Cognitive Function in Patients With Chronic Kidney Disease: Challenges in Neuropsychological Assessments

Sabrina M. Schneider,[*,†] Jan T. Kielstein,[†] Jennifer Braverman,[*] and Marta Novak, MD, PhD[*,‡]

Summary: Cognitive dysfunction is a common symptom in patients with chronic kidney disease (CKD). In this review, we highlight the clinical relevance of cognitive impairment in patients with CKD. After a summary of the different pathophysiological components of this frequently overlooked clinical condition, we summarize and evaluate the available neurocognitive tests and reflect on their utility in everyday clinical practice. Finally, we identify future areas of research and allude to the fact that inclusion of cognitive function testing in routine clinical care of patients with CKD could be cost effective by reducing nonadherence to medication and improving quality of life, and even survival.
Semin Nephrol 35:304-310
Keywords: Cognitive impairment, cognitive dysfunction, chronic kidney disease, dialysis, neuropsychological testing

In 1847, Piorry introduced the term "uremia," describing a multifaceted clinical syndrome consisting of digestive and neurologic abnormalities secondary to renal failure and the resulting endogenous intoxication.[1] This complex clinical condition remained incurable until the advent of renal replacement therapy. Although the treatment of chronic uremia by dialysis prolongs life, in some patients for decades, it does not cure patients from chronic sequelae of uremia, a fact already envisioned and described in the early days of chronic dialysis therapy by Scribner et al.[2] Aside from anemia, sodium and fluid overload, and hypertension, Scribner et al[2] described "increased fatigability, muscle cramps, irritability and lethargy" as symptoms of uremia. Sufficient intensity of dialysis in the first two chronic hemodialysis patients was described as follows "neither patient has yet shown the relentless loss of weight and the mental deterioration which has been encountered in the past when less intensive dialysis therapy was employed."[2] Aside from an early description of neurocognitive problems, Scribner et al[2] epitomized that at least some of the alterations in cognitive function in uremia are reversible in nature. With a focus on the overwhelming cardiovascular risk in chronic kidney disease (CKD), only recently have we made progress in diagnosing and unraveling the mechanisms of neurocognitive alterations in CKD. This condition has profound effects on the quality of life, disease coping, and adherence of patients, as well as on the medical management (development and implementation of treatment strategies) of the nephrology team.

EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE OF COGNITIVE DYSFUNCTION

The number of patients suffering from CKD is increasing worldwide and exceeds 15% of the entire population in industrialized countries.[3] The need for renal replacement therapy increases year by year. Half of the patients aged 70 and older are suffering from CKD. The most prevalent underlying diseases leading to CKD are diabetes and hypertension. Impairment of cognitive function is a common finding in patients with CKD.

Cognition refers to a range of mental processes, such as concentration and attention, learning and memory, language, and executive functions (action planning, impulse control, goal setting, and so forth). In the past decade, CKD has been shown to be a risk factor for cognitive impairment. The prevalence of cognitive impairment among patients with CKD, which occur independently of the general age-related decrease in performance, increases remarkably. Cognitive impairment showed a three-fold increase compared with the healthy population.[4] Because large-scale studies are lacking, we only have estimates of the scale of the problem, likely with a high number of unreported cases suspected. Due to the slow progression of cognitive deficits they are difficult to detect. Commonly, this problem is not discovered until advanced stages of CKD are reached. However, as recent studies have shown, cognitive impairment already might be

*Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.
†Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.
‡Institute of Behavioral Sciences, Semmelweis University in Budapest, Budapest, Hungary.

Financial support: Supported by a research grant from the International Academy of Life Science (S.S.).

Conflict of interest statement: none.

Address reprint requests to Marta Novak, MD, PhD, Department of Psychiatry, University of Toronto, Psychonephrology Unit, University Health Network, 200 Elizabeth St, EN8-212A, Toronto, Ontario, Canada M5G 2C4. E-mail: marta.novak@uhn.on.ca

0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2015.06.002

Table 1. Cross-Sectional Studies of Cognitive Impairment in Patients With End-Stage Renal Disease

