Assessment of executive functions for patients with chronic renal failure

Adina KARNER-HUȚULEAC[1,2]

Initial receipt: 11.08.2012 Final revision received: 31.01.2013 Accepted: 10.02.2013

Abstract: This study is part of a current trend of the neuropsychological research of evaluation of cognitive functions associated with conditions of diffused affliction. We have assessed patients with chronic renal failure. This medical condition may lead to a global deterioration of all cognitive systems by affecting the nervous cell at structural and/or functional levels. These mechanisms include cerebrovascular disease, uraemic encephalopathy, metabolic dysregulation, side effects of the hemodialysis treatment and direct effects of kidney disease that may link chronic kidney disease with impaired executive function (Kurella et al., 2005; Lee et al., 2011; Pereira, Weir, Scott & Sarnak, 2005, Pereira et al., 2007; Yaffe et al., 2010). We found that patients with chronic renal failure show a slower processing of new information as a main executive difficulty, but less impairment occurs in the area of mental flexibility and verbal fluency. Patients are able to manage new life situations (planning, decision making), even if they have a higher latency time and a significantly lower accuracy.
Keywords: executive functions; chronic renal failure; cognitive deficits; neuropsychology; verbal fluency; mental flexibility.

Introduction

Chronic kidney disease (CKD) is a growing public health problem (Madero, Gul & Sarnak, 2008). The incidence of kidney failure is rising in all age groups but particularly in older adults. Individuals in all stages of CKD are at a higher risk for the development of cognitive impairment, and this may be a major determining factor in their quality of life, such as difficulties in dietary modification and medication adherence (Kurella, Chertow, Luan & Yaffe, 2004).
There are several potential mechanisms: including cerebrovascular disease, metabolic dysregulation and direct effects of kidney disease that may link CKD with impaired cognitive functions.

Both traditional (such as age, hypertension, diabetes mellitus and dyslipidemia) and non-traditional vascular risk factors (hyperhomocysteinemia, hemostatic abnormalities, inflammation etc.) are more common in CKD and dialysis patients. There are also several nonvascular risk factors (anemia, hyperparathyroidism, depression etc.) and hemodialysis risk factors (disequilibrium syndrome, subdural haematoma, and Wernicke's encephalopathy) that may be important in patients with CKD and cognitive impairment. Dialysis is associated with neurological syndromes including the disequilibrium syndrome, subdural haematoma and Wernicke's encephalopathy that may be important in patients with

[1] University of Medicine and Pharmacy "Gr.T.Popa": Center for Ethics and Public Healthcare Policies; e-mail: adinakarner@yahoo.com
[2] Alexandru Ioan Cuza University of Iași: Faculty of Psychology and Education Sciences

CKD and cognitive impairment (Flicker & Ames, 2005; Kimmel & Peterson, 2005; Mizumasa et al., 2004; Stivelman, 2000).

Recent data suggest that patients in all stages of CKD may be at higher risk of developing mild and moderate cognitive impairment. But the majority of prior research studies have used global cognitive screening measures mainly to diagnose dementia (e.g. Mini Mental State Examination – MMSE, Modified Mini Mental State – 3MS or California Verbal Learning Trial – CVLT, which measures components like attention, immediate and delayed verbal memory, visuospatial scanning and language) rather than tests of specific domains (Kurella et al., 2004; Madan, Kalra, Agarwal & Tandon, 2007).

Current consensus regarding the executive system as a process or set of processes whose primary purpose is to facilitate adaptation to novel situations (Burgess & Shellice, 1996) by "modulation and control of more fundamental or routine cognitive skills" (McCarthy & Warrington, 1990, p. 343).

Norman & Shallice (1986) outline five situations where routine would not be sufficient for optimal performance: those that involve planning or decision making, those involving error correction or troubleshooting, situations where responses are not well-learned or contain novel sequences of actions, dangerous or technically difficult situations and those which require the overcoming of a strong habitual response or resisting temptation.

There are studies that have demonstrated the existence of a dysexecutive syndrome in patients with chronic kidney failure (Griva et al., 2010; Madero et al., 2008; Odagiri et al., 2011).

These aspects determines us to emphasize the fact that for these chronic patients, it is not enough to establish the diagnosis and treatment but also training for the development of cognitive and emotional abilities to adapt to objective information, as well as doing psycho-education.

Aims of the study

The aim of the present study was to investigate the level of executive deficits to patients with chronic renal failure, without stroke or depressive disorders. In our study all patients received the same dialysis treatment.

