Review

Kidney-brain crossroads in vascular cognitive impairment

Encrucijada riñón – cerebro en el deterioro cognitivo vascular

Abstract

Individuals with chronic kidney disease (CKD), especially older adults, are at increased risk of developing cognitive impairment associated with renal disease, may present as minor neurocognitive disorder (NMS) or as a major neurocognitive disorder (dementia). Studies have shown that up to 87% of patients in the final stage of CKD have some degree of cognitive impairment. Currently, both conditions represent a major social and economic problem for the world's public health systems. Our country is no exception, epidemiological studies have shown the existence of cognitive impairment in all stages of renal disease. The presence of this has a great impact on the quality of life of these patients.

Clinical and subclinical cerebrovascular disease are the main risk factor for cognitive impairment in patients with renal disease, although potential pathophysiological mechanisms such as direct neuronal damage by uremic toxins have also been studied. The aim of the present study is to describe the participation of clinical and subclinical cerebral vascular damage and to analyze the most important pathophysiological mechanisms in the brain-kidney interaction, to better understand the cognitive impairment in patients with CKD.
Resumen

Los pacientes con enfermedad renal crónica (ERC), especialmente los adultos mayores, tienen mayor riesgo de desarrollar deterioro cognitivo asociado a la enfermedad renal. Este deterioro se presenta como un trastorno neurocognitivo menor (TNM) o mayor (TNMa). Estudios relacionados han demostrado que hasta el 87% de los pacientes en etapa final de la ERC tienen algún grado de deterioro cognitivo. Actualmente, ambas condiciones representan un importante problema social y económico para los sistemas de salud pública del mundo; algunos estudios epidemiológicos han demostrado la existencia de deterioro cognitivo en todas las etapas de la enfermedad renal, demostrando el gran impacto negativo sobre la calidad de vida de los pacientes.

La presencia de enfermedad cerebrovascular clínica y subclínica representa uno de los principales factores de riesgo para padecer deterioro cognitivo en pacientes con enfermedad renal, aunque también han sido estudiado otros potenciales mecanismos fisiopatológicos, como el daño neuronal directo por las toxinas urémicas. El presente trabajo tiene como objetivo describir la participación del daño vascular cerebral clínico y subclínico, así como analizar los mecanismos fisiopatológicos más importantes en la interacción cerebro-riñón, para comprender mejor el deterioro cognitivo en pacientes con ERC.

Palabras clave
Enfermedad Renal Crónica, Deterioro Cognitivo Vascular, Enfermedad Cerebrovascular, Envejecimiento.

Corresponding Author:
Dra. Sara Gloria Aguilar Navarro. Servicio de Geriatría. Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”. Vasco de Quiroga 15. CP 14000; Tlalpan, Ciudad de México, México. Phone: +52 (55) 54 87 09 00, #5710. Email: sgan30@hotmail.com
Introduction

Chronic kidney disease (CKD) represents one of the most costly pathologies for health systems in Mexico and Latin America. According to the figures recently published by the Mexican Kidney Foundation, there are about 140,000 patients with CKD, of which only 50% are treated in the Health Sector and, of these, up to 50% are subrogated to private hospitals for attention, generating high costs and a severe economic impact on health services. The growth rate of CKD, not including deaths, has been approximately 11% per year in the last 10 years. Currently, there are approximately 65,000 people in treatment with continuous renal replacement therapy (dialysis) in Mexico.1-2

CKD is defined as abnormalities in the structure and function of the kidney which occur for a period of more than three months, generating health implications. It is classified based on its cause and corroborated with the glomerular filtration rate (eGFR) (<60 ml/min/1.73 m²), amount of albuminuria present, urinary sediment, imaging studies, and/or alterations in the acid-base and electrolyte balance. CKD is divided into five stages according to the eGFR. Stage 1 is where there is evidence of kidney damage but eGFR is normal or high, all the way up to stage 5 where there is renal failure with necessary dialysis and/or transplant.3 (Table 1)

