Cognitive Dysfunction in Chronic Kidney Disease Patients: Time to Prevent

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Abstract
Mild cognitive impairment (MCI) is a neurocognitive deterioration of at least one of the following six cognitive domains in humans: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition. Patients with chronic kidney disease are at an increased risk of developing this disorder, with serious implications for the patient, family, and society. In this article, we aim to increase awareness of the disorder and summarize the existing evidence on the topic.

Keywords: Cognitive Dysfunction; Kidney Failures, Chronic; Renal Dialysis

INTRODUCTION
Mild cognitive impairment (MCI) is a neurocognitive deterioration that affects various cognitive domains, in which the individual remains functionally independent.[1] It is a part of the spectrum in which the opposite limit is dementia. Neurocognitive deterioration affects six cognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition.[2] As the individual maintains independence, it is considered mild.[1]

MCI in patients with chronic kidney disease (CKD) ranges from 10% to 40% or 20 %– 60%,[3-5] depending on the method used to diagnose MCI and CKD stage, as cognitive functions worsen with declining kidney function. It is interesting to note that the relationship between the kidney and brain is bidirectional, as kidney function also declines faster, for instance, in patients after stroke.[3]

The interrelationship between the kidney and brain is particularly relevant in patients with CKD stage 5, specifically in patients on dialysis, and more frequent in hemodialysis (HD).[6] One of the first studies performed in 2006 evaluated 374 patients on HD, and showed that most patients had cognitive abnormalities, with 50% having mild or moderate cognitive impairment, 37.3% with dementia, and only 12.7% with normal cognitive function.[7] In a more recent study, performed in 2019, including 676 HD patients, those with cognitive impairment had a 68% higher adjusted HR for mortality.[8]

This problem is complex and has serious implications for patients, families, and society. The high importance and poor recognition of cognitive impairment in CKD leads nephrologists, geriatricians, neurologists, pharmacologists, and others, to create a collaborative network using the umbrella of the European Union, the CONNECT - Cognitive decline in Nephro-Neurology, aimed at coordinating research in this area (https://connectcost.eu/).

In this article, we discuss the pathophysiology and potential interventions for minimizing MCI in patients with CKD.

PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT
There are two main hypotheses for the interrelationship between CKD and MCI: the vascular hypothesis and the neurodegenerative hypothesis.[9,10]

Impaired cerebral hemodynamics (high volume blood flow, low vascular resistance system) lead to microvascular injury, and cerebral small vessel disease due to increased arterial stiffness is believed to contribute to MCI in CKD. It is accompanied by silent brain infarctions, white matter lesions, cerebral microbleeds, and cerebral atrophy, all of which are important causes of cognitive impairment.

As the vascular hypothesis is insufficient to explain and assemble all the risk factors involved in MCI in CKD patients, the additional neurodegenerative hypothesis grew, relating brain injury to uremic toxins, disturbed blood-brain

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barrier, and others[9] that increase neuroinflammation, with detrimental consequences.

The pathophysiology of cognitive impairment in CKD is complex,[10] and most risk factors play a role in both the vascular and neurodegenerative hypotheses of MCI in CKD.

Age

Patients with CKD are usually aged and have multiple comorbid conditions, multiple cardiovascular risk factors and consequently, a high prevalence of cardiovascular diseases.[5] This causes CKD patients to have a high incidence of cardiovascular events, such as transient ischemic attack or stroke. Perhaps these are the reasons for the fact that CKD patients present with the same cognitive deficits associated with cerebral disease in the general population, which are abnormalities in processing speed and executive functions.[11]

Diabetes and High Blood Pressure

Examples of frequent cardiovascular risk factors in CKD include diabetes, hypertension, and dyslipidemia. All these cardiovascular risk factors are also risk factors for cognitive decline. Diabetes is known to be associated with dementia, and the length and level of hyperglycemia are associated with dementia.[12] It is also known that the cerebrovascular system is vulnerable to microvascular injury in systemic hypertension, and that high blood pressure is associated with cognitive impairment.[13]

Systemic Inflammation & Endothelial Dysfunction

The inflammatory status of CKD accelerates atherosclerosis, leading to a high incidence of both cardiovascular and cerebrovascular diseases, as atherosclerosis may impair cerebral blood flow. Endothelial dysfunction is almost universal in CKD,[14] and is caused by systemic inflammation, although oxidative stress, hypercoagulability, and other factors may also play a role.

