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The Neurological Impact of Uremic Toxins from Chronic Kidney Disease

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ABSTRACT: Chronic kidney disease (CKD) involves the gradual decline in kidney function and has often been associated with cognitive decline. Cognitive decline was thought to be a function of the underlying conditions that people with CKD live with, but there is a growing field of research that directly connects CKD with brain health. CKD can result in the rapid accumulation of uremic toxins, waste products that healthy kidneys normally filter out of the bloodstream. Evidence suggests that these toxins play a damaging role in the developing brain and have lasting effects on cognition. In this paper, we examined how the specific uremic toxins associated with CKD disrupt brain development and contribute to long-term cognitive impairment. Researchers use animal models, neuroimaging, and cognitive testing to link uremic toxins to the brain's structure and function. Research has found that certain uremic toxins from CKD impact the blood-brain barrier, and this is more dangerous during critical periods of brain development. This interdisciplinary research, combining nephrology and neuroscience, suggests new neuroprotective strategies for adults and children with CKD, leading to more areas of exploration.
KEYWORDS: Neuroscience, Nephrology, Uremic Toxins, Cognitive Decline, Chronic Kidney Disease, Brain Development.

Introduction

Almost 58% of people with chronic kidney disease (CKD) in the United States of America have some form of cognitive decline.[1] CKD is the most common form of kidney dysfunction, where the kidneys gradually get weaker as the disease progresses. CKD is often referred to as a silent disease because it shows few initial symptoms and is often not diagnosed until it is severe and, in most cases, irreversible.[2,3] The disease is characterized by lasting abnormalities in kidney structure that continue for over 3 months and impact kidney function.[4] The addition of cognitive decline to the already deadly CKD increases morbidity and decreases the patients' quality of life and can have other social implications. In addition, CKD is a financially unforgiving disease, with patients having to pay hundreds of dollars to take medication and to receive treatment.[5] For patients without health insurance, that number can be far greater, often thousands of dollars. With the cognitive risk, these costs can greatly increase, crippling families who don't have the resources to pay for treatment.

The accumulation of uremic toxins is a challenge to the management of CKD. Before extensive research was conducted on uremic toxins, they were considered to be waste products that could be easily managed with dialysis. Subsequently, it was found that uremic toxins have diverse chemical properties and are not removed by dialysis.[6] These toxins can affect many systems in the body: the cardiovascular, nervous, immune, and endocrine systems.[7] The toxins accumulate in people with CKD and can cross the blood-brain barrier (BBB), leading to neuroinflammation and damage to many brain structures used in cognition.[8,9]

The BBB plays a major role in CKD cognitive complications, since it is one of the key sites of blood and the central nervous system (CNS) connection.[10] It is made of a complicated structure where cerebral endothelial cells, the cells that line the interior of blood vessels,[11] are connected by tight junction proteins (TJP) and associated cells like microglia.[12]

Since cognitive decline covers a very broad spectrum, we will focus our work on a few domains: memory, executive function, attention, language, and visual-spatial function. Uremic toxins impact all of the previously stated domains.[13]

Recent research shows a direct link between CKD and cognitive decline, specifically in relation to the buildup of uremic toxins such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS). These toxins negatively impact brain development and long-term cognitive function by disrupting the BBB and causing neuroinflammation. This paper aims to highlight the need for neuroprotective methods in renal health, especially for individuals with early-onset CKD.

First, we will examine how these specific uremic toxins are associated with cognitive decline in those with CKD. Then, we will discuss how IS and PCS compromise the BBB and enable brain injury. Finally, we will assess how early-life exposure to uremic toxins disrupts neurodevelopment and has long-term consequences.

This paper will synthesize findings from several journals that span the range of neuroscience, nephrology, and psychology. There will be a strong emphasis on the interdisciplinary connection between nephrology and neuroscience. The paper will not use original data, but will analyze evidence and findings from peer-reviewed research sourced from established databases like PubMed and ScienceDirect. The sources presented in this paper were found using Google Scholar, with keywords such as "uremic toxins," "chronic kidney disease," "cognitive decline," and "brain development." The sources were further

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analyzed by assessing whether the source had been cited in research papers before, and ensuring that the authors of the paper were reputable in their field of work.

