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Original Article

Assessment of cognitive dysfunction in kidney disease

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Abstract

Background: Cognitive dysfunction, include reduced mental alertness, intellectual impairment, decreased attention and concentration, memory deficits and diminished perceptual-motor coordination. Both CKD and chronic dialysis patients are thought to be associated with cognitive impairment. Cognitive impairment may decrease an individual's quality of life, increase resource utilization and result in suboptimal medical care. Neurophysiologic tests using imaging techniques are used to evaluate structural and functional abnormalities. Neuropsychological testing uses validated questions and screening tests to evaluate cognition.

Setting and participants: This study was carried out on 120 patients with different stages of CKD from nephrology outpatient clinic and hemodialysis unit in Ain Shams University Hospitals. Group I: 50 CKD patients, stage Ш and stage IV. Group II: 50 ESRD patients on regular hemodialysis with K t/v > 1.1. Group III: 20 acute kidney injury patients, followed up till their renal functions stabilized. Group IV: 20 healthy subjects matched with patients. All patients underwent laboratory investigations and psychometric tests which include trial making test part B, digit span test, digit symbol test, mini-mental state examination.

Results: There were highly significant differences of mean values of cognitive function tests between (groups I,II and III as compared with group IV (control group), stage III CKD and stage IV CKD, CKD and hemodialysis patients, AKI patient at the insult and after recovery) and finally between hemoglobin and cognitive function tests score.

Conclusions: There were significant differences of cognitive function tests results between CKD, III,IV,V, AKI patients as compared with healthy group, suggesting that kidney disease affects cognitive performance, there were significant differences of cognitive function tests results between stage III CKD and stage IV CKD, suggesting that the degree of cognitive impairment is associated with the severity of CKD, also significant differences of cognitive function tests results between CKD and ESRD on hemodialysis, suggesting that dialysis improves cognitive performance. Our results showed significant differences of cognitive function tests results between AKI patients at the insult and after recovery, suggesting that AKI also impair cognitive function. Finally cognitive performance is affected by hemoglobin level in CKD stage III, IV, V on hemodialysis and AKI patients, suggesting that treatment of anemia in AKI, CKD and ESRD patients improve cognitive performance.

Key words: Hemodialysis; cognitive dysfunction; CKD.

Runing title: Cognitive dysfunction and kidney.

Introduction

Cognition is the mental faculty or process of acquiring knowledge by the use of reasoning or perception. Cognition is the foundation that underlies all daily activities, from the most basic to the most complex [1]. Cognitive impairment and chronic kidney disease (CKD) will become increasingly prevalent in the aging population. The incidence of kidney failure is rising in all age groups but particularly in older adults. Individuals with different stages of CKD are at higher risk for development of cognitive impairment and this may be a major determinant in their quality of life. Cognitive dysfunction includes reduced mental alertness, intellectual impairment, decreased attention and

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concentration, memory deficits and diminished perceptual-motor coordination [2]. Cognitive impairment is associated with an increased risk of death in dialysis patients. Cerebrovascular disease is a strong risk factor for development of cognitive impairment and vascular disease is a more likely cause of cognitive impairment than Alzheimer's disease in patients with CKD. Both traditional and nontraditional vascular risk factors are more common in CKD and dialysis patients may also be at risk for cognitive impairment via nonvascular risk factors and the hemodialysis procedure itself [3]. The severity of kidney disease was associated with the severity of cognitive impairment, independent of age, education and other key confounders [4]. CKD is associated with other risk factors for cognitive impairment, including advanced age, diabetes, hypertension and dyslipidemia. Cognitive impairment in patients with CKD also may be mediated by the retention of putative neurotoxins, including byproducts of nitrogen metabolism and parathyroid hormone. Chronic inflammation is well known in CKD patients, and is a risk factor for development of dementia in them [5]. It is important to identify those patients with cognitive impairment to reduce the considerable morbidity associated with this condition and improve their quality of life [6]. Both CKD and chronic dialysis patients are associated with cognitive impairment but cognitive function improves following initiation of dialysis and dialysis patients have less cognitive impairment compared to untreated patients with advanced uremia. Studies have also found improvement in short-term memory both after starting maintenance hemodialysis and following a single hemodialysis treatment and attention functions have been found to improve after starting maintenance dialysis. However, cognitive dysfunction, including reduced concentration capacity, learning and memory as well as cognitive inflexibility and impaired complex novel problem solving, is commonly reported to persist in dialysis patients [7]. Some absolute levels of cognitive function were found to be associated with the adequacy of dialysis. In particular, the attention and concentration test scores were found to be predicted by the adequacy of dialysis, suggesting that these tests may be most sensitive as an impact of renal functioning [8].

