Original Article

Cognitive status in chronic kidney disease elderly patients.

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ABSTRACT

Background: Chronic Kidney disease (CKD) in elderly patients leads to dementia and cognitive impairment which leads to functional dependence and recurrent hospitalization.

Objective: To assess different cognitive domains in CKD elderly patients.

Methods: A prospective observational study conducted in Ain-Shams University hospital outpatient clinics. A total of 100 CKD patients, elderly aged 60 years and older with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 and not on renal replacement therapy were enrolled in the study. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery was utilized to assess cognitive functions domains (executive functions, language functions, verbal learning, visuospatial functions, delayed recall, memory consolidation, and recognition memory) for 100 CKD patients visited Ain Shams University hospital outpatient clinics who scored > 24 in the Mini-mental state examination (MMSE.)

Results: CKD patients had low mean MMSE and mean verbal fluency while language functions score had not been affected. There was a significant positive correlation ($p< 0.001$) between the mean eGFR and the CERAD total score.

Conclusion: CERAD total score was positively correlated to eGFR in CKD patients confirming the association between cognition and renal impairment. Age and educational level significantly affect cognitive performance.

Keywords: cognitive functions; chronic kidney disease; CERAD; eGFR; Mini-mental state examination.

INTRODUCTION

Chronic kidney disease (CKD) is a disease affecting the central nervous system [1]. Elderly CKD patients have cognitive impairment, dementia [2] and depression [3] which reduce quality of life [4].

Cognition decline can be manifested from mild cognitive impairment (MCI), up to clinically relevant dementia, interfering with daily life and independence [1].

Cognitive impairment that occurs with MCI exceeds the normal ageing decline [5]. MCI shows mild impairment in different cognitive domains: executive functions of memory (attention and learning), problem solving (processing) and self-control (depression and emotion) [6]. These can be screened by neuropsychological batteries.

The CERAD test battery (The Consortium to Establish a Registry for Alzheimer's Disease) was evolved for diagnosis of cognitive impairments occurs with early Alzheimer's disease (AD) [7]. It was used after which for diagnosis of cognitive impairment in general. It is reliable, valid

and have inter-rater agreement [8]. It measures 8 items: executive functions, language functions, verbal learning, visuospatial functions, delayed recall, memory consolidation, and recognition memory. Delayed recall of the wordlist and the saving scores (such as delayed recall adjusted for acquisition) on the CERAD are impaired in mild AD but preserved in normal aging [9-11]. MCI should be diagnosed in CKD patients before irreversible damage occurs.

OBJECTIVE

The aim of this study was to assess different cognitive domains in CKD elderly patients.

METHODS

A total of 100 CKD patients, elderly aged 60 years and older were enrolled from Ain Shams University hospital outpatient clinics. Comprehensive geriatric assessment, medical history, and thorough clinical examination were carried out for all studied patients.

Serum creatinine was measured for all participants to calculate estimated glomerular filtration rate eGFR needed to establish diagnosis of CKD which defined as (eGFR < 60 mL/min/1.73m2) according to the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [12].

Ethical approval was granted by Research Ethics Committee, and all participants gave their informed consent for participation in the study.

CKD patients on renal replacement therapy (e.g. Hemodialysis or renal transplant) were excluded. CKD patients with Mini-mental state examination (MMSE) <24 [13, 14], depression assessed by geriatric depression scale (GDS-15) score >5 [15], history of neuropsychiatric disorders, presence of acute illness e.g., history of thyroid disease, visual and auditory impairments, neurological disorders such as cerebrovascular stroke, Parkinson disease, head trauma, epilepsy were excluded from the study.

CERAD cognitive tests were conducted to the CKD patients who scored > 24 in the MMSE. Arabic version of the battery was applied which takes about thirty minutes to finish [13]. It consists of Clinical Dementia Rating (CDR) and 8 subtests (J1-J8) to assess different levels & domains of cognitive and executive function.