Method

Participants

The study population included 33 dialysis patients (DP) recruited from the renal clinic of "Dr. C.I. Parhon" Hospital and Fiterman Clinic from Iasi. The control group (CG) is made of 63 clinically healthy participants (without chronic or actual acute diseases) and patients with very well managed chronic diseases. The patients are between 40 and 60 years old and have been selected on the basis of medical excerpts from observation sheets and on the basis of the screening tests for

dementia and depression. 75.5% of the dialysis patients exhibit at least one comorbidity (diabetes, hypertension). Patients and control group have been matched for age, academic degree and gender. Baseline characteristics for study subjects are summarized in Table 1.

Table 1: Selected characteristics of dialysis patients and control group participants

Characteristics	DP (n=33)	CG (n=63)	p-value
Age (mean ± SD years)	49.3± (10.2)	47.8 (9.8)	0.21
Female (%)	39.4	46	0.74
High school graduate (%)	24.24	28.57	0.65
Time on dialysis (months)	32 (11-46)	-	-
Diabetes mellitus (%)	54.5	23.8	0.002
Hypertension (%)	57.5	30	0.001
Stroke (%)	18.1	-	-

Measure

The most used method of executive evaluation of people with various neurocerebral affectations, and, as well as in the case of clinically healthy subjects, refers to frontal lobe tests. We used Phonemic Verbal Fluency Test to evaluate the subject's ability to generate words beginning with a specific letter (FAS) and efficiently applied an activation strategy (Monsch et al., 1994). In order to evaluate the psychomotor speed, the CODE Subtest from Wechsler Adult Intelligence Scale. This test is, first of all, a sensory-motor duty and its accomplishment requires reaction speed, focus (attention) and to respect the simple spatial-mechanic relationships. The task measures the general psychomotor speed and oculomotor coordination. For the evaluation of mental flexibility we used the Wisconsin Card Sorting Test, task that supposed the monitoring of internal and external goals but also inhibiting of persevered tendencies (Riccio et al., 1994).

Results

We analysed the effect of the independent variable medical condition (CKD stage V on dialysis versus control group) on the three executive functions, obtaining the following results (see Table 2). The psychomotor speed was measured by the CODE Test Wechsler Adult Intelligence Scale, WAIS). In order to evaluate the psychomotor speed we used ANOVA One-Way Test, comparing the performances of the two groups regarding the two relevant indicators: the actual executive performance (number of correct association between symbols) and accuracy (number of errors).

There was an effect of the independent variable on the psychomotor speed ($F(1,95)=24.30$, $p<0.001$) and on the number of errors ($F(1, 95) =5.09$, $p=0.002$), in

the way those dialysis patients demonstrate a significantly lower psychomotor speed (Mdif=3.14, p<0.001) as well as a significantly reduced accuracy (Mdif=-0.41, p=0.007).

In order to evaluate verbal fluency we used ANOVA One-Way Test, comparing the performances of the two groups regarding three important indicators: actual verbal fluency (having three substages: number of correctly pronounced words in the first half of the task, number of correctly pronounced words in the second half of the task and the total number of correctly pronounced words), perseverance (number of repetitions) and accuracy (number of errors) in the same three substages.

Table 2: *Executive performance*

Measure	CKD group M	CKD group SD	Control group M	Control group SD	p
WAIS-R CODE Psych Mot Sp	76.07	2.23	79.20	5.24	<0.001
WAIS-R CODE Accuracy	0.76	3.65	0.35	1.02	0.007
VF Fluency (1st half)	18.26	4.23	19.35	8.65	0.004
VF Fluency (2nd half)	14.72	3.67	15.40	9.23	0.065
VF Fluency (overall)	32.98	4.65	34.75	8.25	0.074
VF Perseverance (1st half)	0.12	1.12	0.09	0.98	0.064
VF Perseverance (2nd half)	2.42	1.24	0.30	0.56	0.024
VF Perseverance (overall)	2.64	1.14	0.39	0.64	0.020
VF Accuracy (1st half)	0.66	1.86	0.03	0.01	0.001
VF Accuracy (2nd half)	0.72	0.74	0.04	0.01	<0.001
VF Accuracy (overall)	1.38	1.04	0.07	0.01	<0.001
WCST Mental flexibility (No. of categories completed)	3.84	0.49	4.43	1.72	0.24

Note. The psychomotor speed was measured by the CODE Test from Wechsler Adult Intelligence Scale; accuracy (number of errors) was measured by the CODE Test from Wechsler Adult Intelligence Scale; actual verbal fluency (number of correctly pronounced words in the first and the second half of the task and overall) was measured by Verbal Fluency Test; perseverance (number of repetitions in the first and the second half of the task and overall) was measured by Verbal Fluency Test; accuracy (number of errors in the first and the second half of the task and overall) was measured by Verbal Fluency Test; mental flexibility was measured by Wisconsin Card Sorting Test.

