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How to Find the Missing Link between Cognitive Decline and Stroke in the Context of Chronic Renal Failure

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Introduction

In a study published this year [1], we used structural, cognitive, and physiological parameters to measure how the brain responds to ischemic stroke in the context of chronic renal failure. Our study, which utilized a prospective cohort of 431 participants, showed that 24 months following stroke, those with chronic renal failure (CRF) as determined by creatinine clearance (CCI < .60 ml/min) had a stronger association with cognitive decline than those without kidney dysfunction. Two known biomarkers of the aging brain, white matter hyperintensities (WMH) and cortical atrophy, along with different measures of cognitive impairment, were found to have a positive correlation with pre-stroke impaired renal function [1]. Previous studies have shown the strong association between kidney dysfunction, stroke and cognitive impairment [1-6]. However, researchers have not yet determined the link between CRF and cognitive decline in patients recovering from stroke. Our study expanded on previous works, including the widely cited Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which showed a strong association between cognitive impairment and kidney decline[1], [3,5]. In this commentary, we evaluate different mechanisms in which CRF may affect cognitive function post stroke and propose pathways through which CRF may inhibit brain recovery, helping us to narrow our focus on specific pathophysiological processes that may yield new approaches to therapy in future clinical trials.

Chronic Renal Failure and Cerebral Small Vessel Disease in Cognitive Impairment Post Stroke

Diabetes and hypertension in particular appear to be obvious targets for neuro-protection post stroke in the context of CRF, however our study and others [1,7,8] have shown consistent results of cognitive decline in CRF regardless of the specific etiology of kidney dysfunction. End-organ damage caused by long-term diabetes is attributed to advanced glycated end products (AGES) which are known to known microangiopathic effects including chronic renal failure, inflammation, retinopathy, stroke, hypertension, and coronary artery disease [9]. The buildup of AGES suppresses endothelial production of the beneficial effects of nitric oxide in cerebral vasculature and throughout the body [1,10], but this does not explain why there is worsened cognitive impairment post stroke. One small study performed by Laible et al. [11] on twelve patients did not find WMH to be related to renal disease as we found in our study, but it did determine that renal disease was associated with increasing amounts of cerebral microbleeds, a known marker of cerebral small vessel disease [12]. Microangiopathies, such as cerebral microbleeds, have been shown by Tang et al. [13] to have an inverse association with reversion of vascular cognitive impairment in stroke, suggesting signs of a microvascular vessel weakness also found in renal disease that may play a role leading to microhemorrhage in the brain parenchyma.

Hypertensive nephroangioscelerosis, the fibrous transformation of smooth muscle in arterial blood vessels, presents another mechanism to exclude from being the possible link between cognitive decline in stroke in renal disease, since it also damages the kidneys and has itself proven to be a source of stroke [14]. An interesting autopsy study conducted in France by Abboud et al describes the histopathological relationship between the kidneys and brain [14]. This study found that hypertensive nephroangiosclerosis is associated with stroke and a history of hypertension in 39.8% of patients, providing evidence of a structural connection between chronic renal damage and cerebral small vessel disease [5,14]. Parenchymal pathologies conversely did not show an association with nephroangiosclerosis, supporting our understanding that the process is governed by reno-vascular disorders such as hypertension and diabetes that result in a propensity for microbleeds and lacunar infarcts, which have also been linked to cognitive impairment [2,8,14,15]. We also note that based on the results of our study, creatinine clearance may function well as a marker for cognitive decline post stroke, and investigating metabolic and biochemical pathways involved in neurological regeneration that are affected by CRF may provide a clue as to its source [2,16–19].

CRF in the Context of Neurological Recovery from Stroke and the Metabolic Consequences on the Brain

Studies on brain regeneration and recovery after stroke can help us understand how the byproducts of kidney damage interrupt the resources that brain tissue, neurons and supporting cells need to recover from a traumatic episode, like an ischemic stroke, in areas such as the penumbra and related neural networks [2,16,19,20]. As described by Dancause et al and others, white matter shows increased axonal growth creating connections to new regions in the cortex after experiencing damage from ischemia or other processes [21,22]. However, in the context of kidney disease, axonal growth processes are inhibited by uremic plasma, which contains high concentrations of nitrogenous waste [20]. Braguer et al. [20] showed through in vitro experiments on the microtubule component of axon growth, that in uremic medium tubulin polymerization is inhibited but is reversed by the addition of the vitamin biotin. These experiments followed a

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study by Yazidis et al. in which nine hemodialysis patients who were given 10 mg of biotin daily experienced improvement in a variety of neurological symptoms, including uremic neuropathy, "disorientation, speech disorders, memory failure, myoclonic jerks, flapping tremor, restless legs, paresthesia and difficulties in walking" underscoring the biochemical connection between neurological processes and renal function [23].

The brain parenchyma recovering from stroke is most susceptible to cognitive impairment because it is less resilient to the metabolic changes found in the context of chronic renal disease [1,2,16,24]. This increased risk of impairment is due to the vast effects of uremic toxins, including the release of inflammatory compounds, breakdown of the blood-brain barrier, autonomic dysfunction, down regulation of nitric oxide synthase, and induction of the vicious RAAS (renin-angiotensin-aldosterone-system) cycle [2,19]. These processes concurrently propagate small vessel disease, end-organ damage and likely prevent full recovery of neurological networks lost in a damaged brain [7, 25] Kidney failure also affects the neurological physiology due to the kidneys' role in managing toxins such as drugs and nitrogenous waste which can disrupt the synthesis of neurotransmitters, energy metabolism, and other routine cell processes [19,20,26].

Another example of neuro-metabolic changes caused by chronic kidney disease can be seen in the neurological recovery processes after brain damage in which the undamaged hemisphere compensates after stroke or other lesions [17]. These biochemical and neurohistochemical compensation processes that occur after damage different parts of the brain modulate the damage according to location. Specifically superficial areas show increased excitability ipsilaterally and deeper areas show increased excitability contralaterally via GABAA receptor modulation [27], which is then blocked by N-methyl-D-aspartate-receptor antagonists [18]. Understanding neuromodulatory pathways such as these, particularly in the context of renal disease, could provide specific targets for therapy for stroke victims and those recovering from brain injury.

Conclusion

In sum, based on our recent study and others, we believe that investigating the metabolic pathways involved in brain recovery in addition to current research on hypertension and diabetes in stroke and cerebral small vessel disease may hold the missing link as to the role of chronic kidney disease in cognitive impairment post stroke. The prevalence of stroke and importance of cognitive function in CRF in medicine will impel continued research on this topic and hopefullyprovide a basis for novel clinical trials and early interventions in the future.

Competing Interests

The authors declare that there are no competing interests.

Authors' Contributions

GM performed background research and wrote the manuscript.EA proposed topic of commentary and edited manuscript;

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