Specific Uremic Toxins and Their Effects on Cognitive Decline in CKD Patients

Uremic toxins, such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), have emerged as key contributors to cognitive decline.[14] These toxins, especially in their protein-bound form, are not efficiently removed through dialysis and tend to accumulate throughout the bloodstream.[15, 8] This is a failure of current dialysis methods. This section will explore how the IS and PCS are related to cognitive decline in people with CKD, focusing on three mechanisms: cognitive performance, insufficient dialysis, and inflammation.

2.1. Protein-Bound Toxins and Neurocognitive Performance:

The cognitive impacts of IS and PCS have become a growing area of interdisciplinary research in nephrology and neuroscience. Lin *et al.* conducted a large study of patients on traditional hemodialysis and found that elevated IS and PCS levels were associated with reduced performance in the cognitive areas of attention, memory, and executive function. These effects remained prominent even after controlling for age and other external factors, suggesting a strong association between the toxins and cognitive decline.

IS and PCS can interfere with synaptic plasticity, the brain's ability to strengthen or weaken synaptic connections in response to activity, which is essential for memory formation and learning.[15] These findings support the idea that the protein-bound toxins IS and PCS are not only related to a decline in cognition but also may have a direct role in impairing brain function. As these toxins circulate throughout the body, they pose a long-term risk to attention, memory, and executive processing in CKD populations.

2.2. Preventing Gut Precursors Is More Effective Than Dialysis:

Although dialysis is one of the most popular treatments for CKD and other forms of kidney dysfunction, it is ineffective at removing protein-bound uremic toxins such as IS and PCS. A major factor driving the challenge of dialysis removal is the binding of IS and PCS to albumin. Albumin is the most abundant plasma protein, and its main role is to transport various molecules, such as hormones, fatty acids, and drugs, throughout the bloodstream. However, when uremic toxins attach to albumin, they are shielded from removal during dialysis because only the unbound part of a molecule can be filtered. Studies have shown that more than 90% of IS and PCS remain bound to albumin, limiting filtration through dialysis.[16] Current dialysis does not solve the main issue of uremic toxin accumulation because the toxins stem from the microbial metabolism of dietary amino acids in the gut.[9]

Even if a CKD patient is on dialysis, IS and PCS can still build up and cause brain damage unless the gut precursors, the substances that turn into IS and PCS, are also removed.[6] Therefore, dialysis does not significantly reduce toxin burden unless coupled with strategies targeting toxin production.6 This underscores the need for approaches that go beyond dialysis to manage cognitive risk from CKD. These findings highlight a critical gap in current CKD management.

To combat the creation of IS and PCS through gut-derived precursors, interventions in the form of prebiotics or probiotics may reduce IS and PCS levels more effectively than increasing the frequency of dialysis.[17] Prebiotics work by promoting the growth of beneficial gut bacteria that favor carbohydrate fermentation over protein fermentation, which reduces the breakdown of amino acids like tryptophan and tyrosine into indole and p-cresol, the direct precursors of IS and PCS. Probiotics further support this process by increasing microbial competition in the gut, limiting the abundance of toxin-producing bacteria, and decreasing overall uremic toxin generation at its source.[17]

2.3. Inflammatory Markers as Mediators:

IS and PCS are believed to induce cognitive decline through neuroinflammation. Pepin *et al.* (2023) found that higher IS and PCS concentrations are associated with increased levels of inflammatory markers, namely IL-6 and TNF-α. These cytokines are able to cross the BBB and trigger glial activation, which leads to synaptic damage and neurodegeneration. These processes are closely linked to cognitive decline.

Similarly, cognitive impairment in standard dialysis patients was associated not only with high uremic toxin appearance but also with elevated inflammation levels.[16] This suggests that inflammation could be a mechanism connecting kidney dysfunction to cognitive impairment. A study by Watanabe *et al.* (2014) showed that IS activates the aryl hydrocarbon receptor (AhR) pathway, stimulating oxidative stress and inflammation in both the kidneys and brain. This mechanism links CKD to injury to the CNS.

These findings suggest that inflammation is a side effect of CKD and also a key mechanism through which cognitive damage can occur. This, therefore, raises the possibility that anti-inflammatory therapies could be used to fight the link between CKD and cognitive decline.

