	.405	1.027	.693	1.500	.200	11.236
5	1.695	.841	.044	5.447	1.048	28.315

In univariate logistic regression by HMMSE various factors like **age (p value 0.011), eGFR (p value 0.022), hemoglobin (p value 0.002), serum iron levels (p value 0.007), transferrin saturation (p value 0.001), blood urea levels (p value 0.0001), TSH levels (p value**

0.006),serum albumin levels (p value 0.0001) and educational status (p value 0.012) were showing significant correlation with cognitive impairment in CKD patients. Out of these factors age, blood urea levels and TSH levels were showing positive correlation with odd's ratio of more than 1 i.e with the increasing age, blood urea levels and TSH levels there is more likelihood of having cognitive impairment while eGFR values, heamoglobin levels, serum iron levels, transferrin saturation levels, serum albumin levels and educational qualification were showing negative correlation with odd's ratio of less than 1 i.e with the increasing eGFR values,

hemoglobin levels, serum iron levels, transferrin saturation levels, serum albumin levels and educational qualification there is less likelihood of having cognitive impairment.

TABLE 3: MMSE INTERPRETATION MULTIVARIATE LOGISTIC REGRESSION (HMMSE)

	BASE COEFFICIENT	STANDARD ERROR	P VALUE	ODDS RATIO	95% confidence interval for Odds ratio	
					Lower	upper
AGE	.106	.049	**.013**	1.112	1.020	1.332
e GFR (ML/MIN/1.73 M2)	.059	.093	.544	1.061	.747	1.518
Hb	-.021	.268	.937	0.979	.473	1.782
SERUM IRON	.067	.040	.193	1.070	.950	1.305
TRANSFERRIN SATURATION	-.202	.098	.068	0.817	.500	1.012
BLD UREA	.014	.010	.242	1.014	0.985	1.056
TSH	.191	.439	.660	1.211	0.431	4.119

S.ALBUMIN	-2.273	1.377	.092	0.103	.000	1.439
EDUCATIONAL STATUS						
1) 8th				1.00		
2) 10th	0.714	2.324	.815	2.042	.009	1071517.504
3) 10+2th	0.807	2.264	.778	2.241	.012	19052214.319
4) GRADUATE	-0.710	1.967	.788	0.492	.001	877.156
5) POST GRADUATE	2.014	2.572	.521	7.497	.006	221325.383
CKD STAGE						
3				1.00		
4	1.366	2.388	.553	3.921	.014	925760.360
5	2.951	3.358	.423	19.126	0.000	68671116.542

After adjusting for confounding factors, **age is the only significant factor which is affecting the cognitive impairment individually** while all other factors like eGFR, hemoglobin, serum iron levels, transferrin saturation, blood urea levels, TSH levels serum albumin levels and educational status affects the cognitive function in presence of other factors along with them and cannot effect cognitive function individually.

TABLE 4: HMOCA INTERPRETATION UNIVARIATE LOGISTIC REGRESSION

	BASE COEFFICIENT	STANDARD ERROR	P VALUE	ODDS RATIO	95% confidence interval for Odds ratio	
					Lower	upper
AGE	.033	.019	.088	1.033	.995	1.073
S. CREATININE	.070	.060	.241	1.072	.954	1.205
e GFR (ML/MIN/1.73 M2)	-.041	.020	**.043**	.959	.922	.999

HEMOGLOBIN	-.495	.151	**.001**	.610	.453	.820
SERUM IRON	-.022	.008	**.005**	.978	.964	.993
TRANSFERRIN SATURATION	-.046	.015	**.003**	.955	.927	.984
FOLIC ACID	.034	.046	.463	1.034	.945	1.132
VIT B12	.000	.000	.437	1.000	.999	1.000
BLD UREA	.019	.005	**.0001**	1.019	1.009	1.030