Two broad classes of tests are used to assess cognitive function in the general population (table 1,2). Neurophysiological testing uses imaging techniques and electrophysiology to evaluate structural and functional abnormalities. Neuropsychological testing uses validated questions and screening tests to evaluate cognition [9].

Four tests were administered in our study. First, the trail making test part B (TMT-B) which assesses attention, visual scanning, psychomotor speed, ability to sequence and ability to shift cognitive set [10]. Second, the digit span test (D-span) which is a widely used auditory verbal short-term (working) memory test. Third, the digit symbol test (D-symbol) which tests the sustained attention, visual searching, and new-learning abilities of the patients [11]. Fourth, the mini-mental state examination (MMSE) which assesses orientation, registration, attention, calculation, recall, and language [12,13].

Our study aims to assess the cognitive function in CKD stage III and IV, Stage V on hemodilaysis (HD) and AKI, and correlates it with hemoglobin level. In addition we study the changes in the cognitive function following dialysis treatment.

Material and methods

This study was carried out on 120 patients with different stages of kidney disease. They were divided into 3 groups:

Group I: Included 50 CKD patients 28 of them with stage III and 22 with stage IV selected from nephrology outpatient clinic.

Group II: Included 50 patients on regular hemodialysis thrice weekly (4 hours each session) with K t/v > 1.1.

Group III: Included 20 patients with acute kidney injury. They were followed up till their renal functions recovered.

Group IV: Included 20 healthy subjects matched with patients as regards age, sex and education.

Patients with evident cerebrovascular disease, thyroid disease, severe anemia, uncontrolled hypertension, malnutrition, major psychiatric illness, major visual or hearing impairment, unstable coronary heart disease, collagen vascular disease and vasculitis were excluded from the study. All the medications were revised to exclude any drugs that had an affect on the cognitive function.

All patients underwent:

1. Through history, clinical examination and laboratory investigations.
2. Psychometric tests was done in dialysis off day which include:

TMT-B: The trial making test part B requires that the subject connect with lines, in a given sequences, circled digits and letters randomly distributed on a page as shown in figure 1. The prescribed sequence is from 1 to A to 2 to B to 3 to C, etc. Performance is scored in terms of time to complete the task correctly. The TMT-B assesses attention, visual scanning, psychomotor speed, ability to sequence to shift cognitive set.

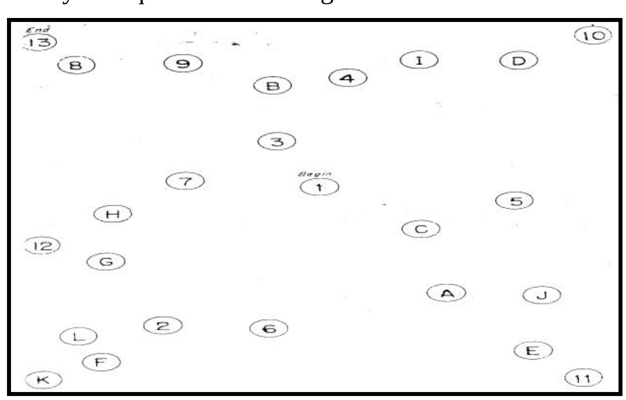

Fig. 1. TMT-B.

- *D-span:* The digit span test is a widely used auditory verbal short-term (working) memory test. It requires the subject to repeat a spoken string of digits, two trials each, for stings three to nine digits in the forward order and two to eight digits in the reverse order. The score is the number of correct trials.
- *D-symbol:* It tests the sustained attention, visual searching, visual sequencing and new learning abilities of the patients. Subjects were given nine different symbols that were matched to numbers and they were required to change the number with its matched symbol as shown in figure 2. The score is the number of symbols changed correctly within 90 seconds.