Study	Sample	Age, y (SD)	Tests	Results
Kurella Tamura et al,[32] 2010	383 HD (daily versus nocturnal)	HD, 51.6 (13.3)	3MS, TMT B	3MS $<$ 80: 16% of HD → cognitive impaired TMT B $\geq$ 300sek: 29% of HD → cognitive impaired
Kalirao et al,[43] 2011	51 PD, 338 HD, 101 CG	PD, 57.5 (14.8) HD, 71.2 (9.5) CG, 68.5 (9.6)	3MS, HVLT, Color Trails 2, BVMT-R, COWAT, Stroop, digit span, Clock	PD: 33.3% mild, 35.3% moderate, and 31.4% severe CI CG: 60.4% mild, 26.7% moderate, and 12.9% severe CI HD: 26.6% mild, 36.4% moderate, and 37% severe CI
Odagiri et al,[44] 2011	154 HD, 852 CG	HD, 65.1 (13.3) CG, 57.8 (12.2)	MMST	HD: 18.8% cognitive impaired CG: 6% cognitive impaired
Weiner et al,[45] 2011	125 HD (non-CVD), 75 HD (+CVD)	Non-CVD, 56.4 (18.3) CVD, 69.9 (12.9)	MMSE, TMT A + B, WMS-III,* WAIS*	CVD is associated with cognitive impairment regarding processing speed and executive functions
Post et al,[46] 2011	50 HD, 26 CG	HD, 63 (10) CG, 64 (10)	MMSE, CVLT-II, COWAT, word fluency, digit span, SDMT, TMT A + B, Stroop-Test	Memory: CG: 51 $\pm$ 10 versus HD: 43 $\pm$ 7 →significant language: CG: 49 $\pm$ 6 versus HD: 40 $\pm$ 7 → significant executive functions: CG: 42 $\pm$ 10 versus HD: 36 $\pm$ 9 → significant attention: CG: 42 $\pm$ 7 versus HD: 36 $\pm$ 7→ significant
Sorensen et al,[47] 2012	168 HD	HD, 62 (17)	COWAT, WMS- III,* TMT A + B, MMSE, NAART, CES-D, KDQOL-CF	KDQOL-CF is a poor determinant of neurocognitive performance
Schneider et al,[47] 2015	28 HD, 20 CG	HD, 54.9 (13.2) CG, 54.6 (14)	TMT A+B, digit span, ROCFT, RWT, BADS, TAP, RBMT	A single dialysis improves logical and visual memory, psychomotor speed, activity planning (executive functions) and concentration

Abbreviations: HD, hemodialysis patients; PD, peritoneal dialysis patients; CG, control group; CVD, cardiovascular disease; 3MS, Modified Mini Mental State Examination; BVMT-R, Brief Visuospatial Memory Test-Revised; SDMT, Symbol Digit Modalities Test; COWAT, Controlled Oral Word Association Test; WAIS, Wechsler Adult Intelligence Scale; CVLT-II, California Verbal Learning Test-II; WMS-III, Wechsler Memory Scale-III; NAART, North American Adult Reading Test; CES-D, Center for Epidemiological Studies Depression Scale; KDQOL-CF, Kidney Disease Quality of Life Cognitive Function; BADS, Behavioral Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioral Memory Test; ROCFT, Rey-Osterrieth Complex Figure Test; RWT, Regensburg Word Fluency; TAP, Test Battery for Attentional Performance.

present in the early stages of CKD. In a community-based, cross-sectional study, Elias et al[5] found that global performance and specific cognitive functions are affected negatively early in CKD. Interestingly, not only decreased GFR, but increased urinary albumin/creatinine ratios have been associated independently with faster deceases in cognitive function.[6] Moreover, moderate renal impairment is associated with an excess risk of incident dementia among individuals in good to excellent health.[7] Therefore, appropriate screening tools need to be used to detect and counteract the cognitive decrease in performance at an early stage of CKD. Table 1 shows a brief outline of studies that found a significant performance loss of cognitive function in patients with CKD5D (ie, patients on chronic dialysis).

CHALLENGES OF LIVING WITH CKD

The diagnosis of advanced renal impairment and the need for renal replacement therapy changes a patient's life dramatically. It requires not only an increased logistical and organizational effort on behalf of patients to manage the demands of dialysis and self-care, but it also brings along significant psychosocial stressors.[8] This demanding lifestyle requires good coping skills with stressors and psychological adaptability/flexibility, as well as self-efficacy. Patients on dialysis have to face a variety of challenges: continued confrontation with disability and death, impaired physical performance and endurance, dependency on medical equipment and nursing staff, complex drug prescriptions and strict diet plans, lack of freedom, and time constraints.[8] Nonadherence to medications and diet restrictions can lead to higher mortality rates. In patients with chronic diseases, nonadherence rates could be as high as 50% because it is difficult to integrate those restrictions into everyday life.

It is essential for successful adherence to treatment that patients are involved in the treatment plan, understand "key rules" of disease management, and can apply them in their everyday life. In this context self-