U. ACID	.033	.106	.753	1.034	.841	1.271
S.CALCIUM	-.133	.259	.609	.876	.527	1.456
S.SODIUM	-.005	.065	.933	.995	.876	1.129
S.POTTASIUM	-.160	.369	.665	.852	.414	1.757
S.PHOSPHORUS	.129	.122	.290	1.138	.896	1.445
Mg	-1.074	.531	**.043**	.342	.121	.966
PTH	.001	.001	.166	1.001	.999	1.003
S.BILRUBIN	-1.514	1.308	.247	.220	.017	2.854
vit D	-.013	.013	.287	.987	.963	1.011
TSH	.397	.244	.104	1.487	.921	2.402
S.ALBUMIN	-2.912	.839	**.001**	.054	.011	.281
SEX						
Female				1.00		
Male	-.799	.597	.181	.450	.140	1.449
OCCUPATION						
BUISENESS				1.00		
FARMER	.981	1.443	.497	2.667	.158	45.141
HOUSEWIFE	.818	1.045	.434	2.267	.292	17.577
JOB	-.087	1.024	.932	.917	.123	6.825
LAWYER	-	-	-	-	-	-
RETIRED	-.223	1.095	.839	.800	.093	6.848
STUDENT	-.405	1.683	.810	.667	.025	18.059
EDUCATIONAL STATUS						
1) 8th				1.00		

2) 10th	-	-	-	-	-	-
3) 10+2th	-	-	-	-	-	-
4) GRADUATE	-	-	-	-	-	-
5) POST GRADUATE	-	-	-	-	-	-
DM	-.065	.547	.906	.938	.321	2.737
HTN	.827	.839	.324	2.286	.442	11.830
H/O SMOKING	-	-	-	-	-	-
PRIMARY DIS OF CKD	-.668	.645	.300	.513	.145	1.815
DN				1.00		

Non DN	.043	.526	.936	1.043	.372	2.926
CKD STAGE	-	-	-	-	-	-
3	-	-	-	-	-	-
4						
5				1.00		
	.395	.843	.639	1.485	.285	7.743
	.199	.600	.741	1.220	.376	3.957
	-	-	-	-	-	-
	-	-	-	-	-	-
				1.00		
	.182	.837	.827	1.200	.233	6.185
	1.345	.706	.057	3.840	.963	15.310

In univariate logistic regression by HMOCA various factors like **eGFR (p value 0.043), hemoglobin (p value 0.001), serum iron levels (p value 0.005), transferrin saturation (p value 0.003), blood urea levels (p value 0.0001), TSH levels (p value 0.043) and serum albumin levels (p value 0.0001)** were showing significant correlation with cognitive impairment in CKD patients. Out of these factors blood urea levels was the only factor showing positive correlation with odd's ratio of more than 1 i.e with the increasing blood urea levels there is more likelihood of having cognitive impairment while eGFR values, heamoglobin levels, serum iron levels, transferrin saturation levels, serum albumin levels and magnesium levels were showing negative correlation with odd's ratio of less than 1 i.e with the increasing eGFR values, heamoglobin levels, serum iron levels, transferrin saturation levels, serum albumin levels and magnesium levels there is less likelihood of having cognitive impairment.

TABLE 5: HMOCA INTERPRETATION MULTIVARIATE LOGISTIC REGRESSION

	BASE COEFFICIENT	STANDARD ERROR	P VALUE	ODDS RATIO	95% confidence interval for Odds ratio	
					Lower	upper
e GFR (ML/MIN/1.73 M2)	.003	.039	.938	1.003	.929	1.083
Hb	-.314	.224	.162	.731	.471	1.134
SERUM IRON	-.003	.016	.861	.997	.967	1.028
TRANSFERRIN SATURATION	-.045	.035	.189	.956	.893	1.023
BLD UREA	.008	.009	.396	1.008	.990	1.026
Mg	-2.133	.857	.013	.118	.022	.636
S.ALBUMIN	-2.459	1.083	.023	.086	.010	.714

In multivariate logistic regression by HMOCA after adjusting for confounding factors, none of the factors were found to be independently affecting the cognitive impairment in CKD patients.

