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Mini review

Novel Insights into the Relationship between Chronic Kidney Disease and Cognitive Dysfunction

Maria Zaimi* and Eirini Grapsa

National and Kapodistrian University of Athens, Aretaieio Hospital, Athens, Greece

***Corresponding author:** Maria Zaimi, National and Kapodistrian University of Athens, Aretaieio Hospital, Athens, Greece

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Abstract

Chronic kidney disease (CKD) constitutes a major health burden with more than 850 million people being affected by chronic kidney disease globally. CKD causes a number of complications, among which cognitive impairment has a detrimental impact on the life of patients. The pathophysiologic mechanisms behind the cognitive dysfunction among CKD patients are based on two hypotheses: the vascular and non-vascular/neurodegenerative hypothesis. A comprehensive understanding of the underlying pathophysiology and the development of novel studies are important to fully elucidate the affected kidney-brain axis among CKD patients with cognitive impairment.

Keywords: Chronic kidney disease; cognitive dysfunction; neurodegenerative hypothesis; blood-brain barrier

Abbreviations: CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; CKD-MBD: Chronic Kidney Disease- Mineral and Bone Disorder; CI: Cognitive Impairment; BBB: Blood Brain Barrier; MMA: Methylmalonic Acid

Introduction

Chronic kidney disease (CKD) is a major health problem worldwide and according to the 2023 edition of the ISN-Global Kidney Health Atlas 850 million people are affected by chronic kidney disease across the world [1]. The definition of CKD describes a glomerular filtration rate (GFR) <60 ml/min per 1.73 m2 or positive markers of kidney damage or both, for more than three months [2,3]. Most importantly, CKD is associated with a wide range of complications such as progression towards End Stage Renal Disease (ESRD), hypertension [4], cardiovascular complications [5], anemia [6], chronic kidney disease-Mineral and Bone Disorder (CKD-MBD) [7] and cognitive impairment (CI) [8]. CI constitutes a major complication among patients with CKD. CI is defined as a decline in one or more key brain functions (memory, learning, concentration, and decision making) and it can range from mild to severe, with severe resulting in dementia [9].

The prevalence of CI among patients with CKD ranges from 10% to 40%, depending on the CI definition and CKD stage [10]. A recent cross-sectional study including data from 6215 Japanese individuals found that both mild (eGFR=45-59.9 mL/min/1.73m2) and moderate-to-severe eGFR (eGFR<45 mL/min/1.73m2) reductions were associated with cognitive impairment (Mini-Mental State Examination (MMSE) score ≤ 26) with ORs = 1.49 and 2.35, respectively. Moreover, each increase of eGFR by 10 mL/min/1.73m2 was associated with 4.8% lower odds of cognitive dysfunction highlighting the fact that eGFR management may protect against CI [11].

Pathophysiologic mechanisms

The pathophysiology behind CI among patients with CKD is a complex entity. Two major hypotheses are proposed: the vascular hypothesis and the non-vascular or neurodegenerative hypothesis [12].

Vascular hypothesis

Both kidney and brain, sharing similar physiologic vascular characteristics as end organs in parallel, are sensitive to the same cardiovascular risk factors including hypertension, diabetes, and smoking [13]. Owing to autoregulation they are able to maintain the blood flow despite blood pressure fluctuations resulting in adequate cerebral perfusion pressure in brain and GFR in kidney. However, hypertension renders juxtamedullary afferent arterioles and cerebral perforating arteries vulnerable to injury resulting in proteinuria and GFR decrease on the one hand and in stroke, cerebral small vessel disease and CI on the other hand [14]. Moreover, the increased artery stiffness and microvascular damage observed in CKD affects brain microcirculation and results in cognitive impairment [15]. Furthermore, situations found in CKD, such as hyperhomocysteinemia, hypercoagulable states, inflammation, and oxidative stress, damage the vasculature and are found to decrease cognitive function [16].

High homocysteine levels have a prothrombotic effect on the vascular system, damage the endothelial layer of large and small vessels and may also cause endothelial inflammation. Simultaneously, homocysteine, activating the N-methyl-D-aspartate receptor or by converting into homocysteic acid, leads to cell death and neurotoxicity. Oxidative stress, which occurs in CKD and further impairs kidney function, increases the risk of CI through Amyloid precursor protein (APP) cleavage and beta-amyloid (Aβ) production. Regarding the Klotho protein, coreceptor of FGF23 produced by the kidney, a recent study found for the first time an association between reduced levels in serum Klotho and negative results in neuropsychological tests among CKD patients. Interestingly, the same study found an association between decrease of Klotho levels and increase of VCAM-1, an endothelial damage biomarker also associated with worse scores in neurocognitive tests. These findings support the hypothesis of endothelial damage and vascular disease playing a role in the pathophysiology of CI among CKD patients [17].

Non-vascular hypothesis

The neurodegenerative/ non-vascular hypothesis is based on the neuroinflammation possibly induced by cytokine/chemokine and reactive oxygen species (ROS) production. In CKD patients the cytokines interact with neurotrophic factors through a disrupted blood-brain barrier (BBB) activating immune cells, neurons and glial cells leading to enhanced inflammation and CI development. Results from the BREIN study recently confirmed that ESKD patients have an increased BBB permeability compared to healthy volunteers, and cognitive impairment [18]. Another proposed pathological mechanism behind cognitive dysfunction among CKD patients is uremic toxicity, as accumulation of uremic toxins may break BBB and disturb the function of the neurotransmitters. Uremia along with high calcium-phosphate levels and other metabolic disorders increases the inflammatory and oxidative response, causing damage of the brain vasculature and causing CI [19].

Furthermore, uremic toxins may accelerate cognitive damage via binding to the Aryl hydrocarbon receptor (AhR), a transcription factor expressed in endothelial cells, which is associated with induction of inflammation [20]. An important role in cognitive dysfunction among CKD patients is found to play methylmalonic Acid (MMA), as a recent cross-sectional study found for the first time an association between MMA and cognition in CKD patients [21]. MMA may contribute to CI via several mechanisms, including inhibition of the respiratory chain, plasma membrane depolarization and neuronal cell apoptosis, ROS generation and oxidative stress.

Conclusion

The pathogenesis behind cognitive impairment in CKD patients is multifactorial including both vascular and neurodegenerative underlying mechanisms. However, further research is needed to elucidate the pathophysiologic communication between kidney disease and brain damage and as a result, to prevent or reduce the risk of CI in this group of patients. For this reason, the cooperation between nephrologists and neurologists is fundamental.

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Conflict of interest statement

The authors declare no competing interests for this work.

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