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Mechanisms of Cerebral Microvascular Disease in Chronic Kidney Disease

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Abstract

Numerous studies report linkage between chronic kidney disease (CKD) and cerebrovascular disease. This association has been particularly strong for cerebral small vessel disease. Significant findings have emerged from studies ranging from case reports, small case series, and larger cohort investigations. The latter show a relationship between declining renal function, microvascular disease, and cognitive impairment. One troubling aspect has been the relative paucity of mechanistic investigations addressing the CKD-cerebrovascular disease linkage. Nevertheless, mechanistic observations have begun to emerge, showing cerebral microhemorrhage development in animal models of CKD independent of hypertension, an important co-morbidity in clinical studies. Initial cell culture studies show endothelial monolayer disruption by CKD serum, suggesting blood-brain barrier injury. It is noteworthy that CKD serum is known to contain multiple plausible mediators of microvascular injury. Further studies are on the horizon to address the critical question of the linkage of renal dysfunction with vascular cognitive impairment.

Keywords

kidney; microvascular disease; microbleeds; animal models

Introduction

Over the past decade, the linkage between chronic kidney disease (CKD) and stroke has been demonstrated repeatedly (see Symposium paper by Webster/Coull for details). This association has been particularly strong for cerebral small vessel, or microvascular, disease (1). Despite those observations, the nature of the linkage has been obscure. The purpose of this paper is to review how this important area of biomedical inquiry has developed, and suggest areas for future directions. I will emphasize observations that have emerged from our particular research group, which demonstrate how one path forward has emerged.

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Cerebral microvascular disease represents a spectrum of brain changes that are generally considered either ischemic or hemorrhagic. The ischemic side consists of small, deep infarcts, sometimes referred to as lacunes; microinfarcts; and white matter disease of aging, sometimes referred to as leukoaraiosis. The hemorrhagic side includes cerebral microhemorrhage, believed to be the pathological substrate of cerebral microbleeds. Finally, cerebral atrophy is an important but often underappreciated component of the neuropathological spectrum of cerebral microvascular disease (2).

Clinical Observations

Our initial observations focused on a patient with end stage renal disease on hemodialysis. This 67 year old woman showed striking progression of cerebral microbleeds over a two year period of observation, with concurrent cognitive decline. The patient also had labile hypertension, a common feature of end stage renal disease. This coexistence of hypertension with end stage renal disease is a common confounder in any attempt to attribute neurological decline to CKD (3).

Encouraged by this initial case report, we began a more systematic survey of cerebral microbleeds and CKD. We performed a retrospective analysis of CKD patients, with and without hemodialysis dependence, along with a control group; all had multiple brain MRIs over the course of an average of approximately one and a half years. Microbleeds were present in half the hemodialysis patients, and even with a small sample size (eight-ten subjects per group), the hemodialysis group was significantly more likely to show microbleed progression (4).

In a larger series of subject, we studied 193 elderly members of an ongoing longitudinal study of the oldest old (5). We measured levels of cystatin C, an index of renal function independent of muscle mass, in relation to cognitive function and microvascular disease. Elevated cystatin C levels (indicating declining renal function) predicted global cognitive impairment as well as reduced performance on specific neuropsychological tests of executive and visual-spatial function. In the subset of 129 subjects who had brain MRI, increasing cystatin C was significantly associated with number of infratentorial cerebral microbleeds and reduction in grey matter volume (5).

Mechanistic Considerations

While our clinical and epidemiological observations were all consistent with the ongoing hypothesis linking CKD with cerebral microvascular disease and cognitive decline, the question of mechanisms immediately arose. How exactly is CKD linked to changes in brain structure and function? Are these changes specific for CKD, or do they simply reflect common comorbidities, especially hypertension? Here several nontraditional mechanisms are noteworthy.

Ectopic calcification is an important systemic component of CKD, resulting from phosphate overload and parathyroid disorders disrupting the normal role of bone acting as a calcium reservoir (1). In addition, phosphate overload drives both induction of vascular smooth muscle cells assuming an osteogenic phenotype as well as apoptosis of the smooth muscle

cells. These pro-calcification effects are amplified by loss of a variety of calcification inhibitors, eg, klotho, matrix glutamate protein, pyrophosphate, and fetuin-A (1). The net effect is vascular calcification and other elements of vascular injury, with the arteriole as a key target.

Arteriolar injury will impact the brain's capacity to regulate cerebral blood flow, and this is one proposed mechanism of cerebral microvascular disease (6). CKD is, as noted above, characterized by vascular calcification, transformation of smooth muscle cell phenotype, and smooth muscle apoptosis (1). Evidence supporting the microvascular significance of this scenario includes association of extent of intracranial vascular calcification and cerebral microbleeds (7). Thus, vascular calcification represents an important potential mechanism linking CKD and cerebral microvascular disease.

