

Cognitive alterations in chronic kidney disease: an update

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ABSTRACT

Impairment of cognitive functions occurs frequently in chronic kidney disease (CKD). The conditions most associated with this decline are depression, *delirium*, mild cognitive impairment and dementia. The mechanisms involved have not been established yet, but some factors, as neuronal damage by uremic toxins, cerebrovascular ischemic lesions, oxidative stress, chronic inflammation, anemia, hyperhomocysteinemia, the endothelial dysfunction may play a critical role. The neuropsychological performance improves with the initiation of dialysis, although some cognitive dysfunctions remain even after treatment, especially in the areas of attention, cognitive flexibility, memory and learning. Kidney transplantation may improve and even reverse some cognitive deficits detected in the dialysis period, despite some compromise in verbal memory and executive functions remain after transplantation. The diagnosis of cognitive decline in patients with CKD may have an important impact on the management and prognosis. This paper presents an update on the decline of cognitive function in patients with CKD.

Keywords: cognition disorders; dialysis; kidney failure, chronic; kidney transplantation.

INTRODUCTION

The term “cognition” covers aspects of brain function related to various domains such as attention, language, memory, learning, reasoning, decision making, and problem solving. Cognitive impairment can be understood as a decline in patient baseline functions possibly at a level severe enough to interfere with

the performance of activities of daily living by the individual. Cognitive involvement and dementia are commonly seen in patients with chronic kidney disease (CKD), particularly in subjects with advanced stage disease, but are poorly recognized by nephrologists.¹ However, individuals with disease in any stage are susceptible to cognitive disorders² associated with increased risk of death, lower levels of compliance to proposed treatment, higher incidence of cerebrovascular disease, and prolonged hospitalization.^{1,3,4}

The identification of cognitive deficits may produce positive impacts on patient outcome, particularly when the impairment is secondary to potentially treatable conditions such as depression and delirium.¹ The prevalence of depression symptoms in patients with end-stage renal disease (ESRD) ranges between 20% and 25%,⁵ ranking them second only to hypertension in the roster of comorbidities observed in patients with ESRD.^{5,6}

Delirium is a syndrome characterized by rapid onset of alternating consciousness and cognitive function alterations caused by the physiologic dysfunctions introduced by a medical condition.⁷ Psychomotor and sleep architecture disorders are commonly seen in patients suffering from delirium.³ The predisposing factors for delirium in patients with CKD include sensory loss, cerebrovascular disease, subclinical metabolic disorders, and polypharmacy. Hospitalization and alterations in the metabolism of certain

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drugs (opioids, psychotropic drugs, antibiotics, antiviral medication) and their toxic metabolites also boost occurrences of delirium.^{3,8}

In addition to potentially reversible conditions, mild cognitive involvement and dementia have also been correlated with mental function decline. CKD has been strongly correlated with vascular dementia in particular.^{9,10} When compared to the general population, the prevalence of cognitive impairment is higher in individuals with renal failure and even more significant in patients on dialysis.¹¹ In qualitative terms, mild cognitive involvement is similar to dementia, although its impact on the performance of activities of daily living is not as significant as the one produced by dementia.

Dementia appears to complicate the management of patients with ESRD and has been correlated with poorer prognosis.¹ Patients with dementia present deficits in at least two of the following cognitive functional areas: memory, executive function, attention, visuospatial skills, speed of information processing, and language. Signs of decline in lower functional levels materialize as compromised performance in various areas of the affected individual's life, such as work and interpersonal relationships.⁷ Murray *et al.*¹² looked into the neuropsychological performance of 338 hemodialysis patients through memory, language, and executive function tests and found that over a third of the subjects had three times the prevalence of dementia estimated for the general population.

However, dementia is not limited to cases of advanced kidney disease. Patients initially diagnosed with moderate renal disease without dementia had higher incidences of vascular dementia over six years of follow-up¹⁰ in association with higher serum creatinine levels.

Given the context, this paper aims to present an update on the most frequent cognitive alterations seen in CKD patients and further emphasize the relevance of the topic in nephrology care.

WHAT ARE THE MECHANISMS INVOLVED IN THE COGNITIVE DYSFUNCTIONS OF PATIENTS WITH CKD?

Most studies suggest that CKD severity and progression of cognitive decline go hand in hand.¹³ Feng *et al.*¹⁴ followed a group of patients for four years and correlated the estimated glomerular filtration rate (GFR) decreases in CKD patients aged 55 years and older with greater functional and global cognitive decline.

Helmer *et al.*⁸ studied a cohort of 7,839 patients aged 65 and older and did not report increases in the risk of cognitive impairment or dementia in association with low estimated GFR. In the seven-year follow-up, however, more rapid declines in the GRF were associated with global cognitive impairment and increased incidence of vascular dementia. In any case, other recent studies comparing patients with CKD and subjects without renal disease have confirmed the correlation between all stages of CKD and greater risk of cerebral function impairment.^{2,15,16}

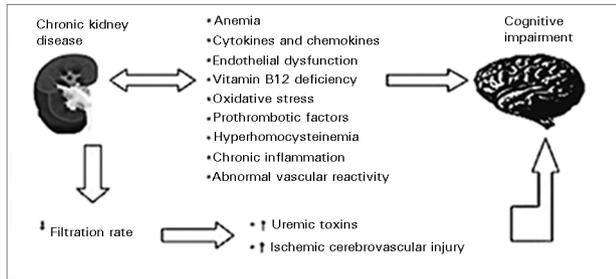
The mechanisms involved in this process have not been completely elucidated, but research indicates that, in addition to neuronal damage induced by uremic toxins, the risk of cognitive involvement and dementia in these patients may be due to the high prevalence of symptomatic and asymptomatic brain ischemia.² This vascular mechanism may explain the association between the risk factors affecting both the brain and the kidneys and its potential exacerbation in renal disease.⁸

Oxidative stress,^{17,18} immuno-inflammatory processes,¹⁸ anemia,^{19,20} hyperhomocysteinemia,²¹ and vitamin B12 deficiency²¹ may be involved in neurocognitive performance decline. CKD patients on hemodialysis have more prothrombotic factors,^{22,23} endothelial dysfunction,^{18,22-24} abnormal vascular reactivity,²⁴ atherosclerosis,²⁵ and cardiovascular events.²⁵ By their turn, renal transplant patients have particularly higher levels of urinary chemokines and cytokines, which may serve as a sign of graft prognosis.²⁶ Figure 1 shows a schematic representation of the pathophysiological mechanisms related to cognitive dysfunction in CKD patients.

