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 © 2015 Elsevier Inc. All rights reserved.

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 al2 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 al2 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
present in the early stages of CKD. In a community-based, cross-sectional study, Elias et al 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 decreased GFR, but increased urinary albumin/creatinine negatively early in CKD. Moreover, moderate renal impairment is associated with an excess risk of incident dementia among individuals in good to excellent health. 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. 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. 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-
management is essential. This includes skills and behavior that ensure the correct use of medication and dietary requirements, as well as the development of cooperative relationships with the nursing team. Patients on dialysis take a median of 19 tablets a day. For most of the patients, the prescriptions may even change between dialysis and nondialysis days, such as for antihypertensive medications. Moreover, phosphate binders, which comprise 50% of all tablets in CKD5D patients, ideally should be adapted to the intake of phosphorous, which might change from meal to meal. It cannot be assumed that these complex and changing prescription patterns are implemented by the patient himself/herself easily. To meet the challenge of adherence, spouses, family, and nursing staff in assisted-living facilities of dialysis units address intake of medication when patients have failed. To pave the way for better self-management of the patient, executive cognitive function should be measured and addressed because cognitive dysfunction in patients with CKD represents a major barrier to effective self-management.

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT

The pathophysiological mechanisms leading to cognitive impairment in CKD are multifactorial and still are not understood clearly. Potential causes of cognitive deficits in CKD include vascular damage from disease processes leading to CKD (such as diabetes and hypertension), physiological changes stemming from CKD (such as uremia and depression), and side effects of CKD therapies (such as antihistamines, opioids, aluminum, and intradialytic hypotension). The variety of factors also might explain why we need multifactorial intervention programs to manage the problem of cognitive deterioration. A representative figure showing the underlying factors are shown in Figure 1.

**Figure 1.** Potential causes of cognitive impairment in CKD. ADMA, asymmetric dimethylarginine.

Underlying Disease and Comorbidity

It already has been established that underlying diseases that cause CKD (mostly arterial hypertension and diabetes) lead to cognitive impairment, mainly owing to vascular damage. In addition, impaired renal function itself increases the risk of vascular calcification. This is supported by the six-fold, age-adjusted, relative risk of stroke among patients with CKD5D compared with the general population. Dialysis patients also have a prevalence of asymptomatic silent cerebral infarction that is four to five times higher than in age-matched and sex-matched controls; silent cerebral infarctions are predictors for future cardiovascular events.

Dialysis patients also have a higher prevalence of depression, which may contribute to decreased cognitive performance. A number of studies have sought to examine the relationship between depression and cognitive function in patients with CKD and end-stage renal disease. A study by Agganis et al examined the relationship between depression and cognitive function specifically in hemodialysis patients (n = 241). A total of 23.7% of participants had significant depressive symptoms. Participants with greater depressive symptoms performed significantly worse on tests assessing processing speed, attention, and executive function, including Trail Making Test B (P = .02) and digit-symbol coding (P = .01). The study pointed to the vulnerability of the dialysis patients with concurrent depression and cognitive impairment, possibly requiring greater health care resources and being more resistant to treatment. The investigators also commented on the underlying neuro-pathology of both conditions. They stated that the increased risk of vascular disease in hemodialysis patients likely puts them at an increased risk of white matter disease, which potentially leads to both cognitive decline and depression.

As another often underdiagnosed and undertreated entity, sleep disorders also are very common in patients with CKD. They can impact cognitive function (concentration, memory) in everyday life and lead to daytime fatigue and sleepiness, which also can affect cognitive abilities directly. Sleep-disordered breathing (sleep apnea), characterized by repeated arousals from sleep and intermittent hypoxemia, is common in patients with CKD, affecting up to 50% of patients. There have been only a few studies on the relationship between sleep-disordered breathing and cognition in the setting of CKD. In one study involving 169 patients with CKD stages 4 to 5, sleep-disordered breathing was diagnosed in 83 (49.1%) individuals. This sleep-disordered group also was found to have significantly lower scores on tests measuring verbal memory, working memory, attention, and psychomotor speed.
Another recent study analyzed whether any seasonal variation exists regarding cognitive function, depressive behavior, sleep disorders, and quality of life in 66 enrolled CKD5D patients. Measurements were assessed first in January and then in July. Quality-of-life scores were higher in July versus January, and depression scores were lower in July versus January. Sleep quality and cognitive function did not show seasonal variability in these patients. Further research is needed to understand the relationship between sleep disorders, depression, and cognitive impairment in the CKD patient population. This research direction will become even more important as our population ages, and obesity, diabetes, and CKD become even more common.