Significant differences were obtained between the control group and chronic patients, in the first half only (Mdif=z1.09, p=0.004), which means that chronic patients activate a significantly smaller number of correct words at the beginning of the task, but succeed in recovering themselves on the way, even if perseverance was significantly higher than the control group (Mdif=2.12, p=0.024) in the second half of the task and overall (Mdif=0.19, p=0.018), and the accuracy was significantly lower in all the substages of the task. So, dialysis patients do not

have difficulties regarding verbal fluency, even if they have a weaker start than the clinically healthy subjects and show significant low accuracy and high perseverance.

For the evaluation the mental flexibility we used ANOVA One-Way Test, comparing the performances of the two groups regarding only one indicator: number of identified rules.

There was not been any effect of independent variable on the obtained results for mental flexibility. There was any significant differences for mental flexibility between the two groups (Mdif=2.25, p=0.24).

Conclusions and discussion

This study found that chronic renal failure dialysis patients recruited in the present study have some executive difficulties, especially when it comes to the new information processing speed and verbal fluency only for the first half of the task. This means that patients show a significant improvement in executive performance in the second half, even if this return is made with a significant loss in terms of accuracy. Dialysis patients had no significant mental flexibility dysfunction. The patients were able to manage new life situations (planning, decision making), even if they had a higher latency time, difficulties in correcting errors (the presence of the persevereance phenomenon) and a low ability of inhibition.

Because a decrease of psychomotor speed was observed, as well as a decrease of cognitive accuracy performances (markers for global cognitive deficiency), we can conclude that patients with chronic kidney failure suffer a mild global cognitive decline, which affects the cognitive processes in a non linear way and which manifests itself, especially in cases of new and more complex tasks, in comparison to the more simple and/or overlearnt ones.

The results of this study support partially the main findings that decreased kidney function is associated with poorer cognitive performance test scores in patients not requiring dialysis (Kurella et al., 2004; Madan et al., 2006) or dialysis patients (Sehgal, Grey, DeOreo & Whitehouse, 1997). These associations were independent of age, education and other confounding factors (Kurella et al., 2004). However, there is a discrepancy between the general results of previous studies which emphasized that executive function may be especially affected in subjects with CKD (Kurella et al., 2004) and our findings (selective executive dysfunctions). This discrepancy may be attributed to a high percentage of chronic patients in a control group. Additionally, some of the most widely used tests of executive functioning (e.g. Wisconsin Test) can be performed normally by some patients with obvious executive impairments "because they are unable to act effectively on their own initiative" (Rabbitt, 1997, p.242).

In the same time, it is important to point out two aspects: "executive functions are potentially fractionable and in situations of cerebral afflictions, a

certain level of cognitive congruence can be maintained, even if the absolute level of general abilities changes" (Rabbitt, 1997, p.94).

The results for Wisconsin Test were also been influenced by executive functions (working memory) as well as non executive factors (Shallice & Burgess, 1991). This test detects an abnormal variation of the level of executive function, but it is less sensitive to mild or moderate executive dysfunctions, a phenomenon we expect to describe in patients with chronic kidney failure (Murray & Knopman, 2010).

When referring to qualitative details as well, we can add that fact that during the verbal fluency task, clinically healthy subjects were activated to a great deal certain strategies to find the right words, for example naming certain objects from the testing room, phonological or semantic strategies. For dialysis patients it was less clear if they created a reply strategy, the necessary effort to activate the randomization of words being much bigger.

All these aspects that have been investigated can bring a great deal of understanding to cognitive affectations from the chronic patients, as well as an increase of effort of mental management and compensation along the difficult road of rehabilitation.

Acknowledgement

This research was supported by POSDRU/89/1.5/S/61879, *"Postdoctoral studies in the field of ethics of policy in public healthcare"*, University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania.

Reference List

Burgess, P. W., & Shallice, T. (1996). Response suppression, initiation and frontallobe lesions. *Neuropsychologia*, 34, 263-273.

Flicker, L., & Ames, D. (2005). Metabolic and endocrinological causes of dementia. *International Psychogeriatric*, 17(Suppl. 1), S79–S92.