DIALYSIS AND COGNITION

Although underdiagnosed, the prevalence of cognitive impairment is significant among individuals with CKD on dialysis.¹⁶ A recent study found that patients on dialysis performed more poorly than the general population on tasks assessing executive function, a finding correlated with vascular disease and vascular risk factors.²⁷ Normal scores on the Mini Mental State Examination (MMSE), the main test used for cognitive screening in clinical practice,²⁸ do not rule out cognitive involvement, as individuals scoring high in the MMSE may perform poorly on more comprehensive neuropsychological tests.²⁷

Figure 1. Mechanisms involved in cognitive impairment of patients with chronic kidney disease (CKD).



Individuals on hemodialysis had low scores in logical reasoning, verbal learning, motor skills, verbal fluency, visuospatial memory tests.²⁹ The risk of multi-infarct dementia in elderly patients on hemodialysis appears to be seven times greater than in the general population, possibly due to increased prevalence of comorbidities such as diabetes mellitus, atherosclerosis, and hypertension in this patient group.³⁰

Similarly to hemodialysis patients, most individuals on peritoneal dialysis have moderate to severe cognitive impairment, especially in areas related to executive function, decision-making, and capacity for abstraction. Such impairment may interfere with the self-administration of dialysis and compliance with complex medication regimens.³¹ Patients doing well on hemodialysis, in good nutritional condition, and clinically stable do not appear to differ significantly from their counterparts in equal condition on peritoneal dialysis.^{16,32}

Dialysis processes directly contribute to cognitive involvement by inducing brain ischemia. Acute decreases in intravascular volumes and fluid exchanges occurring during dialysis sessions may cause edema and diminish cerebral perfusion.¹⁶ More specifically, patients with acute kidney injury are more susceptible to cerebral hypoperfusion during intermittent hemodialysis than patients with ESRD.³³

Neuropsychological performance tends to improve after the introduction of dialysis, and patients on dialysis have lesser cognitive deficits than untreated individuals and patients with uremia. Short-term memory improves with maintenance hemodialysis,³⁴ despite the possible persistence of other cognitive dysfunctions in the domains of attention, cognitive flexibility, memory, and learning.³⁴

COGNITIVE FUNCTION AND KIDNEY TRANSPLANTATION

Studies have described memory improvements after renal transplantation and reversion of some neuropsychological deficits, memory impairments in particular, detected during dialysis.³⁵ Although in a study published in 1984 Fennel *et al.*³⁶ indicated that improvements in cognitive performance were not sustained in children and adolescents, the benefits of kidney transplantation do not seem to be transient or limited to the early stages of the post-transplant period, and may persist for at least a year after the procedure.^{37,38}

Improvements in cognition may be observed in intelligence tests after renal transplantation, both in adults and children.^{35,39} Nevertheless, after transplantation patients may still have to endure deficits in verbal memory and executive function.⁴⁰ Despite the improvements in the metabolic factors associated with CKD, cognitive impairment is thought to persist as a consequence of the patients' remaining clinical comorbidities.⁴⁰

Evidence suggests that kidney transplantation and dialysis positively impact the cognitive status of patients with CKD. However, the literature does not support the prescription of dialysis based solely on the presence of cognitive impairment. Patients with chronic kidney disease might benefit from therapies devised specifically to improve cognitive performance, such as cognitive rehabilitation, but no specific studies have been carried out on the matter. Likewise, little research has been done on the efficacy and safety of drug therapies for dementia and mild cognitive impairment in the context of kidney disease; management, therefore, must be individualized.

CLOSING REMARKS

Depression, delirium and dementia are commonly seen in any stage of CKD, and are generally associated with complications and poorer prognosis.¹² CKD appears to be a risk factor for cognitive impairment and dementia. Renal disease severity walks hand in hand with loss of neurocognitive function.⁹

Although evidence suggests that hemodialysis improves cognition in patients with CKD,⁴ a significant, yet underestimated, portion of the individuals on hemodialysis presents moderate to severe cognitive impairment. There appears to be no difference in the cognitive disorders affecting patients with CKD treated with hemodialysis or peritoneal dialysis.¹⁶

The identification of patients with cognitive impairment is an important step in the process to improve quality of life and mitigate the morbidities associated with this condition. The ideal time to assess cognitive function and the choice of screening scale must take the patient's clinical status into account.¹ Evaluations should take little time, as is the case with the administration of the MMSE,²⁸ the best known and studied screening test for dementia. However, neuropsychological testing requires more time and may be needed in more thorough investigations of the cognitive domains.

The reasons behind the onset of cognitive impairment in patients with CKD are yet unclear, but evidence indicates the involvement of factors such as inflammation, endothelial dysfunction, atherosclerosis, oxidative stress, anemia, hyperhomocysteinemia, and uremic toxins.^{18,21,23} More studies are needed to shed light on the possible strategies that may be used to delay or prevent the onset of cognitive impairment in patients with chronic kidney disease.

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