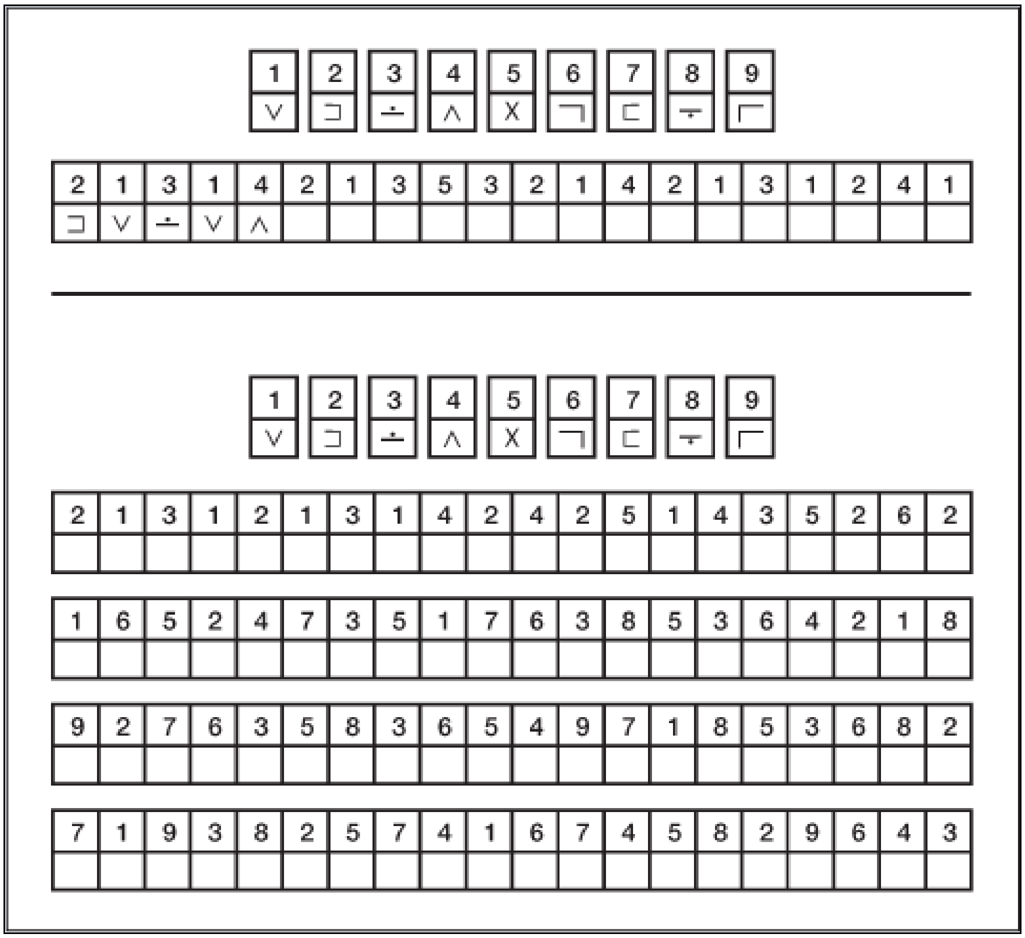

Fig. 2.

The mini-mental state examination as shown in table 1, is a widely used well validated screening tool for cognitive impairment. It tests five areas of cognitive function. The first area of cognitive function, orientation, is assessed by asking the usual questions about time, day, date and location. Second area of cognitive function, registration, is actually a short term memory test where the subject must recall three objects named by the examiner. Third and fourth area, attention and calculation, are measured by having the subject begin with 100 and count backwards by 7 (serial 7s). Recall, the subject must recall the three objects named previously. Language functions are assessed by having the subject name simple objects, repeat a sentence and follow a three stage command. A constructional task is also included in the language section where the subject must copy overlapping pentagons. Each discrete subtask completed correctly earns 1 point toward a maximum score of 30. Mild cognitive impairment score is between 26 -28, moderate cognitive impairment score is between 18-25, while severe impairment is below 18.

The statistical analysis: Done by using Excel program and SPSS program statistical package for social science version 10. The description of the data was done in form of mean (+/-) SD for quantitative data. The analysis of the data was done to test statistical significant difference between groups. For quantitative date student t-test was used to compare between 2 groups paired sample t-test was used to compare one group at different measurements. One way Anova test was used to compare more than 2 groups. Pearson correlation Co-efficiency test was used to test association between variables.

Table 1. MMSE.

Items on the Mini-Mental State Examination [12,13].