Physiologically, renal function decreases with age and so does the glomerular filtration rate; however, despite this decrease, the kidney has the ability to maintain homeostasis in healthy older adults. On average, the renal flow decreases by about 10% per decade, beginning at around 30 years when the glomerular filtration rate begins to decrease persistently at a rate of 1 ml/min/year, while between 70 and 100 years the decrease rate is usually 1.5 ml/min/year. There is a loss of muscle mass associated with aging, for which the production of creatinine (dependent on muscle tissue) is reduced; despite this, serum creatinine levels remain within normal ranges due to the concomitant decrease in the glomerular filtration rate.4-5 This decrease in glomerular filtration is accompanied independently by cardiac output, decreased renal mass, and increased resistance of afferent and efferent arterioles. It is thought that these

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
<th>eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Kidney damage with normal or high eGFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>Stage 2</td>
<td>eGFR reduced slightly</td>
<td>60 – 89</td>
</tr>
<tr>
<td>Stage 3 a</td>
<td>eGFR reduced slightly to moderately</td>
<td>45 – 59</td>
</tr>
<tr>
<td>Stage 3 b</td>
<td>eGFR reduced moderately to severely</td>
<td>30 – 44</td>
</tr>
<tr>
<td>Stage 4</td>
<td>eGFR reduced severely</td>
<td>15 – 29</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure</td>
<td>≤ 15 or dialysis</td>
</tr>
</tbody>
</table>

To stratify the risk, KDIGO proposes to add the amount of albuminuria/creatinuria detected in a urine sample: A1 (<30 mg/g), A2 (30-300 mg/g) or A3 (albuminuria>300 mg/g).
changes decrease the ability to respond to the increase or decrease of fluids and electrolytes due to an external stimulus. On the other hand, diagnostic methods such as fMRI show a decrease in the modulation capacity of renal medullary oxygenation due to aging, which is why there is susceptibility for acute renal failure of ischemic origin. In summary, all these changes can be observed in a relatively healthy kidney and are attributable to the passage of time.6-7

**Relationship between chronic kidney disease and cognitive impairment**

A direct association between the presence of kidney disease and cognitive deterioration has been demonstrated, since there is evidence of affected executive functions (cognitive skills that direct our behavior—cognitive and emotional activities) at the beginning of CKD, progressing to cognitive impairment in a global way, as the kidney disease progresses.8 Epidemiological studies have shown that cognitive function declines considerably in patients with eGFR < 45 ml/min/1.73 m2.9 Epidemiological studies, such as the Cardiovascular Health Study, have shown a relationship between eGFR and dementia by demonstrating an association between elevated serum creatinine levels (indirect eGFR marker) in moderate CKD and a 37% increase in risk of dementia (HR 1.37, 95% CI (1.06-1.78)).10

The physiopathological mechanisms proposed in the relationship between CKD and cognitive deterioration are chronic degenerative changes in the central nervous system, alterations in the microscopic anatomy of the cerebrovascular regulation, and bidirectional hormonal pathways between the brain and the kidney. These pathophysiological mechanisms of cognitive deterioration in CKD seem to share a pattern very similar to an accelerated process of vascular cognitive impairment.11-12 This review aims to describe the relationship between cerebrovascular damage (clinical and subclinical) and the most important pathophysiological mechanisms in the brain-kidney interaction, to better understand cognitive deterioration in patients with CKD.