The CERAD subtests measure seven different domains: Language function (naming), verbal learning (sum score of 10 learned words in Wordlist learning over three trials, maximum score is 30), visuospatial functions (constructional praxis, i.e. copying of four geometric figures), delayed recall (delayed recall of wordlist learning and constructional praxis tasks), memory consolidation (savings scores represent the percentage of items that were initially learned/copied that were retained at the delayed recall), recognition memory (the percentage of correctly recognized words in the wordlist recognition task including the 10 target words and 10 distractors), and executive functions (verbal fluency). Then, CERAD total score was calculated by summing the scores of six tests including the Verbal Fluency [VF] (maximum score 24), Boston naming test [BNT], Word List Memory [WLM], Construction Praxis [CP], Word List Recall [WLR], and Memory List Recognition [WLRc]. The maximum of Total Score 1 [TS-1] is 100 points [7].

CDR was used to assess cognitive impairment in six areas: community affairs, home & hobbies, judgment & problem solving, memory, orientation, and personal

care. Each domain is graded on 5-point scale: 0 for no impairment; 0.5 for mild cognitive impairment; 1 for mild dementia; 2 for moderate dementia; and 3 for severe dementia [16].The global CDR score was calculated using the Washington University web algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html).

Statistical methods

Quantitative data was expressed as mean, standard deviation while qualitative data was expressed as frequencies and percentages. Comparison between quantitative variables was done using t-test. IBM SPSS statistics for windows version 23 (IBM Corp., Armonk, NY, USA) was used for data analysis. Pearson correlation coefficient was used in analysis of this study A "P value" of less than 0.05 was considered statistically significant.

RESULTS

The study was conducted on 100 elderly patients with CKD, mean age 68.0 (± 6.1). 61% of the participants were males and 39% were females. Demographic, clinical background data are shown in Table 1.

Table (1) Demographic and clinical characteristics of the studied CKD patients

	CKD **Mean ± SD *or* No. (%)**
Age (years)	68 ± 6.1
Gender	
Male	61(61%)
Female	39(39%)
Education	
Illiterate	30 (30%)
Read and write	44 (44%)
Primary education	10 (10%)
Secondary education	9 (9%)
college	7 (7%)
Smoking	
Non-smoker	48 (48%)
Ex-smoker	20 (20%)
Current smoker	32 (32%)
Medical background	
Diabetes mellitus	80 (80%)
Hypertension	70 (70%)
Heart disease	28 (28%)
Chronic Pulmonary disease	17 (17%)
Others	5 (5%)
Serum creatinine (mg/dL)	2.7 ± 1.1
eGFR (mL/min/1.73m2)	27.7 ± 11.9
CKD stages	
Stage 3a (mild)	17 (17%)
Stage 3b (moderate)	32 (32%)
Stage 4 (advanced)	30 (30%)
Stage 5 (ESRD)	21 (21%)

Others: Osteoarthritis. ESRD= End-Stage renal disease.

Illiterates: who cannot read or write or <4 years of education; read and write: ≥4 years of education; primary education: completed 6 years of formal education; secondary education: completed 12 years of formal education; college: 16 years of education

Table 1 shows that 17% of the CKD cases were in stage 3A (mild), 32% in stage 3B (moderate) and 30% in stage 4 (advanced)while 21%of cases are in stage 5 (pre-dialysis). Also, there is high percentage of diabetes and hypertension among CKD patients.

Table (2) Mean, Standard deviation on the CERAD subtests for the CKD patients.