Uremia-Associated Factors

The second component of cognitive dysfunction are the biochemical alterations associated with uremia. Uremia has multiple associations with cognitive impairment, including but not limited to the several hundred uremic toxins and resultant diseases such as anemia. Furthermore, newer uremic toxins such as asymmetric dimethylarginine have been found to affect neurologic function severely. The CKD mineral and bone disorder of metabolism of calcium, phosphate, parathyroid hormone, fibroblast growth factor-23, and fetuin contributes to the acceleration of vascular calcification. Alterations in vitamin D metabolism is one of the key features of CKD mineral and bone disorder. Vitamin D deficiency has been shown to contribute to depression and memory disorders.

Beyond disturbances of autoregulation of the kidney, autoregulation of cerebral perfusion also is disturbed and also may compromise the oxygen supply to the brain. Anemia can be an additional factor, the correction of anemia by erythropoiesis-stimulating agents is one of the more well-studied interventions in CKD. Administering erythropoiesis-stimulating agents is one of the more well-studied interventions in CKD. Administering erythropoiesis-stimulating agents can lead to a slight improvement in cognitive performance. In addition to the correction of anemia, iron in the brain is important for efficiency and attention, has an influence on the signal transmissions between neurons, and may result in loss of memory disorders. It has been shown to improve memory function in women of childbearing age with healthy kidneys, as well as in a geriatric patient population (measured by the Mini Mental State Exam).

Treatment-Associated Factors

The third component that contributes to the cognitive impairment of patients with CKD is treatment-related factors. There are nonpharmacologic components, such as an impairment of cerebral blood during dialysis, as well as the side effects of pharmacologic treatment.

The most prominent medications associated with cognitive impairment in CKD5D are H1-receptor antagonists and opioids. If possible, these compounds should be reduced or avoided. Whether newer, more specific antihistamines are associated with fewer effects on neurocognitive function still is unclear. It also is important to consider the potentially reversible components of cognitive dysfunction in CKD. The ultimate proof for both the effect of uremia and the hypothesis of a reversible component of cognitive dysfunction in CKD(5D) would be the fact that, as some studies have suggested, it can be improved by renal transplantation. However, frequent hemodialysis (neither in daily nor in nocturnal dialysis) failed to improve executive function or global cognition. Yet a single dialysis session is able to improve logical and visual memory as well as executive function.

NEUROPSYCHOLOGICAL TESTING OF COGNITION

The diagnosis of cognitive impairment is made by the use of comprehensive neuropsychological test batteries. These test batteries cover a wide variety of functional areas of the brain (memory, attention, perception, language, executive function, and so forth). They are resource- and time-consuming to administer, and challenging to use in routine clinical care due to the expenses and organizational aspects of testing.

There are no neuropsychological tests that are designed exclusively for patients with CKD and that are used on a regular basis in routine nephrological care. Table 2 summarizes the most frequently used tests for neuropsychological profiling of patients with CKD. A comprehensive neuropsychological assessment could be a major challenge. Mostly, it implies a long duration of testing with a minimum of 2 hours,

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Memory Scale (WMS)</td>
<td>75 min</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Test (ROCF)</td>
<td>30 min</td>
</tr>
<tr>
<td>Benton test</td>
<td>10-20 min</td>
</tr>
<tr>
<td>California Verbal learning Test (CVLT)</td>
<td>30-40 min</td>
</tr>
<tr>
<td>Trail Making Test A (TMT A)</td>
<td>3 min</td>
</tr>
<tr>
<td>Trail Making Test B (TMT B)</td>
<td>5 min</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test (WCST)</td>
<td>20-30 min</td>
</tr>
<tr>
<td>Behavioral Assessment of Dysexecutive Syndrome (BADS)</td>
<td>60 min</td>
</tr>
<tr>
<td>Symbol Digit Modality Test (SDMT)</td>
<td>20 min</td>
</tr>
</tbody>
</table>
which is intense for both patients and clinicians. Instead, short screening tests can be used; if they indicate a remarkable deficiency, they can trigger further diagnostic investigations. The following are some commonly used short screening tests for cognitive function in CKD.

**Mini–Mental State Examination**

The most widely used method for the initial assessment and progress evaluation in CKD is the Mini-Mental State Examination (MMSE), developed by Folstein et al in 1975. It is commonly used for the diagnosis and treatment of dementia and Alzheimer’s disease, as it is simple and requires only little time to implement. By using an interview technique, the MMSE gathers orientation, memory (visual and auditory), attention, language comprehension, and visuoconstruction on a minimum dimension. It thus allows only a general, global statement of the cognitive performance. There are no age-related norms available because of the low requirements of the test. The test is subject to strong criticism and is considered to be unsuitable for early detection of dementia or mild cognitive impairment.