**Relationship between cerebrovascular disease and ckd**

Patients with CKD are five times more likely to present clinical and subclinical cerebrovascular disease (CVD), since they tend to have a greater number and severity of neurological symptoms, worse adverse clinical outcomes, with greater functional disability, and morbidity than patients without CKD. The presentation of CVD in patients with CKD is usually of the ischemic (white matter injury, cerebral infarction, lacunar infarction, silent brain infarction) and/or hemorrhagic (microhemorrhage) type. (Figure 1)

The brain and kidneys are the organs with the greatest capacity for vascular self-regulation of the organism. The vascular capacity allows maintaining a constant level of blood flow in response to changes in tissue perfusion pressure. This self-regulation is achieved through an adequate microvascular function. Both the kidney and the brain are exposed to high volumes of blood flow through the cardiac cycle, making them more susceptible to microvascular damage.13

The cerebrovascular damage can be divided into small vessel disease, white matter injuries, and cerebral infarction.

**Small vessel disease**

Microvascular damage or small vessel disease refers to any pathological damage that affects small vessels (arteries, capillary arteries, and venules) causing ischemia and cerebral hemorrhage.14 Recently, a nomenclature has been established with the purpose of standardizing the terminology of small vessel disease, incorporating the following types: lacunar infarction (small subcortical infarction), hyperintensities, perivascular spaces, and microbleeds.15 Small vessel disease affects the brain and kidney, since both share vascular risk factors (diabetes, dyslipidemia, smoking, and high blood pressure). Small vessel disease manifests in the kidneys with alterations in glomerular filtration, while in the brain it manifests with alterations in memory, behavior, and mood.16-17
From the physiological point of view, the kidney and the brain share susceptibility to vascular damage since the vessel regulation of the microvasculature of the two organs are similar from the anatomical and functional point of view.\textsuperscript{18}

Markers of small vessel disease, perivascular spaces are associated with proteinuria and deterioration in the glomerular filtration rate. Xiao et al. demonstrated the association between perivascular spaces and chronic kidney disease in a clinical trial of 413 patients with lacunar infarction. It showed that the presence of proteinuria and the deterioration in the glomerular filtration rate was associated with greater severity of perivascular spaces.\textsuperscript{19}

In small vessel disease, in addition to the vascular risk factors that precipitate the damage, other changes in different elements are also observed in patients with CKD, such as low intracellular levels of folate and thiamine,\textsuperscript{20} aberrant nitric oxide metabolism, increase in free radicals and oxidative stress, which cause inflammation, and premature cell death. Through direct damage to the brain, all these factors increase the susceptibility for cerebral infarcts, small vessel disease, and white matter lesions, increasing the risk of cognitive deterioration.\textsuperscript{21}

**White matter lesions**

The incidence and severity of white matter lesions (WMLs) increase with age.\textsuperscript{22} Martinez-Vea et al. performed brain MRI studies on a group of non-diabetic patients under 60 years of age with kidney disease and compared them with a control group, showing that WMLs are more frequent in subjects with CKD (33\% vs 6\%).\textsuperscript{23}

Initially, the WMLs are asymptomatic, but with their progression they tend to produce nonspecific symptoms from a mild neurocognitive disorder to a major one, depression, psychosis, falls, and gait abnormalities. Additionally, their presence increases the risk of producing symptomatic cerebral infarction.\textsuperscript{24} These WMLs (also called white matter hyperintensities), are named after the bright areas of high signal intensity seen by
MRI in the fluid attenuation inversion recovery (T2 FLAIR) and correspond to ischemic demyelination, areas of gliosis, and occasionally to silent infarcts. These lesions are directly related to the reduction in the glomerular filtration rate (15-60 mL/min/1.73 m²) since several clinical trials have demonstrated the association between this and the increase in the volume of the white matter lesion. Punctuate and confluent white matter is characterized by ischemic tissue with perivascular alterations with loss of myelinated fibers and marked arteriolosclerosis; the hyperintense periventricular caps and halo are areas of demyelination associated with subependymal gliosis (with loss of the ependymal lining).