CERAD-NB subtests	CKD patients (No.=100) Mean ± SD	CKD stage 3 (No. = 49) Mean ± SD	CKD stage 4 (No. = 30) Mean ± SD	CKD stage 5 (No. = 21) Mean ± SD	P-value
Screening test					
MMSE (/30)	26.3 ± 1.3	1.32 ± 26.57	1.2 ± 25.93	1.6 ± 26.52	0.111
Executive Function					
Verbal Fluency (/24)	7.8 ± 2.7	2.51 ± 8.29	2.74 ± 7.03	3.16 ± 7.76	0.145
Language Function					
Boston Naming Test (/15)	15 ± 0	15 ± 0	15 ± 0	15 ± 0	---
Verbal Learning					
Word List Memory – sum (/30)	13.5 ± 3.8	3.55 ± 14.18	3.78 ± 12.03	4.12 ± 14.05	0.039
WLM trial-1 (/10)	3.3 ± 1.2				
WLM trial-2 (/10)	4.4 ± 1.3				
WLM trial-3 (/10)	5.6 ± 1.6				
Visuospatial Functions					
Construction Praxis copy (/11)	7.3 ± 2.0	2.03 ± 7.65	1.91 ± 6.83	2.18 ± 7.38	0.223
Delayed recall					
Word List Recall (/10)	4.8 ± 1.9	1.84 ± 5.24	1.81 ± 4.13	2.17 ± 4.9	0.046
Construction Praxis Recall (/11)	5.4 ± 2.1	2.23 ± 5.88	1.79 ± 4.63	2.01 ±5.57	0.036
Memory Consolidation					
Word List Saving (%)	82.5 ± 18.1	17.39 ± 85.89	15.27 ± 80.07	22.38 ± 78.45	0.192
Construction Praxis Saving (%)	72.5 ± 13.7	13.65±74.91	14.65±67.34	11.18±74.44	0.046
Recognition Memory					
Memory List Recognition (/10)	6.9 ± 2.2	2.15 ± 7.37	1.86 ± 6.2	2.62 ± 6.9	0.074
CERAD total score (/100)	55.4 ± 11.9	11.23 ± 57.73	11.23 ± 51.23	13.67 ± 56	0.062

Word list saving: proportion of correctly recalled words during Word List Recall compared to Word list learning trial 3. Construction Praxis saving proportion of correctly drawn figures during Construction Praxis Recall compared to Construction Praxis

Table (2) demonstrates significant differences in cognitive subtests scores (wordlist memory, wordlist recall and construction praxis recall) in different stages of CKD. The severity of kidney disease was directly related to the severity of cognitive impairment, such that lower kidney function was associated with poorer verbal learning and delayed recall.

CKD patients had low mean verbal fluency and mean MMSE among CKD patients while language functions score had not been affected. As regard– sum WLM, WLR and

WLRc subtests, there were lower mean among CKD patients.

Distribution of CDR scores among studied patients was as follows: 0 among 61 CKD cases (61%); 0.5 among 27 CKD cases (27%); 1 among 7 CKD cases (7%); 2 among 4 CKD cases (4%) and 3 among 1 CKD case (1%).

Table (3) Comparison between the mean CERAD total score regarding different demographic and co-morbidities of the studied CKD patients

CERAD Total Score	Mean	SD	t	P
Gender				
Male N=61	56.7	12.1	1.3	0.1
Female N=39	53.3	11.6		
Education				
Illiterate/Read N=74	56.0	12.3	7.0	<0.01
Education N=26	74.6	7.3		
Smoking				
Non smoker N=48	53.5	11.4	1.4	0.1
Smoker-ex N=52	57.1	12.3		
Diabetes				
Negative N=20	63.1	9.6	3.3	<0.01
Positive N=80	53.5	11.7		
Hypertension				
Negative N=30	56.1	10.6	0.3	0.7
Positive N=70	55.1	12.6		
Heart disease				
Negative N=72	62.4	8.3	1.4	0.6
Positive N=28	61.1	9.1		

Table (3) shows a lower mean total score-I among illiterate, read write group compared to patients with higher education level and the difference is highly statistically significant. This table shows lower mean total score-I in patients with diabetes in comparison to patients without diabetes and the difference is highly statistically significant.