Disruption of the Blood-Brain Barrier by Uremic Toxins

This section analyzes how IS and PCS compromise the durability of the BBB by impacting its selective permeability and allowing uremic toxins and other neurotoxic compounds to enter the brain. As CKD progresses, the accumulation of these toxins in the bloodstream poses a direct risk to the integrity of the BBB by weakening the endothelial structure and disrupting the tight junction proteins that maintain its barrier function.[10] Tight junction proteins (TJP) are specialized proteins that form close connections and contact between adjacent cells.[18]

Once the BBB becomes more permeable, uremic toxins and inflammatory cytokines can enter the brain, contributing to neuroinflammation, glial activation, and synaptic dysfunction. These are all implicated in cognitive impairment.[9, 19]

3.1. Tight Junction Degradation:

TJP, including claudin-5, occludin, and zonula occludens-1 (ZO-1), helps maintain the BBB's selective permeability by forming a seal between the cells.[18,20] The seal ensures that most molecules cannot pass freely through the BBB and forces most molecules to be selectively transported through cells. CKD patient studies and experimental models have shown that IS and PCS damage TJP, which weakens the paracellular barrier and lets harmful substances enter brain tissue.[10,21]

The degradation of the junctions is not only structural, but also triggers many permeability changes in the BBB that can lead to neuroinflammation and oxidative stress. Specifically, tight junction degradation changes the electrical resistance of the barrier and allows the unregulated entry of hydrophilic compounds.[21] Liabeuf *et al.* (2022) found that IS exposure led to decreased claudin-5 in brain endothelial cells, and Faucher *et al.* (2023) found that PCS was associated with the disorganization of occludin and ZO-1. Andrews *et al.* (2025) further show that once the proteins have degraded, the BBB becomes susceptible to oxidative stress. Weakening the structure of the BBB not only increases permeability but also creates an entrance for inflammatory agents and other toxins, accelerating cognitive decline.

3.2. Oxidative Stress and Endothelial Damage:

Oxidative stress, a condition where the body can't keep up with harmful oxygen byproducts because it lacks enough antioxidants,[22] plays a major role in damaging the BBB in people with CKD. These harmful oxygen byproducts, known as reactive oxygen species (ROS), are produced naturally in the body but can accumulate when antioxidant defenses are overwhelmed, leading to oxidative stress. IS and PCS are inducers of ROS in endothelial cells. They shift the redox balance, the equilibrium between oxidation and reduction reactions,[23] towards a pro-oxidant state.[17] The overproduction of ROS can damage essential molecules that impact endothelial viability. For example, lipids will oxidize early, proteins will be oxidatively modified, and DNA strands will be more susceptible to breaks.

Assem *et al.* (2018) demonstrated that IS-related oxidative stress can lead to mitochondrial depolarization in endothelial cells, showing a potential reason for the lack of energy for the BBB repair process. Induced ROS activates inflammatory pathways, such as NF-κB, which stimulates cytokines such as TNF-α and IL-6.[7]

The inflammation not only directly harms endothelial cells, but also promotes more ROS generation. Over time, oxidative damage destabilizes the cytoskeleton and reduces the strength of TJP, which accelerates BBB leakage.[24] The cycle of inflammation and oxidative stress results in progressive endothelial damage, leading to further toxin accumulation and ongoing brain injury.[21] Abbott *et al.* (2010) noted that the oxidative injury to endothelial cells is one of the most significant molecular events leading to the breakdown and decline of the BBB, making it a therapeutic target in CKD-related cognitive decline.

3.3. Experimental BBB Models:

Experimental models of the BBB have been key in showing the specific effects of IS and PCS on barrier function. In-vitro transwell systems, which culture endothelial cells on semi-permeable membranes alongside astrocytes or pericytes, allow researchers to measure the integrity of the barrier through parameters like transendothelial electrical resistance (TEER) and tracer permeability.[25] Faucher *et al.* (2023) report that exposure to IS and PCS led to a marked reduction in TEER and increased leakage of fluorescent markers, indicating a loss of tight junction stability.

Animals with CKD provide more *in vivo* evidence. For example, Watanabe *et al.* (2021) found that CKD-induced uremic toxin accumulation correlates with reduced amounts of claudin-5 in brain tissue and greater permeability to small-molecule dyes. These models also revealed inflammatory shifts within the brain, such as increased astrocytic GFAP expression, which further influences the vulnerability of the BBB.[19] Although the animal *in vivo* evidence is useful, it is difficult to translate the findings and make them applicable to humans; this evidence should be further studied.

By combining the *in vitro* mechanistic studies with the *in vivo* validation, these experimental models confirm that IS and PCS impair the structure and function of the BBB in animals, yet further studies need to be done to extend that confirmation to humans. They also highlight molecular targets, namely specific TJP and antioxidant pathways, for potential intervention and treatment.