Items	*Maximum score*
Orientation	
What is the (year) (season) (date) (day) (month)?	5
Where are we (state) (country) (town) (hospital) (floor)?	5
Registration	
Name 3 objects: (1 second to say each). Ask the patient for all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until the patient learns all three. Count the trials and record.	3
Attention and calculation	
Serial subtraction of 7. 1 point for each correct. Stop after 5 answers. Alternatively spell "World" backwards.	5
Recall	
Ask for 3 objects repeated above. 1 point for each correct answer	3
Language	
Name a pencil; name a watch	2
Repeat the following "No ifs, ands, or buts."	1
Follow a three stage command:"Take a paper in your right hand, fold it in half, and put it on the floor."	3
Read and obey the following:"Close your eyes."	1
Write a sentence	1
Copy a design	1

Results

Population characteristics: This study included 120 patients divided into 3 groups. Group I which included 50 CKD patients in stage III and stage IV CKD. Stage III CKD included 28 patients, 53.6%) males and 46.4% females. The mean age was 44.75±10.157 years old. Mean education years was 8.1429±3.56645 years. Stage IV CKD included 22 patients, 40.9% males and 59.1% females. The mean age was 45.59±11.677 years old. Mean education years was 6.2273±3.77879 years.

Group II which included 50 CKD patients stage V on regular hemodialysis, 54% males and 46% females. The mean age was 40.42 ± 12.588 years old. Mean education years was 8.66±3.685 years. The mean dialysis duration was 4.64±3.148 years. The etiology of ESRD in the participating subjects is hypertension (48%), diabetes (38%), congenital (6%), glomerulonephritis (4%), analgesic (2%), and obstructive uropathy (2%).

Group III, which included 20 acute kidney injury (AKI), 60% males and 40% females. They were studied throughout the course of their illness till their renal function stabilized. The mean age was 45.35±10.163 years old. Mean education years was 8.2±3.381 years. The etiology of AKI in the participating subjects is 40% due to drug induced, 20% blood loss, and 40 % due to fluid loss from gastrointestinal tract.

In addition, there was group IV (control group), which included 20 healthy subjects; 50% males and 50 % females. The mean age was 39.6 ± 10.096 years old. Mean education years was 9.35±2.961 years.

Table 2 shows, that there is highly significant differences between mean values of cognitive function tests of groups I,II and III as compared with group IV (control group) as indicating that uremia has a major influence on the cognitive function in CKD patients.

Table 2. Comparison between mean values of cognitive function tests of group I, II, III, as compared with control group.

Group		*Number*	*Mean±SD*	*t-value*	*P-value*
MMSE					
	Control/	20	29.25±0.851		
	CKD	50	23.86±2.109	15.235	<0.001
	HD	50	26.52±1.46	9.723	<0.001
	AKI	20	27.8±1.473	3.813	0.001
TMT-B					
	Control/	20	171.10±15.148		
	CKD	50	413.70±79.839	20.580	<0.001
	HD	50	316.8±51.337	18.187	<0.001
	AKI	20	207.35±17.969	6.898	<0.001
D-SYM					
	Control/	20	11.95±0.686		
	CKD	50	6.92±0.944	21.610	<0.001
	HD	50	7.82±1.848	13.626	<0.001
	AKI	20	9.8±1.735	5.153	<0.001
D-SPAN					
	Control/	20	13.7±2.430		
	CKD	50	6.86±1.414	11.813	<0.001
	HD	50	8.22±2.093	9.448	<0.001
	AKI	20	9.5±1.85	6.150	<0.001

Progression of kidney disease is associated with decline of the cognitive function as shown in table 3.

Table 3. Comparison between mean values of cognitive function tests of stage III and IV CKD.

Group	*Number*	*Mean±SD*	*t-value*	*P-value*
MMSE				
stageIII	28	25.32±1.249	8.914	<0.001
stageIV	22	22.00±1.380		
TMT-B				
stageIII	28	357.32±38.381	8.954	<0.001
stageIV	22	485.45±57.857		
D-symb				
stageIII	28	7.50±0.577	6.792	<0.001
stageIV	22	6.18±0.795		
D-span				
stageIII	28	7.75±0.752	6.734	<0.001
stageIV	22	5.73±1.241		

Our study clarifies that dialysis improves the cognitive function as patients under regular efficient hemodialysis for more than 1 year perform better in the tests of evaluation of cognitive function than the predilysis patients with stage III, and Stage IV CKD as shown in table 4.

Table 4. Comparison between mean values of cognitive function tests of group I and II.

Group	*Number*	*Mean±SD*	*t-value*	*P-value*
MMSE				
HD	50	26.52±1.460	7.332	<0.001
CKD	50	23.86±2.109		
TMT-B				
HD	50	316.8±51.337	7.219	<0.001
CKD	50	413.70±79.839		
D-symb				
HD	50	7.82±1.848	3.066	<0.01
CKD	50	6.92±0.944		
D-span				
HD	50	8.22±2.093	3.807	<0.001
CKD	50	6.86±1.414		

Although there are limited studies on AKI and cognitive function, our 20 patients with AKI had mild cognitive impairment and was corrected within the recovery of kidney function as shown in table 5.