The actual vascular source of cerebral microbleeds in CKD remains undetermined. While arteriolar tears are assumed to be the predominant site (8), animal models of cerebral microhemorrhage have demonstrated a capillary site of origin of bleeding, consistent with disruption at the level of the blood-brain barrier (9). Nevertheless, novel microhemorrhage-generating mechanisms have been described that are of particular relevance to CKD. Specifically, endothelial erythrophagocytosis has been demonstrated in cell culture systems and limited in vivo studies, and these are highly relevant to microhemorrhage formation in CKD. Endothelial erythrophagocytosis appears to require substantial abnormalities of the erythrocyte membrane prior to initiation of phagocytosis, particularly exposure of phosphatidylserine that is characteristic of aged red blood cells (10). It is therefore noteworthy that CKD is characterized by highly prevalent erythrocyte membrane abnormalities consistent with what may predispose to endothelial phagocytic activity (11). The role of endothelial erythrophagocytosis in CKD microbleed formation represents an intriguing speculation that will be the subject of intense investigation.

Cerebral Microvascular Disease in CKD Models

The optimal way to investigate mechanistic linkage between CKD and cerebral microvascular disease requires CKD models. These models have been developed, both *in vitro* and *in vivo*, and have provided important initial insights into the relationship. The models show a varying degree of complexity and adequacy, but do represent an important first step.

Two CKD animal models have been used with some success. These are the adenine diet-induced model, which demonstrates tubulointerstitial nephritis, and the 5/6 nephrectomy model, requiring removal of one kidney and two-thirds of the other (4). Use of these two models has been quite helpful in mechanistic investigations, due to the fact that both induce renal insufficiency. However, the adenine diet model does not generate hypertension, while the 5/6 nephrectomy model induces hypertension. Interestingly, both models generate cerebral microhemorrhages to a similar extent, suggesting that the microvascular consequences of CKD may occur independent of hypertension (4).

Cell culture work has been developed with a goal of producing a genuine *in vitro* model of cerebral microbleeds. Published work to date has used the bEnd.3 immortalized mouse brain microvascular endothelial cell line. The endothelial monolayer represents a good initial model of the microvasculature; substantial disruptive effects are demonstrable with CKD serum beginning at six hours, peaking at 13 hours, and normalizing over the course of one week (4). The limited blood-brain barrier properties of this endothelial cell type warrant caution in interpreting these findings. However, they are consistent with microvascular disrupting effects, including blood-brain barrier injury, of CKD serum.

What serum components of CKD may be damaging to the brain microvasculature? In fact, there are many candidates from which to choose. A variety of colon-derived bacterial toxins are of particular interest, ie, indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide (TMAO) (12,13). These have all been studied extensively and have been convincingly demonstrated to show their capacities to generate oxidative stress and induction of inflammatory mediators (1). These candidate mediators are thus the subject of intense ongoing investigation, from the perspective of their capacity to injure the brain's microvasculature.

There are multiple therapeutic approaches that relate to these mechanistic issues. These include use of dietary supplements such as prebiotics (to induce a more beneficial gut flora) and probiotics (to supplement the gut microbiome) (13). For hemodialysis patients, use of cooled dialysate may produce hemodynamic stability with improved intestinal barrier (14). The latter is thought to reduce translocation of gut bacterial toxins to the systemic vasculature (13) and limited clinical trial data suggest that it may provide white matter neuroprotection (15).

Summary and Conclusions

The relationship between CKD and cerebral microvascular disease is an area of emerging interest, with importance of vast potential. There already is a substantial body of literature, clinical and epidemiologic, linking CKD and microvascular disease. The consequences of microvascular disease in this population are substantial, and are particularly relevant for cognitive decline due to vascular cognitive impairment.

There are multiple plausible mechanisms that potentially link CKD and cerebral microvascular disease. Some of these are novel mechanisms. For example, vascular calcification, highly prevalent in CKD, may impact development of cerebral microbleeds. Another novel process is endothelial erythrophagocytosis, which may mediate microhemorrhage development without requiring disruption of the microvasculature.

To date, the most convincing mechanistic linkage between CKD and cerebral microvascular disease comes from *in vitro* and *in vivo* studies. Cell culture investigations have demonstrated substantial disruption of the brain endothelial barrier by CKD serum, and there are multiple CKD serum components capable of mediating this effect (eg, endotoxin, urea, indoxyl sulfate, p-cresyl sulfate, and TMAO) by generating oxidative stress or induction of

inflammatory mediators. Importantly, multiple CKD animal models have shown microbleed-induction effects of CKD, effects that are independent of hypertension.

We are left with an intriguing body of data on the nature of the CKD-microvascular disease relations. There is much preliminary mechanistic data, and a substantial body of clinical literature. Linkage between advanced CKD, i.e., hemodialysis-dependent patients, and microvascular disease seems highly likely if not assured. There is, however, a greater question, currently very much in the open: Is vascular cognitive impairment substantially mediated by renal function? This would appear to be a question of fundamental importance with paradigm shift-inducing implications.

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