Table (4) Correlation between CERAD total score and age, education, eGFR, serum creatinine , CKD stages among CKD patients.

Correlations		
CKD patients		**CERAD total score**
Age	**r**	-0.480
	P-value	P<0.001
Education	**r**	0.660
	P-value	P<0.001
eGFR	**r**	0.208

	P-value	0.03
Serum creatinine	**r**	-0.099
	P-value	0.3
CKD stages	**r**	-0.125
	P-value	0.2

Table (4) shows a significant negative correlation between the mean total CERAD total score and the mean age. There is a significant positive correlation between the level of education of the patients and the CERAD total score. The higher the educational level the better CERAD total scores and performance. There is a significant positive correlation between the mean eGFR and the CERAD total score, poorer cognitive tests performance were expected in sever renal impairment. There is no statistically significant correlation between the CERAD total score and the mean serum creatinine or the stage of the CKD.

DISCUSSION

Cognitive decline is common in individual with CKD. The aim of this study was to assess different cognitive domains in CKD elderly patients. CERAD cognitive tests were conducted to the CKD patients.

In the present study, the executive function, verbal memory, MMSE and CERAD total score were more affected in CKD patients as shown lower mean scores. CERAD total score is useful global cognitive measurement for cognitive function decline regardless of etiologic background. There was no effect on language function in CKD patients.

The current study shows a higher percentage of diabetes mellitus and hypertension among CKD patients. Diabetes mellitus occurs in 40% of end-stage renal disease cases, while hypertension occurs in 30% of them [17].

In CKD, the memory deficit was associated with inefficient learning and recall both immediately and after a delay. It is unclear the mechanisms of cognitive impairment in CKD. It was found that incidence of dementia in elderly with CKD and end stage renal disease (ESRD) were more strongly associated with vascular dementia than Alzheimer's dementia [18, 19].

Previous studies showed that patients with CKD have poor cognitive functions, such as attention, memory, visuospatial and executive functions [20, 21]; each cognitive domain can be influenced by another one [22], and they may be inter-correlated [23].

A correlation was done in the CKD patients regarding their age and educational status and cognitive tests performance as represented by CERAD total score, showing that there was a high statistically significant difference between the level of education and the CERAD total score. CKD patients with primary, secondary educations and higher/college education got the highest results than illiterates. There is positive correlation between the level of education and CERAD total scores and a negative correlation between age and CERAD total scores and cognitive performance in CKD patients.

This result agrees with previous studies that described the association between CKD and

cognitive impairment. ***Kurella et al., 2004*** found that less-educated elderly were most vulnerable to negative effects of renal impairment on cognitive tests and concluded that higher levels of education may protect against the neurobiological consequences of renal impairment [24]. eGFR was positively correlated to performance tests of verbal memory and global cognitive function, independent of age, race, and other potential confounders [25].

CKD is associated with different proposed factors as mediators for cognitive impairment in CKD patients, including oxidative stress, high inflammatory cytokines, lipid, and homocysteine metabolism abnormalities [26]. Also, anemia has been correlated with cognitive impairment in elderly with or without CKD [27]. Adjustment of cardiovascular risk factors and elimination of several abnormal hazardous mediators associated with CKD might diminish cognition decline in those patients. Renal transplantation improves cognitive function better than renal dialysis. New dialysis techniques and activation of cholinergic anti-inflammatory pathway are needed to confirm their potential effect on reduction of cognition decline in ESRD patients [28].

Considering the rapidly increasing incidence of CKD in elderly individuals, diagnosis of cognitive impairment and dementia in CKD patients may help the preventive strategies to reduce its burden.

CONCLUSION

CERAD total score was positively correlated to eGFR in CKD patients confirming the association between cognition and renal impairment. Age and educational level significantly affect cognitive performance.

RECOMMENDATION

CKD patients have high risk of cognitive decline. Renal function tests could be included in a comprehensive assessment of patients with cognitive impairment especially in elderly patients.

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