Endothelial dysfunction is accompanied by an increase in blood-brain-barrier permeability. This leads to leakage of uremic toxins across the blood-brain barrier into the brain tissue, causing not only a detrimental effect on vasculature, but also inducing neuroinflammation in CKD patients,[9] through suppression of the glymphatic system. The glymphatic system, formed by astroglial cells, is very important in this setting, as it is the waste clearance system in the central nervous system.

The neurodegenerative hypothesis has been linked to an increase in neuroinflammation. Recently, in a randomized controlled study published in 2019, Tardif and colleagues randomized 4745 patients 30 days after myocardial infarction to receive an anti-inflammatory drug (low-dose colchicine) or placebo. Patients in the drug arm had fewer central nervous system events, such as stroke, compared to patients in the placebo.[15] This study supports the belief that neuroinflammation is related to MCI.

Nevertheless, other studied measures to decrease inflammation, such as vitamin B or folate supplementation, which reduce homocysteine levels, or randomized controlled studies with vitamin E (which is an antioxidant) or vitamin D did not result in better cognition or showed a relevant effect on cognition.[9,15]

Sleep Disturbances

Sleep disturbances are common in CKD patients, and range from reduction in total sleep time, insomnia and/or sleep fragmentation, daytime somnolence due to central sleep apnea or restless legs syndrome. Any of those affects nearly 50% of patients with early CKD and up to 80% of patients in dialysis.[16] The mechanisms are multifactorial, and, in theory almost the same for MCI.

As the glymphatic system works better during sleep, there is an increase in neuroinflammation in CKD,[9] linking sleep disorders to MCI.

CKD-MBD Syndrome

Calcitriol deficiency is one of the first events in CKD--mineral and bone disorders (CKD-MBD) syndrome, a clinical syndrome almost universal in CKD stage 5, which has detrimental consequences, such as high mortality, cardiovascular events, and fractures.[17] In a paragraph, high phosphate levels and the reduction of the fractional excretion of phosphate in CKD are central and lead to an increase in fibroblast growth factor 23 (FGF-23) to promote phosphaturia. FGF-23 also inhibits calcitriol synthesis, which, in turn, reduces phosphate and calcium absorption. Both hypocalcemia and hyperphosphatemia are strong stimuli for PTH synthesis, which can result in secondary hyperparathyroidism.[17]

Therefore, CKD-MBD may, theoretically, be related to cognitive disturbances. Recent studies have associated FGF23[18] and its co-receptor, klotho,[19] with dementia, and PTH, which is considered a uremic toxin, might influence brain function. Phosphate is also toxic to endothelial cells, increasing endothelial damage and dysfunction.

Uremic Toxins

Nephrologists know that later stages of CKD are related to brain changes. For instance, encephalopathy can be a late complication of uremia, a rare complication due to the common use of kidney replacement therapy.

According to the European Uremic TOXin workgroup of the European Society of Artificial Organs (EUTOX), approximately 9% of uremic toxins are neurotoxic and may influence brain function.[20] The maintenance of these toxins over time, has detrimental effects on cognition, as the duration of CKD, rather than the severity of renal impairment, correlates with cognitive impairment.[20] Although patients on dialysis have more cognitive dysfunction when compared to patients with early CKD stages, the levels of uremic toxins are higher in dialysis patients and the

duration of CKD is usually longer in dialysis patients, when compared to non-dialysis CKD. Probably these factors contribute to this correlation.

These toxins can be small water-soluble compounds, which are eliminated by dialysis, but there are also protein-bound compounds and middle molecules (such as PTH, already mentioned),[21] which are poorly cleared by dialysis, and are potential contributors to MCI.