**Montreal Cognitive Assessment**

Another screening method to detect cognitive dysfunction is the Montreal Cognitive Assessment (MoCA), which was developed in 1996 by Nasreddine et al. The test assesses several cognitive domains such as memory, attention, orientation, executive functions, language, visuoconstructional skills, conceptual thinking, and calculations. The test is available in several different languages. It takes 10 to 15 minutes to administer the test, which makes it very efficient for use in daily hospital routine. Tiffin-Richards et al compared the MMSE and the MoCA in a study from 2014 and found that the MoCA represents a suitable cognitive screening tool for hemodialysis patients. With good sensitivity and specificity levels the MoCA discriminated better than the MMSE between cognitive impaired and cognitive healthy dialysis patients.

**Trail Making Test B**

When cognitive function is impaired, not every functional area (memory, executive functions, attention, speech, and so forth) is affected equally. However, for patients with CKD, intact executive functions are most important as they contribute to control and regulation of behavior. Executive functions are considered to be metacognitive processes, defined as controlling the flexible coordination of several subprocesses to achieve defined objectives. One such instrument to provide a first impression of executive functions and mental flexibility is the Trail Making Test B (TMT B). It was developed in 1944 by Reitan for the US Army for intelligence testing and today is a proven diagnostic tool in the clinical setting for evaluation of cognitive dysfunctions in brain damage. The task in TMT B is to connect numbers and letters in an alternate sequence (1-A-2-B-3-...). The time (number of seconds) required to complete the task is scored. Lower scores indicate better cognitive function. If there is no impairment, then the test is completed after approximately 1 minute. In addition, in relation to studies with kidney patients, the TMT B shows strong explanatory power regarding a loss of cognitive function. Figure 2 shows a comparison between healthy subjects and TMT B measures of

![Figure 2. Comparison of study results using the TMT B test. Circles, CKD patients; squares, healthy controls. TMT B was measured in seconds, age was measured in years. Reprinted with permission from Tombaugh.](image-url)
CKD5D patients from several studies. The data from the healthy sample were taken from the meta-analysis by Tombaugh. In contrast to the MMSE, the TMT B not only detects impairment in CKD5D, but also in the early stages of CKD. In one study using TMT B, patients with CKD stage 3 needed more than twice the time of a control group to complete the test.

Because of its sensitivity, the TMT B is able to detect cognitive performance loss already in an early phase of the disease. This has been shown in patients with CKD in the CRIC study. Compared with the performance in the Modified Mini-Mental State Test, patients with CKD showed a much greater decrease of TMT B performance over the stages of CKD. With decreasing renal function (glomerular filtration rate, ≤60 mL/min to >30 mL/min), the mean Modified Mini-Mental State Test value decreased by only a few points (from 92.8 to 91.0, with a maximum value of 100). The mean TMT B value increased significantly (increasing value represents worse performance): from 143.3 to 170.0 seconds. Only valid test performances (increasing value represents worse performance): from 100). The mean TMT B value increased significantly (increasing value represents worse performance): from 143.3 to 170.0 seconds. Only valid test performances were used, meaning that test performance was achieved when the TMT B was completed within 5 minutes. It should be noted that a high number of patients were not able to perform the TMT B within this time limit. The study by Kurella Tamura et al indicated that this was true for approximately 29% of the subjects. In another study by Rocco et al this was true for only 23.5%.

However, because of the short implementation time of less than 5 minutes and its simplicity and sensitivity to detect deficits, the TMT B is an excellent tool to provide a first impression on available cognitive functions in patients with CKD5D. If test results are below average, in-depth neuropsychological diagnostics to evaluate the whole extent of cognitive impairment are indicated.

CONCLUSIONS

Cognitive impairment is common in patients with chronic kidney disease but often is under-recognized and underdiagnosed. This lack of awareness and the absence of a magic bullet (usually meaning pharmacologic treatment) are key components for the undertreatment of this condition. The importance of addressing cognitive function is underscored by the essential role of cognition in good medical outcomes, the basis for adherence to medication prescriptions, dietary advice, and fluid restrictions. Therefore, we contend it is important to include a brief neuropsychological assessment in the routine medical care of patients with CKD. Short tests are necessary to screen patients for first signs of cognitive deterioration. Tests for executive functions (eg, TMT B), should be preferred to the MMSE, which is used only to screen for dementia. Executive cognitive function underlies the ability to plan and control behavior and manage complex situations. The development of an approach that combines both medical and psychological aspects of disease is extremely valuable to develop optimal management strategies.

REFERENCES