Table 5. AKI patients at the insult and after recovery."Paired samples statistics".

		Number	*Mean±SD*	*T -value*	*P-value*
Pair 1	MMSE	20	27.80±1.473	5.688	<0.001
	A-MMSE	20	28.85±1.040		
Pair 2	TMT-B	20	207.35±17.969	9.516	<0.001
	A-TMT-B	20	191.15±12.807		
Pair 3	D.symb	20	9.80±1.735	6.11	<0.001
	A-D.symb	20	11.15±0.933		
Pair 4	D.SPAN	20	9.50±1.850	5.638	<0.001
	A-D.SPAN	20	11.15±1.631		

Anemia is one of the factors responsible for cognitive dysfunction in predialysis CKD, hemodialysis patients, and AKI patients as shown in table 6,7 and table 8.

Table 6. Correlation between hemoglobin and cognitive function tests in CKD patients.

	MMSE	*TMT-B*	*D.SYMB*	*D.SPAN*
Hb pearson correlation	0.650	-0.661	0.655	0.613
P value	<0.001	<0.001	<0.001	<0.001
Number	50	50	50	50

In CKD stage V on hemodialysis there was a highly significant correlation between hemoglobin and cognitive function tests score, as shown in table 8.

Table 7. Correlation between hemoglobin and cognitive function tests in hemodialysis patients.

	MMSE	*TMT-B*	*D.SYMB*	*D.SPAN*
Hb pearson correlation	0.262	-0.430	0.308	0.356
P value	0.033	0.002	0.030	0.011
Number	50	50	50	50

Table 8. Correlation between hemoglobin and cognitive function tests in AKI patients.

	MMSE	*TMT-B*	*D.SYMB*	*D.SPAN*
Hb pearson correlation	0.622	-0.653	0.645	0.633
P value	<0.001	<0.001	<0.001	<0.001
Number	50	50	50	50

In hemodialysis patients there was no significant correlation between dialysis duration and cognitive function tests score as shown in table 9.

Table 9. Correlation between dialysis duration and cognitive function tests in ESRD patients.

	MMSE	*TMT-B*	*D.SYMB*	*D.SPAN*
Dialysis duration pearson correlation	-0.225	-0.035	-0.201	-0.251
P value	>0.05	>0.05	>0.05	>0.05
Number	50	50	50	50

Discussion

Cognitive impairment is a well-recognized manifestation of uremia. This is characterized by quiet stupor, dullness of intellect, sluggishness of manner, and drowsiness [5]. The severity of kidney disease is associated with the severity of cognitive impairment, independent of age, education and other key confounders. The prevalence of global cognitive impairment in persons with CKD was more than twice that of the age matched general population and was not explained by commonly measured metabolic alterations associated with kidney disease [3]. Both CKD and chronic dialysis patients are thought to be associated with cognitive impairment, but cognitive status improves following initiation of dialysis and dialysis patients have less cognitive impairment compared to untreated patients with advanced uremia as shown in our study [6]. Cognitive impairment, manifesting typically as a vascular dementia, develops in a considerable proportion of patients on dialysis, and improves with renal transplantation [14]. Murray 2008, found that up to 70% of hemodialysis patients aged 55 years and older have moderate to severe chronic cognitive impairment, yet it is largely undiagnosed [15].

There was highly significant difference between CKD stage V patients on HD and control groups as regards mean values of cognitive function tests score. This was in agreement with the results of Fazekas et al., 1995, who conducted his study on 30 subjects with CKD stage V on regular hemodialysis and 30 healthy controls, and found that CKD stage V on regular hemodialysis subjects had highly significant cognitive impairment (P<0.001) as compared with controls [16]. Also our results were supported by the results of Sehgal et al., 1997, who conducted his study on 336 hemodialysis patients and found significant prevalence of cognitive impairment among hemodialysis patients compared to controls [17].