CKD-Associated Anemia

Iron deficiency and anemia are common in CKD, and both are risk factors for MCI.[2] Many factors are associated with anemia in CKD, but the presence of inflammation is one of the contributors to the high prevalence of anemia, through hepcidin.[22] Other factors, such as absolute iron deficiency, reduced erythropoietin synthesis, poor bone marrow responsiveness, and shortened red blood cell survival are important contributors to this problem. Anemia has been linked to MCI and stroke.[2] It Increases cerebral blood flow, causing an upsurge in the distribution of uremic toxins to the brain, and reduces oxygen delivery to the brain, which has a detrimental effect on brain metabolism.

Polypharmacy

Polypharmacy (≥5 drugs) is frequent in CKD patients, both in non-dialysis and dialysis patients, and is estimated to occur in 69% of patients.[23] It has direct and indirect costs for patients and is related to lower health-related quality of life.[24] Those patients have higher prevalence of depression, anxiety, and mental disability. As such, chronic antidepressant prescription is very frequent in CKD patients,[25] such as other psychotropic agents, anticholinergic or GABAergic drugs, opioids, and others. All those have negative effects on cognition, as published recently in a review article.[26]

Dialysis

Peritoneal dialysis (PD) seems to be associated with less cognitive impairment than hemodialysis (HD).[27] The reasons advanced by experts are related to a gentle hemodynamic shift and the lack of need for heparin (reducing microbleeds).[28] Nevertheless, the prevalence of MCI in PD patients remains high, although the risk of MCI is higher in HD patients than in PD or transplant patients. Flinday and colleagues measured cerebral blood flow with doppler in 97 individuals and showed that the mean flow velocity declined during HD. The subgroup of patients with a greater decrease in blood flow, presented with worse cognitive function.[29]

In contrast to PD, HD can lead to intradialytic changes in blood pressure, causing intradialytic hypotension (and, in some cases, hypertension), which has been linked to cerebral atrophy.

INTERVENTIONS

Interventions aimed at slowing cognitive decline in patients with CKD are limited, therefore it is very important to identify and minimize the risk factors for the MCI in CKD.[10]

Age and genetics are non-modifiable risk factors for MCI, and currently there are no interventions for it. Modifiable risk factors need further attention from nephrologists and should be assessed and treated accordingly.

CKD patients are a very high-risk population for cardiovascular events, and patients with CKD <30 mL/min/1.73 m^2 are considered a priority for advice and management for all cardiovascular risk factors, with a level of evidence of IC.[30] Interventions for general cardiovascular risk factors for declining the risk of MCI are very important, as for general population. Lifestyle modifications, such as exercise, smoking eviction, and reducing salt intake are very important.

Dyslipidemia

Dyslipidemia is a topic for controlling cardiovascular risk factors in the general population. The European Society of Cardiology (ESC) guidelines from 2019 recommend the use of statins or statins/ezetimibe in stage 3 – 5 CKD patients (level of evidence IA), although naive patients already on dialysis, with no cardiovascular events, should not initiate treatment (level of evidence IIIA). Nevertheless, patients should not stop statins or statins/ezetimibe after initiating dialysis, if already under treatment.[30]

Blood Pressure

Control of blood pressure is also very important. ESC guidelines recommend lowering systolic blood pressure in diabetic and non-diabetic kidney disease to a value of 130-139 mmHg (level of evidence IA),[31] with a combination of angiotensin-converting enzyme inhibitor (ACEi) / angiotensin receptor blocker (ARB) plus calcium channel blocker (CCB) or diuretics, and this recommendation is still performed in the latest (2023) ESH Guidelines.[32] After the SPRINT trial[33] (a randomized control study for comparison between intensive blood pressure control and standard blood pressure control) had showed a benefit in terms of cardiovascular events and mortality for intensive blood pressure control, the SPRINT MIND study was published in 2019, which also showed that intensive blood pressure control significantly reduced the risk of MCI, with an HR of 0.81.[13] Based on these studies, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend to lowering systolic blood pressure in patients with CKD to less than 120 mmHg (with level evidence IIB),[34,35] preferentially with an ACEi or ARB. Despite these recommendations, we must be aware that in real clinical practice, with aged patients, it is sometimes very difficult to obtain these values. It is important to highlight that the care of blood pressure should be individualized, as aggressive blood pressure control can also lead to hypotension, which can, potentially, exacerbate cognitive impairment.