TABLE 6: COGNITIVE DYSFUNCTION CHANGES AFTER HEAMODIALYSIS INTIATION

	Sample size	Mean ± Stdev	Median	Min-Max	Inter quartile Range	P value
HINDI MMSE SCORE	30	19.4 ± 6.7	20	7-28	15-26	0.0001
HINDI MMSE SCORE POST HD	30	21.67 ± 5.01	22	11-28	18-26	
HINDI MOCA SCORE	30	18.97 ± 6.89	20.5	5-27	14-25	<.0001
HINDI MOCA SCORE	30	21.33 ± 5.11	22	11-28	17-26	

POST H D						

Result of both the group was statically significant, showing improvement in cognitive dysfunction after hemodialysis initiation. P vaue by both HMMSE and HMOCA score was less than 0.05.

4. DISCUSSION

The present study was a cross sectional prospective observational study in which 65 patients were taken, 11 patients were of CKD stage III, 12 patients were of CKD stage IV and 42 patients were of CKD stage V. In our study the mean age of the patients was 55.8 years with Male to Female ratio of 1.95:1. CKD stage V was most common of all stages on presentation with Diabetic nephropathy as most common etiological cause of CKD. Incidence of hypertension was 84.62% and diabetes mellitus type 2 was 64.62%.

Similar demographic details of age, sex, CKD stage, hypertension and diabetes were demonstrated in other studies[3,] done to evaluate cognitive dysfunction in CKD patients.
We found that prevalence of cognitive impairment in CKD patients in Indian population was more common in comparison to an earlier study by Kurella et al.[4] in 2004 who reported 23–28% prevalence (n = 80) . Analysis of Cognitive dysfunction in our study by Hindi mini mental score examination (HMMSE) was present in 28 (43.08%) patients. Out of these, 28 (43.08%) patients with HMMSE there was mild dysfunction in 13(20%), moderate in 11 (16.92%) and severe in 4 (6.15%). When assessed with Hindi Montreal cognition assessment (HMOCA) cognitive impairment was present in 43(66.15%) which can be attributed to the fact that MOCA is more sensitive in detecting mild cognitive impairment in comparison MMSE.

Despite of male to female ratio of 1.95:1, the incidence of cognitive impairment was more in females with 54.55% impairment by HMMSE and 77.27% by HMOCA , which can be possibly due to less social support, less educational qualification and more stress over them.

Cognitive impairment was more prevalent with comorbid condition eg: diabetes and hypertension. Diabetes mellitus type 2 is a risk factor for atherosclerosis and small vessel disease these factors along with chronic inflammatory state clearly increases the risk of multi-infarct dementia and cognitive dysfunction. Hypertension may promote alterations in brain structure and function through a process of cerebral vessel remodeling, which can lead to disruptions in cerebral auto regulation, reductions in cerebral perfusion, and limit the brain's ability to clear potentially harmful proteins such as β-amyloid [5,6,7]

However in our study, with HMOCA analysis, diabetic (66.67%) and non diabetic (65.22%) were having same prevalence. Better control of sugar and blood pressure with exclusion of patient having infection and neurological disorder could be factor for this result. We also noticed that cognitive dysfunction was present in 40% of the hypertensive against 60% in non hypertensive patient's and this can be due to less number of patient's (n=10) in non hypertensive group(15%).

CKD stage progression with lowering of eGFR was related to increased cognitive dysfunction in present study also as in other previous studies[8], with HMMSE showing that

18.18% of CKD stage III were having cognitive impairment while it increased to 25% in stage IV and 54.76% in stage V. Analysis by HMOCA showed cognitive dysfunction was prevalent in 45.45% of CKD

stage III, 50% in CKD stage IV and 76.19% in CKD stage V patients. All the cases of those having severe impairment were having CKD stage V.
In regression analysis by HMMSE various factors like age, eGFR, hemoglobin, serum iron levels, transferrin saturation, blood urea levels, TSH levels, serum albumin and educational status were showing significant correlation with cognitive impairment in CKD patients.