Griva, K., Hankins, M., Thompson, D., Davernport, A., Harrison, M., & Newman, S. (2010). Mild cognitive impairment predicts 7 year mortality in dialysis. *American Journal of Kidney Diseases*, 56(4), 693-703.

Kimmel, P. L., & Peterson, R. A. (2005). Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. *Seminars in Dialysis*, 18, 91–97.

Kurella, M., Chertow, G. M., Fried, L. F., Cummings, S.R., Harris, T., Simonsick, E., Satterfield, S., Ayonayon, H., & Yaffe, K. (2005). Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *Jornal of American Society of Nephrology*, 16, 2127–2133.

Kurella, M., Chertow, G. M., Luan, J., & Yaffe, K. (2004). Cognitive impairment in chronic kidney disease. *Journal of the American Geriatrics Society*, 52, 1863-1869.

Lee, J. J., Chin, H. J., Byun, M. S., Choe, J. Y., Park, J. H., Lee, S.B., …Kim, K. W. (2011). Impaired Frontal Executive Function and Predialytic Chronic Kidney Disease, *Journal of the American Geriatrics Society* , 59(9), 1628–1635.

Madan, P., Kalra, O. P., Agarwal, S., & Tandon, O. P. (2007). Cognitive impairment in chronic kidney disease, *Nephrology Dialysis Transplantation*, 22, 440–444.

Madero, M., Gul, A., & Sarnak, M. J. (2008). Cognitive function in chronic kidney disease. *Seminars in Dialysis*, 21, 29–37.

McCarthy, R. A., & Warrington, E. K. (1990). *Cognitive neuropsychology: A clinical introduction.* London: Academic Press.

Mizumasa, T., Hirakata, H., Yoshimitsu, T., Hirakata, E., Kubo, M., Kashiwagi, M., Tanaka, H., Kanai, H., Fujimi, S., & Iida, M. (2004). Dialysis-related hypotension as a cause of progressive frontal lobe atrophy in chronic hemodialysis patients: a 3-year prospective study. *Nephron Clinical Practice*, 97, 23–30.

Monsch, A. V., Bondi, M. W., Butters, N., Paulsen, J. S., Salmon, D. P., Brugger, P., & Swenson, M. R. (1994). A comparison of category and letter fluency in Alzheimer's disease and Huntingdon's disease. *Neuropsychology*, 8, 25-30.

Murray, A. M., & Knopman, D. S. (2010). Cognitive impairment in CKD: no longer an occult burden. *American Journal of Kidney Diseases*, 56, 615-618.

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behaviour (reprinted in revised form). In R. J. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and Self-Regulation: Advances in Research and Theory*. New-York: Plenum Press.

Odagiri, G., Sugawara, N., Kikuchi, A., Takahashi, I., Umeda, T., Saitoh, H., Yasui-Furukori, N., & Kaneko, S. (2011). Cognitive function among hemodialysis patients in Japan. *Annals of General Psychiatry*. 10, 10-20.

Pereira, A. A., Weiner, D. E., Scott, T., Chandra, P., Bluestein, R., Griffith, J., & Sarnak, M. J. (2007). Subcortical cognitive impairment in dialysis patients. *Hemodialysis International*, 11, 309–314.

Pereira, A. A., Weir, D. E., Scott, T., & Sarnak, M. J. (2005). Cognitive function in dialysis patients. *American Journal of Kidney Diseases*, 45, 448–462.

Rabbitt, P. (1997). *Methodology of Frontal and Executive Function.* New-York: Psychology Press.

Riccio, C. A, Hall, J., Morgan, A., Hynd, G. W., Gonzalez, J. I., & Marshall, R. M. (1994). Executive function and the Wisconsin Card Sorting Test: Relationship with behavioural ratings and cognitive ability. *Developmental Neuropsychology*, 10, 215-229.

Sehgal, A. R., Grey, S. F., DeOreo, P. B., & Whitehouse, P. J. (1997). Prevalence, recognition, and implications of mental impairment among hemodialysis patients. *American Journal of Kidney Diseases*, 30, 41–49.

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, 114, 727-741.

Stivelman, J. C. (2000). Benefits of anaemia treatment on cognitive function. *Nephrology Dialysis Transplantation*, 15(Suppl. 3), 29–35.

Yaffe, K., Ackerson, L., Kurella Tamura, M., Le Blanc, P., Kusek, J. K., & Sehgal, A. R. (2010). Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. *Journal of the American Geriatrics Society* , 58(2), 338–345.