There were highly significant differences between stages III, IV CKD and stage V on hemodialysis as regards mean values of cognitive function tests score, these results were in agreement with the results of Kurella et al., 2004, who conducted his study on 80 subjects with CKD stage III, IV and found that cognitive impairment is associated with the severity of kidney disease. In contrast, Kurella et al., 2004 studied 80 subjects with CKD stage V on hemodialysis with a mean age+/- standard deviation of 62.5+/-14.3. Three standardized cognitive tests, the modified mini-mental state examination (3MS), trailmaking test B (trails B), and California Verbal Learning Trial (CVLT) were applied. Mean scores on the 3MS, trails B, and CVLT immediate and delayed recall were significantly worse for subjects with stage V on HD than for subjects with CKD or published norms [3]. The difference from our results in HD patients may be due to advanced age population selected in their study. Murray, 2008 found that conventional hemodialysis may induce recurrent episodes of acute cerebral ischemia, which, in turn, may contribute to acute decline in cognitive function during dialysis. Thus, the worst time to communicate with dialysis patients may be during the hemodialysis session. Symptomatic and occult, and subclinical ischemic cerebrovascular diseases appear to play a large role in a proposed model of accelerated vascular cognitive impairment in these populations. Severe cognitive impairment among hemodialysis patients is associated with an approximately 2-fold increased risk of both mortality and dialysis withdrawal. So awareness of cognitive function in dialysis patients improves quality of care and outcomes by raising clinicians' awareness of the potential effects of cognitive impairment on medication, fluid, and dietary compliance [15].

As regards to severity of CKD our results were supported by that of Kurella et al., 2005, who conducted his study on 1015 CKD women, and found that cognitive impairment is associated with CKD and increases with decreasing kidney function [4]. Khatri et al., 2009, found that decreased kidney function is associated with greater cognitive decline, even in those with mild CKD so kidney disease may represent a novel mechanism leading to cognitive impairment and a target for early intervention [18]. Thorleif et al., 2009 found that moderate-to-severe impaired renal function is associated with incident cognitive impairment initially and after 2 years in a large cohort of elderly subjects [19]. Minesh et al., 2009 found that participants with a creatinine clearance (CCl) 60 ml/min and those with a CCl between 60 and 90 ml/min performed significantly worse on the modified Telephone Interview for Cognitive Status over time than those with a CCl 90 ml/min, decreased kidney function associates with greater cognitive decline, even in those with mild CKD [20].

As regards to hemoglobin, there was significant correlation between hemoglobin level and cognitive function tests in CKD stage III, IV, V on HD and also AKI patients. This was in agreement with the results of Lee et al., 2004 who conducted his study on 56 ESRD on regular hemodialysis, and found that correction of anemia in ESRD has been shown to improve cognitive performance [11]. Our results also were in agreement with that of Marsh et al., 1991, who found improvement in cognitive performance in TMT-B, and D.SYM test with increased hemoglobin level in ESRD [21]. Also supported by that of Brickman et al., 1996, who conducted his study on 426 hemodialysis patients and Madan et al., 2007 who enrolled patients each of CKD stage 3, 4 and 5 (undialysed), they found significant correlation between hemoglobin level and cognitive performance [22,23].

In our study, we were the first to follow cognitive performance in AKI patients at the insult and after recovery and stabilization of renal function tests and we found significant differences in cognitive performance at the insult and after recovery, suggesting that AKI per say impair cognitive performance and that the uremic toxins may have a major independent role in cognitive dysfunction.

Conclusion

There were significant differences of cognitive function tests results between CKD, III,IV,V, AKI patients as compared with healthy group, suggesting that kidney disease affects cognitive performance, there were significant differences of cognitive function tests results between stage III CKD and stage IV CKD, suggesting that the severity of cognitive impairment is associated with the severity of CKD, also significant differences of cognitive function tests results between CKD and ESRD on hemodialysis, suggesting that dialysis improves cognitive performance. Our results showed significant differences of cognitive function tests results between AKI patients at the insult and after recovery, suggesting that AKI also impair cognitive function. Finally cognitive performance is affected by hemoglobin level, suggesting that treatment of anemia in CKD and ESRD patients improve cognitive performance.

References

1. Teri L, McCurry SM and Logsdon RG: Memory, thinking and aging. What we know about what we know. West J Med, 1997; 167: 269-75.
2. Pliskin NH, Yurk HM and Ho LT: Neurocognitive function in chronic hemodialysis patients. Kidney Int, 1996; 49: 1435-40.
3. Kurella M, Chertow GM, Luan J and Yaffe K: Cognitive impairment in chronic kidney disease. J Am Geriatric Soc, 2004; 52: 1863-9.
4. Madero M, Gul A, Sarnak MJ: Cognitive function in chronic kidney disease.Semin Dial, 2008; 21:29-37.