Regression analysis by HMOCA showed all above factors except age and educational qualification were showing significant correlation with cognitive impairment in CKD patients. Out of these factors age, blood urea levels and TSH levels were showing positive correlation with odd's ratio of more than 1 i.e with the increasing age, increasing blood urea levels and higher TSH levels there is more likelihood of having cognitive impairment while eGFR values, hemoglobin levels, serum iron levels, transferrin saturation levels, serum albumin levels and educational qualification were showing negative correlation with odd's ratio of less than 1 i.e with the increasing eGFR values, low hemoglobin levels, low serum iron levels, low transferrin saturation levels, low serum albumin levels and less educational qualification there is less likelihood of having cognitive impairment.

Serum albumin plays a vital role in the binding of drugs, hormones, iron and free fatty acids, and reduced levels may contribute to cognitive impairment resulting from toxicity . Study by Llewellyn DJ[9] also stated that low levels of serum albumin are associated with increased odds of cognitive impairment mimicking the results of our study.

In present study hemodialysis was initiated in 30 patients, Cognitive status improves following initiation of dialysis in comparison with the untreated advanced CKD patients and this can be explained by the theory that dialysis leads to decrease in levels of toxins like uremia, metabolic acidosis.

5. CONCLUSION

This study is an important step in advancing understanding of the important role that kidney function may play in cognitive aging. In light of the rapidly growing population of individuals with CKD and ESRD, further prospective studies are needed to determine the natural history and consequences of cognitive decline in individuals with CKD, as well as the optimal methods for detection, prevention, and therapy.

Our study also emphasizes on the fact that with the increasing CKD population there are more chances of cognitive dysfunction. Early evaluation of cognitive impairment in these patients is important because it affects the quality of life and adding life to years is adding years to life.

6. REFRENCES

1. Kurella M., MapesDL.,Port FK., Chertow GM., Correelates and outcomes of dementia among dialysis patients : the dialysis outcomes and practice patterns study. Nephrol Dial Transplant 2006 Sep 21(9) 2543-8,Epub 2006 Jun 4.

2. Thorleif Etgen .Kidney disease as a determinant of cognitive decline and dementia.Alzheimer's Research & Therapy20157:29 https://doi.org/10.1186/s13195-015-0115-4
3. Thorleif Etgen, Dirk Sander, Michel Chonchol, Claus Briesenick, Holger Poppert, Hans Förstl, Horst Bickel, Chronic kidney disease is associated with incident cognitive impairment in the elderly: the INVADE study, Nephrology Dialysis Transplantation, Volume 24, Issue 10, October 2009, Pages 3144.
4. Kurella M., Chertow G. M., Luan J., Yaffe K. Cognitive impairment in chronic kidney disease. Journal of the American Geriatrics Society. 2004;52(11):1863–1869. doi:10.1111/j.1532-5415.2004.52508.x.
5. Harhay, Meera N.Appel, Lawrence J. et al. Cognitive Impairment in Non–Dialysis-Dependent CKD and the Transition to Dialysis: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. American Journal of Kidney Diseases, Volume 72, Issue 4, 499 – 508.
6. Susan M. Hailpern, Michal L. Melamed, Hillel W. Cohen, Thomas H. Hostetter. Moderate Chronic Kidney Disease and Cognitive Function in Adults 20 to 59 Years of Age: Third National Health and Nutrition Examination Survey (NHANES III). JASN Jul 2007, 18 (7) 2205-2213; DOI**:** 10.1681/ASN.2006101165.
7. Walker, K. A., Power, M. C., & Gottesman, R. F. (2017). Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. Current hypertension reports, 19(3), 24. doi:10.1007/s11906-017-0724-3.
8. Ulf G. Bronas, HouryPuzantian, and Mary Hannan. Cognitive impairment in chronic kidney disease: Vascular milieu and potential therapeutic role of exercise.Biomed Res Int. 2017; 2017: 2726369.
9. Llewellyn DJ, Langa KM, Friedland RP, Lang IA. Serum albumin concentration and cognitive impairment. Curr Alzheimer Res. 2010;7(1):91–96.