■ Pediatric Exposure and Long-Term Neurodevelopment Outcomes

This section examines the effects of uremic toxins during periods of critical neurodevelopment in children with CKD, emphasizing how the toxins may contribute to cognitive impairment in the long-term. CKD during childhood presents a different neurological risk that cannot be fully understood using data from adult patients. Children are in a dynamic and ever-changing state of brain development, where brain structure, connectivity, and function are maturing and changing.[26] This developmental stage, essential for establishing proper cognitive capacity, is a period of vulnerability to the accumulation of uremic toxins and other brain injuries. Unlike the adult nervous system, the developing brain has to navigate the challenges of growth and environmental stressors, making it less likely to compensate for damage and more likely to have long-lasting consequences.[27,28]

4.1. The Cognitive Risk Associated with Pediatric CKD:

Children with CKD exhibit higher rates of cognitive impairment than children without, with attention, working memory, and executive function being most impacted.[28,29] These outcomes stem from protein-bound uremic toxins, such as IS and PCS, which, as stated earlier in the paper, are not eliminated through dialysis.[16] In children, the cognitive impact is amplified because uremic toxin exposure overlaps with processes that are essential for refining neural networks, namely synaptogenesis, myelination, and pruning.[27,28]

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Some longitudinal neuroimaging studies in pediatric CKD populations have shown patterns of structural brain alterations that emerge early on and progress over time. Van der Plas *et al.* (2025) demonstrated that children with CKD exhibit reduced cortical thickness across the frontal and parietal regions, areas that are involved with executive function and working memory, compared to children without CKD. In this study, there was also evidence of accelerated changes during adolescence. Similarly, Moodalbail *et al.* (2013) used diffusion tensor imaging (DTI) to show widespread reductions in white matter integrity, which is a measure of how well the brain's communication pathways are maintained. The most affected areas were association fibers like the superior longitudinal fasciculus, which are critical for efficient communication between regions in the cerebral cortex. The white matter reductions are significant because they occur during periods of rapid brain maturation, meaning that early structural disruptions can alter brain development. The accelerated cortical thinning and white matter degradation observed in pediatric CKD suggest more disruptive neurodegeneration than in adults with CKD, as these changes interfere with the development of the brain, not the degeneration of preexisting neural pathways. This distinction helps explain why children with CKD experience broader and more persistent cognitive impairments, highlighting early-life CKD as a uniquely high-risk window for long-term neurological consequences.

Both studies indicated that there was subcortical volume loss, especially in the hippocampus and the basal ganglia, which are important for learning, memory, and motor regulation.[29,30] The trajectory of the changes in children appears more aggressive than in adults, reflecting the effects of CKD stress on the body and neurodevelopmental vulnerability.

4.2. Animal models in the Developmental Stage:

Animal models have been significant in demonstrating how early-life exposure to uremic toxins disrupts brain development. In a few studies, young rodent models of CKD show signs of impaired hippocampal neurogenesis, the generation of new neurons in the hippocampus, and synaptic plasticity, along with spatial learning deficits that are carried through adulthood.[8,9]

Other *in vitro* studies further show that the uremic toxins IS and PCS elevate oxidative stress, which damages proteins, lipids and DNA, disrupt the function of mitochondria, limiting the cell's ability to produce energy, and trigger apoptosis in neurons.[22, 24] Importantly, the effects of IS and PCS are more pronounced in younger and more immature neurons compared to mature ones, likely because developing neurons have higher metabolic needs and less effective antioxidant defenses, making them more vulnerable to toxin-induced harm.

Evidence from clinical and experimental studies suggests that when uremic toxins intersect with key stages of brain development, they can create many changes in structure and function, and they can persist well into adulthood. A major factor in the vulnerability of the brain is the developing BBB, which is more easily compromised by uremic toxins.

4.3. Vulnerability of the Developing BBB:

The developing BBB is not just a smaller version of the adult barrier: it differs in structure and function.[12, 20] In early life, TJP's are not yet fully developed, properly localized, or functionally advanced.[18] The incomplete TJP assembly increases permeability of the BBB, allowing a wider range of molecules, including harmful neurotoxins, to pass through into the brain.

