

Age-Dependent Effects of Chronic Kidney Disease–Associated Gut Microbiota Dysregulation on Cerebral Microhemorrhages in Experimental Mice

Yan Zhao*, Zing Shi

The Key Laboratory of Geriatrics of NHC; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, 100730, P. R. China

***Corresponding author:**

Yan Zhao, The Key Laboratory of Geriatrics of NHC; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, 100730, P. R. China. E-mail: yan.z@163.com

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Abstract

Chronic kidney disease (CKD) is increasingly recognized as a systemic disorder that extends beyond renal dysfunction, influencing neurological health through disturbances in the gut–kidney–brain axis. Alterations in intestinal microbial communities promote the accumulation of uremic toxins, systemic inflammation, oxidative stress, and endothelial dysfunction, all of which may compromise cerebrovascular integrity. Aging further amplifies these pathological mechanisms, increasing susceptibility to cerebral microvascular injury. This review examines age-related differences in gut microbiota alterations and their association with brain microhemorrhages in experimental models of CKD.

Keywords: Chronic kidney disease (CKD), Gut dysbiosis, Gut–kidney–brain axis, Brain microhemorrhages, Aging.

Introduction

Chronic kidney disease (CKD) is a progressive disorder characterized by irreversible loss of renal function and the accumulation of metabolic waste products (1). Although CKD primarily affects the kidneys, it also exerts systemic effects on multiple organs, including the cardiovascular system, gastrointestinal tract, and central nervous system. Increasing evidence supports the concept of the gut–kidney–brain axis, which describes the bidirectional communication among these organs through immune signaling, microbial metabolites, endocrine pathways, and neural networks (2).

The healthy gastrointestinal tract contains a diverse microbial ecosystem that contributes to nutrient metabolism, immune

regulation, and maintenance of intestinal barrier integrity (3). CKD disrupts this microbial balance by altering intestinal pH, slowing gastrointestinal transit, increasing urea secretion into the intestinal lumen, and promoting chronic inflammation. These changes favor the expansion of pathogenic bacteria while reducing beneficial microorganisms responsible for producing short-chain fatty acids (SCFAs) (4).

Microbial imbalance increases the production of uremic toxins such as indoxyl sulfate, p-cresyl sulfate, trimethylamine N-oxide (TMAO), and phenyl sulfate (5). These compounds enter systemic circulation because of impaired renal clearance, contributing to oxidative stress, endothelial dysfunction, vascular injury, and neuroinflammation. Consequently, CKD becomes not only a renal disorder but also a disease affecting cerebral vascular health (6).

Understanding the gut–kidney–brain axis has therefore become essential for identifying mechanisms responsible for neurological complications associated with CKD (7).

A comprehensive review of preclinical studies was conducted to evaluate the interactions among CKD-induced gut dysbiosis, aging, neuroinflammation, blood–brain barrier dysfunction, and cerebral microhemorrhage formation in murine models. Evidence describing microbial composition, inflammatory mediators, vascular pathology, oxidative stress, and neurological outcomes was critically synthesized to identify common mechanistic pathways and age-dependent responses.

Available evidence demonstrates that CKD disrupts intestinal microbial homeostasis by reducing beneficial bacterial populations while promoting the expansion of pathogenic taxa capable of producing uremic toxins. These microbial alterations intensify systemic inflammation and oxidative stress, impair endothelial function, and weaken the blood–brain barrier. Young mice exhibit modest cerebrovascular alterations with relatively preserved repair mechanisms, whereas aged mice develop more pronounced neurovascular injury characterized by increased cerebral microhemorrhages, heightened microglial activation, and greater cognitive impairment. Age-associated immune dysregulation and diminished vascular resilience substantially exacerbate CKD-induced neurological damage.

Gut dysbiosis contributes to cerebral injury through several interconnected biological pathways. One of the earliest events is disruption of the intestinal epithelial barrier, commonly referred to as a "leaky gut." Increased intestinal permeability permits bacterial endotoxins, particularly lipopolysaccharides (LPS), to enter systemic circulation and activate innate immune responses (8).

Activation of inflammatory pathways stimulates the release of cytokines including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Persistent systemic inflammation promotes endothelial dysfunction by reducing nitric oxide bioavailability while increasing reactive oxygen species (ROS) production (9).

Oxidative stress damages cerebral endothelial cells and weakens tight junction proteins that maintain blood–brain barrier (BBB) integrity. Simultaneously, circulating uremic toxins activate cerebral microglia and astrocytes, further amplifying neuroinflammation (10).

The resulting vascular injury increases capillary fragility, promotes leakage of erythrocytes into surrounding brain tissue, and ultimately leads to cerebral microhemorrhages. These microscopic vascular lesions are increasingly recognized as important contributors to cognitive decline, impaired motor coordination, and neurodegenerative changes observed in CKD (11).

Thus, gut dysbiosis serves as a major upstream driver linking renal dysfunction with cerebrovascular pathology (Table 1).

Age-Related Differences in Young and Aged CKD Mice

Experimental mouse models have demonstrated that aging substantially modifies the neurological consequences of CKD. Young mice generally possess greater vascular elasticity, more efficient antioxidant defenses, and stronger regenerative capacity, enabling them to partially compensate for CKD-induced systemic inflammation (12).