Diabetes

Diabetes is another important risk factor, not only for CKD, but also for cerebrovascular diseases, and demencia.[36] The management of glycemia in diabetic CKD patients is discussed in the new KDIGO guidelines, which are very similar to the new American Diabetes Association (ADA) guidelines. In addition to lifestyle changes, control of blood pressure, and dyslipidemia, patients with diabetic kidney disease with an estimated glomerular filtration rate (eGFR) greater than 20 mL/min/1.73 m^2 should begin pharmacological treatment with a SGLT2i, and if eGFR greater than 30 mL/min/1.73 m^2 metformin should also be added. GLP-1 agonists should also be considered for additional cardiovascular risk reduction.[37,38] A nonsteroidal mineralocorticoid receptor antagonist should be considered for additional cardiovascular event risk reduction, if eGFR is greater than 25 mL/min/1.72 m^2 in the presence of elevated urinary albumin/creatinine ratio (ACR)[37] in diabetic patients. If eGFR is lower than 20 mL/min, the initial treatment should rely on GLP1 receptor agonists, with additional therapy if needed (DPP4 inhibitor, insulin, sulfonylureas, or alpha-glucosidase inhibitors).[37]

Sleep Disturbances

Although frequent, current evidence is inadequate to dictate interventions. According to a recent Cochrane review, the best available interventions are sleep hygiene education and acupressure.[16] Overall, nocturnal hemodialysis seems to have a beneficial effect in some sleep disturbances, such as insomnia, daily sleepiness, or central sleep apnea.

CKD-MBD

Although vitamin D supplementation is not associated with cognitive improvements, control of secondary hyperparathyroidism might attenuate the cognitive implications of CKD-MBD, as hypothesized in a recent epidemiological study.[39] Epidemiological observations have correlated cognitive performance with calcitriol levels. In these studies, patients with low levels of vitamin D had cognitive impairment and reduced cognitive performance.[40]

Anemia

Anemia should be treated with iron supplementation and/or erythropoietin-stimulating agents (ESA) or hypoxia inducible factor – prolyl hydroxylase inhibitors (HIF-PHIs). It should be noted that high doses of ESA can have contrasting effects and increase the risk of stroke in CKD patients.[41]

On the other hand, HIF-PHIs are promising agents for neuroprotection, as they are involved in neurogenesis, nerve cell differentiation and neuronal apoptosis.[42]

Polypharmacy

Polypharmacy should be evicted in CKD patients and non-essential drugs discontinued. Agents that modulate the brain's neurotransmitter systems or that block neurotransmitter receptors could either enhance or impair cognitive functions and should be used with caution in CKD patients. Sedative properties of certain drug classes (such as antihistaminic agents and hypnotics) have been associated with cognitive impairment and should be avoid in CKD patients.[43]

Renal Replacement Therapy

If there are no contraindications, uremic patients should start dialysis (HD or PD) and should be listed for kidney transplantation as soon as possible. Compared to dialysis, kidney transplantation is preferable when discussing protein-bound compounds and middle molecule elimination.

Concerning HD, colling the dialysate (35ºC) to achieve better hemodynamic control and reduce intradialytic hypotension may be a good option. In a study enrolling 73 patients on HD, cooler dialysate was related to no changes in brain white matter, while patients with warmer dialysate displayed significant white matter changes.[44] A meta-analysis showed that cooling the dialysate resulted in a 70% reduction in intradialytic hypotension[45].

CONCLUSION

To summarize, the strategy aimed at reducing CKD-associated MCI rests on prevention.

Controlling traditional cardiovascular risk factors, specifically blood pressure and diabetes, should be one of the first steps in decreasing MCI.

During dialysis, cooling of the dialysate seems to be important in patients with intradialytic hypotension. Referring patients to kidney transplantation is essential, as it appears to improve cognition, although not in frail patients.

Sleep improvement, depression treatment, and eviction of sedating drugs are other general measures that are important for CKD patients.

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