Cerebral infarction
A cerebral infarction is the acute neurological damage resulting from thrombosis, embolism, or systemic hypoperfusion and is associated with renal dysfunction and cognitive deterioration. At some time cerebral infarction and CKD were separate issues; however, currently there is evidence of the interaction of these two pathologies and the subsequent development of cognitive impairment. A meta-analysis evaluating the risk of cerebral infarction in relation to the level of albumin that included 12 studies with 46,638 patients (1,479 with a diagnosis of cerebral infarction), showed an independent association between microalbuminuria and the appearance of cerebral infarction—that is, the higher the albuminuria, the greater the risk of cerebral infarction (RR 2.65, 95% CI 2.25-3.14).

There have been efforts to establish cut-off points to determine the risk of cerebral infarction in relation to eGFR, demonstrating that the risk increases when eGFR < 60 ml/min/1.73 m² and albuminuria > 30 mg/g. On the other hand, for every 10 ml/min/1.73 m² decrease in eGFR, the risk of cerebral infarction increases by 7% (valid for eGFR values < 90 ml/min/1.73 m²).

The best example of bidirectional brain-kidney interaction is in the relationship between CKD and silent cerebral infarction (SCI). SCI is a lesion that is identified in brain imaging studies (CAT scan or MRI) in people without a clinical history of transient ischemic attack or cerebral infarction, and who generally do not present clinical data of neurological involvement. These vascular lesions, despite what their name suggests, are not benign, so some authors propose replacing the term silent with covert. A silent cerebral infarction is an independent predictor of aggravation of renal function in patients with CKD (HR, 2.16; IC 95%, 1.01-4.64, p=0.04). It is also associated with the risk of cognitive impairment, dementia, and death.

Cognitive impairment in all stages of ckd
Cognitive impairment refers to a decrease in one or more cognitive domains such as learning, memory, language, executive functions, attention, social cognition, and judgment, among others. The deficits must demonstrate a decrease in the previous level of functioning and be serious enough to interfere with daily function and independence. These characteristics allow us to differentiate a mild neurocognitive disorder (TNM—in which there is evidence of a modest decrease in cognitive function in one or more cognitive domains but which does not affect the basic and instrumental activities of daily living) from a major neurocognitive disorder (TNMa—in which there is evidence of a significant cognitive decline which interferes with independence in the activities of daily life).

Seventy percent of patients in the final stage of CKD have cognitive impairment; however, at any stage of CKD, some degree of cognitive deterioration may occur. In patients with CKD and cognitive impairment, mortality increases, hospitalization episodes increase, adherence to treatment decreases, and their disability worsens.

The Third National Health and Nutrition Examination Survey showed in 4,849 patients a worse performance in learning (OR 2.4, 95% CI 1.3-5.6), and in visual spatial attention (OR 2.7, 95% CI 1.0-7.4) in association to moderate CKD (eGFR of 30 to 59 ml/min/1.73 m²). The Chronic Renal Insufficiency Cohort Study showed in 3,591 patients a greater incidence of cognitive alterations in those with one per renal function state (OR 1.5,
The Health, Aging, and Body Composition Study showed in a sample of 3,034 elderly people that baseline cognitive function was worse in patients with lower eGFR. The German Intervention Project on Cerebrovascular Diseases and Dementia in the Community of Ebersberg also showed in a sample of 3,697 participants (with follow-up at 2 years) an incidence of cognitive deterioration of 5.8% in patients with normal function, 9.9% in patients with mild CKD, and 21.5% in moderate to severe CKD.

Etegn et al. conducted a systematic review of the literature to demonstrate the association between cognitive impairment and kidney disease, finding in 54,779 patients that those who have CKD have a statistically significant risk of developing cognitive impairment (OR 1.65, 95% CI 1.32-2.05, p<0.001). This systematic review also showed that although most cross-sectional and longitudinal studies support the association with cognitive impairment in patients with CKD, some do not show this association, possibly due to the difference in the tests used for cognitive diagnosis.