Parameter	Young CKD Mice	Aged CKD Mice	Biological Significance
Gut microbial diversity	Mild to moderate reduction	Marked reduction	Indicates progressive dysbiosis with aging
Beneficial SCFA-producing bacteria	Slightly decreased	Significantly depleted	Reduced anti-inflammatory protection
Pathogenic bacterial abundance	Moderately increased	Markedly increased	Higher production of uremic toxins
Intestinal permeability	Mild increase	Severe increase	Greater endotoxin translocation
Circulating uremic toxins	Elevated	Highly elevated	Increased neurovascular toxicity
Systemic inflammation	Moderate cytokine elevation	Pronounced chronic inflammation	Accelerates vascular injury
Oxidative stress	Mild to moderate	Severe oxidative damage	Promotes endothelial dysfunction
Blood–brain barrier integrity	Slight disruption	Extensive disruption	Increased vascular leakage
Microglial activation	Moderate	High	Enhanced neuroinflammation
Cerebral microhemorrhages	Few lesions	Numerous lesions	Greater cerebrovascular damage
Cognitive performance	Mild impairment	Significant impairment	Reflects cumulative neurological injury
Overall disease severity	Moderate	Severe	Aging exacerbates CKD-associated brain injury

Table 1: Comparison of Gut Dysbiosis and Cerebral Pathology in Young and Aged Mice with Chronic Kidney Disease

Although young CKD mice exhibit measurable gut microbial alterations and increased circulating uremic toxins, cerebral vascular injury tends to remain relatively limited. Blood–brain barrier disruption is mild, inflammatory cytokine expression is lower, and cerebral microhemorrhages occur less frequently (13).

In contrast, aged CKD mice experience profound deterioration in multiple protective mechanisms. Aging itself is associated with reduced microbial diversity, chronic low-grade inflammation (inflammaging), mitochondrial dysfunction, endothelial senescence, and impaired immune regulation. CKD superimposed upon these age-related changes markedly accelerates disease progression (14).

Aged mice display significantly greater accumulation of circulating microbial metabolites, increased oxidative stress, enhanced activation of microglia, extensive BBB breakdown, and widespread cerebral microhemorrhages. Histological studies consistently demonstrate increased iron deposition, hemosiderin accumulation, vascular degeneration, and neuronal loss compared with young animals (15).

Behavioral assessments further reveal greater impairment in learning, memory, spatial navigation, and executive function in aged CKD mice, highlighting the interaction between aging and CKD in promoting neurovascular injury.

Molecular Pathways Linking Gut Dysbiosis to Brain Microhemorrhages

Several molecular mechanisms mediate communication between the dysbiotic gut microbiome and the cerebral vasculature during CKD.

Inflammatory signaling through the nuclear factor-kappa B (NF-κB) pathway promotes continuous production of pro-inflammatory cytokines, perpetuating vascular inflammation. Oxidative stress generated through NADPH oxidase activation damages endothelial mitochondria and accelerates cellular apoptosis (16).

Loss of protective SCFAs—including butyrate, acetate, and propionate—reduces anti-inflammatory signaling and weakens intestinal barrier function. Reduced SCFA availability also diminishes regulatory T-cell activity, thereby enhancing systemic immune activation (17).

Matrix metalloproteinases (particularly MMP-2 and MMP-9) become upregulated in response to chronic inflammation and degrade extracellular matrix proteins surrounding cerebral vessels. This degradation weakens vascular basement membranes and increases susceptibility to microvascular rupture.

Simultaneously, endothelial nitric oxide synthase (eNOS) dysfunction decreases nitric oxide production, impairing cerebral blood flow regulation. Activation of microglia further releases neurotoxic mediators, perpetuating neuronal injury and blood–brain barrier disruption.

Together, these interconnected pathways create a pathological environment favoring cerebral microhemorrhage formation, especially in aged organisms where compensatory repair mechanisms are diminished (18).

Therapeutic Perspectives and Future Directions

Targeting gut dysbiosis has emerged as a promising strategy for reducing neurological complications associated with CKD. Dietary interventions rich in dietary fiber may restore beneficial microbial populations and increase production of anti-inflammatory short-chain fatty acids. Supplementation with probiotics, prebiotics, and synbiotics has demonstrated potential to improve intestinal barrier integrity, reduce systemic inflammation, and decrease circulating concentrations of uremic toxins in experimental studies (19).

Novel therapies directed toward microbial metabolism—including oral adsorbents, enzyme inhibitors, and microbiota-modulating compounds—may further reduce production of nephrotoxic and neurotoxic metabolites. Anti-inflammatory therapies targeting NF-κB signaling, oxidative stress pathways, and endothelial dysfunction may help preserve blood–brain barrier integrity and minimize cerebral vascular injury.

Future investigations should integrate multi-omics approaches, including metagenomics, metabolomics, transcriptomics, and proteomics, to identify biomarkers that predict neurological complications during CKD progression. Longitudinal studies comparing young and aged animal models are necessary to clarify the temporal sequence of microbiome alterations and cerebrovascular injury (20).

Translational clinical studies are also required to determine whether microbiota-targeted therapies can reduce cerebral microhemorrhages, improve cognitive outcomes, and enhance quality of life in patients with CKD. A better understanding of age-dependent mechanisms will facilitate the development of personalized interventions aimed at preserving both renal and neurological health.

Conclusion

Gut microbiota dysregulation represents a key mechanistic link connecting chronic kidney disease with cerebrovascular injury. Aging significantly magnifies the detrimental effects of CKD on cerebral microvascular integrity, resulting in increased susceptibility to brain microhemorrhages. Therapeutic approaches targeting the gut microbiome, reducing systemic inflammation, and preserving blood–brain barrier function may provide promising strategies to mitigate neurological complications associated with CKD, particularly in older populations. Further mechanistic investigations and translational studies are needed to validate these findings and support the development of microbiota-based interventions.

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