Experimental work shows that during the development period, small lipophilic compounds, inflammatory mediators, and protein-bound toxins like IS and PCS cross at rates higher than in adults.[10] In pediatric CKD, these structural vulnerabilities are compounded by systemic inflammation, driven by uremic toxic-induced cytokine release, which can downregulate TJP expression, alter endothelial signaling, and increase transport through the BBB.[7, 21] Elevated oxidative stress further weakens the barrier by damaging endothelial membranes and the cytoskeleton, making the BBB more reactive to injury and more permeable.

The combined effects of immature BBB structure, intensified inflammatory agents, and heightened toxin load form an environment for neurodevelopmental harm. The developing brain will face prolonged exposure to substances that a more experienced barrier would usually block.

■ Conclusion

This paper argues that uremic toxins found in CKD patients, specifically IS and PCS, play a direct and harmful role in both brain development and long-term cognitive function by disrupting the BBB and promoting neuroinflammation. Through an exhaustive review of existing studies and research, we show that these toxins are not only byproducts of CKD but also active agents in contributing to neurological decline.

We began by reviewing the association between high IS and PCS levels and cognitive decline in patients with CKD. This underscores the systemic impact of CKD, where circulating toxins correlate with impairments in memory, executive function, and attention. Next, we explored the mechanisms by which IS and PCS compromise the structure and function of the BBB. We discussed that the toxins degrade TJP, increase oxidative stress, and damage endothelial cells, thereby weakening the BBB's protective function. The disruption increases permeability, allowing neurotoxic substances to infiltrate the brain and cause inflammation. Finally, we analyzed that early-life exposure to neurotoxins was even more stark, as pediatric patients with CKD face different vulnerabilities. The developing BBB is structurally different and less effective in fighting the damage from uremic toxins, which may result in long-lasting neurodevelopmental deficits. The early disruption impairs cognitive domains during childhood and also accelerates cognitive decline later in life.

Although the link between CKD and cognitive decline is becoming more recognized, there is still limited understanding of the biology and psychology behind this, and even more so in pediatric or early life cases. A review by Pépin *et al.* (2023) noted that few studies use neuroimaging to track brain changes in CKD patients over time, and even fewer research the long-term effects of early exposure to uremic toxins. Given the

global rise in CKD due to diabetes and other lifestyle factors, and the lifelong cognitive consequences of early brain disruption,[31] more research is essential to improve early detection and develop neuroprotective and treatment strategies.

Several important questions remain. What are the precise molecular pathways where IS and PCS exert neurotoxic effects during critical neurodevelopmental windows? Can new therapeutic strategies, such as targeted toxin clearance or BBB stabilizers, reduce these impacts? Can there be improvements in dialysis methods that can filter out uremic toxins? How can we bring awareness to the pediatric risks where the cognitive damage can be more severe and long-lasting? Could advanced neuroimaging and biomarker analysis provide deeper insight into the reversibility and timing of BBB damage?

Longer studies tracking neurocognitive outcomes from childhood through adulthood in CKD populations are essential to fully understand the trajectory of uremic toxic-caused cognitive decline. Because these studies will likely take decades, new information will not be immediate. However, awareness among healthcare professionals about the link between kidney disease and cognitive impairment can help in monitoring and treatment options. Integrating advanced neuroimaging techniques with cerebrospinal biomarkers of BBB integrity may help identify early indicators of neurological vulnerability before cognitive decline becomes apparent. Additionally, earlier prevention for CKD and more measures for BBB protection in developing brains can lessen the risk of cognitive decline. Addressing these gaps in our research and awareness will be crucial to developing approaches that safeguard brain health in the context of kidney disease.

While this paper synthesizes evidence and findings linking IS and PCS to BBB disruption, neurodevelopmental vulnerability, and cognitive decline, it has limitations. Firstly, much of the available literature remains based on small groups, and this review is constrained by the limited number of novel studies directly investigating uremic toxin exposure in pediatric health. Secondly, the reliance on cross-sectional rather than longitudinal data restricts the ability to assess causality or developmental trajectories over time. Thirdly, while animal and *in vitro* studies provide some insight, translating these findings to human neurodevelopment is a challenge. Finally, this paper highlights the connection between CKD-derived uremic toxins and cognition, but emerging therapies, such as advanced neuroimaging biomarkers, were only briefly touched upon due to their novelty. As chronic kidney disease becomes increasingly prevalent, the lack of understanding of uremic toxic-driven neurodevelopmental injury underscores a critical need for more comprehensive, multidisciplinary research.

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