Causes of cognitive impairment in patients with CKD

There are several factors that explain the higher prevalence of cognitive deterioration among patients with CKD. These can be divided into traditional and non-traditional risk factors. The traditional factors are higher frequency of hypertension, diabetes, dyslipidemia, smoking, in addition to ischemic heart disease, and atrial fibrillation. Non-traditional vascular factors include hyperhomocysteinemia, oxidative stress, inflammation, and endothelial dysfunction, without forgetting that CKD by itself is an independent risk factor for cognitive impairment. Figure 2.

Patients with CKD usually have high levels of homocysteine (>15 mcmol/L), which has a toxic effect on endothelial cells, vascular smooth muscle, platelets, coagulation, and fibrinolytic factors. All these factors are related to accelerated atherosclerosis, prothrombotic state, and endothelial inflammation. Homocysteine also has a direct neuronal toxic effect by activating the glutamate binding site at the N-methyl-D-aspartate (NMDA) receptors. Although it has not been possible to demonstrate that the reduction of homocysteine in patients receiving renal transplant with hyperhomocysteinemia is associated with better overall cognitive performance, a positive association has been found in the supplementation with folic acid since it produces a better performance of the executive functions.

On the other hand, uremia generates oxidative stress, endothelial dysfunction, and vascular calcification, inducing neurotoxic and vascular changes that contribute to cognitive deterioration. These changes arise from an imbalance between the production and elimination of free radicals, which cause denaturation of proteins, lipids, and nucleic acids, initiating tissue damage characterized by apoptosis and necrosis, leading to dysfunction and neuronal death. Likewise, the accumulation of uremic toxins generates endothelial dysfunction and calcification of the vascular walls, decreasing relaxation and vascular integrity.

Other non-vascular risk factors that contribute to cognitive deterioration in patients with CKD are anemia, elevated levels of parathyroid hormone, alterations in sleep (which generate diurnal drowsiness and decreased quality of life), depression, and social isolation (which prevents adequate social and cognitive stimulation). Risk factors related to the hemodialysis procedure that may be associated with cognitive deterioration include intradialytic hypotension, osmolar changes, chronic microembolism during the procedure, or subclinical cerebral edema.
Cognitive impairment in patients with CKD is the result of both traditional and non-traditional cardiovascular risk factors. Both produce alterations in the cerebral vasculature of small (white matter lesions, microhemorrhages) and large vessels, as well as endothelial dysfunction. The “non-traditional” factors cause neuronal dysfunction and toxicity, as well as damage to the blood vessel and even endothelial damage. All this demonstrates the clear relationship between cerebral and renal vascular function and its contribution to cognitive deterioration.
Conclusions

Cognitive impairment is common in patients at any stage of CKD. The pathophysiological link between brain and kidney damage is complex, manifested through small vessel disease, cerebral infarcts, micro and macro hemorrhages, silent cerebral infarctions, hyperintensities of white matter, oxidative stress, endothelial dysfunction, and vessel wall calcifications.

Considering that this damage is present even in the early stages of CKD, it is convenient to evaluate cognitive function as soon as possible in these patients to detect alterations in the execution of tasks, speed of thought, attention, and memory, for a prompt identification of cognitive issues and timely intervention to delay the progression of these problems. Because of the frequency of symptomatic and silent vascular damage, it is convenient to use neuroimaging studies such as CT or MRI scans.

Despite the clinical evidence of the interaction between CKD and cognitive impairment, more clinical studies are needed to better identify how vascular risk factors change as kidney disease progresses, and in what way eGFR and albuminuria (alone or combined) modify the risk of dementia.

Aging in the population will increase the number of older adults with CKD, so it will be necessary to study cognitive function in a systematic, organized, and structured way in the initial assessment. This would allow these patients to benefit from comprehensive care in the early stages of cognitive decline and we could, in this way, establish recommendations regarding the preventive treatment for cognitive impairment associated with CKD.

Conflicts of interest
There are no conflicts of interest on the part of any of the authors, for this scientific report.

Funding sources
The authors declare no funding source for this scientific report.
References


