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Cerebrovascular Disorders in Patients with End-Stage Chronic Kidney Disease

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Annotation: Given the increasing worldwide prevalence of chronic kidney disease (CKD), it is critical to decrease the associated risk of debilitating vascular complications, including stroke, congestive heart failure, myocardial infarction, and peripheral vascular disease. Treatment options for reducing the risk of all subtypes of stroke in patients with CKD remain limited. For patients with end-stage kidney disease (ESKD), novel applications of noninvasive imaging may help personalize the type of dialysis and dialysis prescription for patients at high-risk.

Keywords: Stroke, Cerebral autoregulation, Cerebral blood flow, Chronic kidney disease, Arteriosclerosis.

Chronic kidney disease (CKD) affects both brain structure and function. Patients with CKD have a higher risk of both ischemic and hemorrhagic strokes. Age, prior disease history, hypertension, diabetes, atrial fibrillation, smoking, diet, obesity, and sedimentary lifestyle are most common risk factors. troke is one of the most frequent neurological conditions and the leading cause of death. As patients with CKD have more risk factors for atherosclerosis, it is estimated that the risk for developing cardiovascular diseases, including stroke, is 5–30 times greater than in the general population (2). The prevalence of coronary artery disease increases as kidney function declines (~40% in patients with end stage kidney disease) (3, 17). The risk of stroke in CKD patients is particularly high. From a global perspective, the burden of CKD is on the rise with a prevalence estimate of 9.1% (8.5–9.8) for all CKD stages.(1) It is well established that impaired kidney function is an independent risk factor, above and beyond traditional risk factors, for cardiovascular disease. Nontraditional CKD-related risk factors such as chronic inflammation, uremic toxins, reactive oxygen radicals, anemia, and mineral-bone disorder are proposed to contribute to risk by triggering vascular injury and endothelial dysfunction.(17) Uremia can cause protein carbamylation which has proatherosclerotic effects via enhanced dyslpidemia.(20) It can also impair platelet adhesiveness and platelet endothelial interaction, increasing the risk of hemorrhagic stroke.(21) Hyperphosphatemia, arising from CKD-related mineral-bone disorder, causes arterial medial calcification by inducing an osteogenic phenotype change of vascular smooth muscle cells. Chronic kidney disease (CKD) is associated with a high prevalence of cerebrovascular disorders such as stroke, white matter diseases, intracerebral microbleeds and cognitive impairment. This situation has been observed not only in end-stage renal disease patients but also in patients with mild or moderate CKD. The occurrence of cerebrovascular disorders may be linked to the presence of traditional and non-traditional cardiovascular risk factors in CKD. Here, we review current knowledge on the epidemiological aspects of CKD-associated neurological and cognitive disorders and discuss putative causes and potential treatment. CKD is associated with traditional (hypertension, hypercholesterolaemia, diabetes etc.) and non-traditional cardiovascular risk factors such as elevated levels of oxidative stress, chronic inflammation, endothelial dysfunction, vascular calcification, anaemia and uraemic toxins.

CKD increases the risk of large vessel stroke via its effects on carotid artery stenosis, plaque size, and carotid intima-media thickness [19]. In a series of prospective carotid ultrasound and CT imaging studies of patients after a stroke, those with CKD had significantly higher internal carotid artery stenosis and plaque size, including after adjustment for conventional CVD risk factors [14]. CKD was independently associated with carotid atherosclerosis in patients with hypertension [12]. Many patients in these studies were of Asian descent, limiting the generalizability of results; however, the effect of CKD on large vessel and intracranial hemodynamics in other patient populations is an area of active research.

There are unique influences whereby CKD can impact the risk of stroke. Many factors are involved, including endothelial dysfunction, accelerated arteriosclerosis, and impaired cerebral autoregulation [6, 7]. However, stroke prevention measures in patients with CKD remain similar to those in populations without kidney disease. Thus, there is an unmet need for stroke prevention measures specific to individuals with CKD. Intracranial imaging is not currently standard of care in patients with CKD or ESKD. In patients with ESKD, noninvasive imaging modalities may inform individualized prescriptions for dialysis or choices of dialysis modality (discussed below). Patients at high risk for stroke might be more likely to benefit from dialysis options that reduce the risk of systemic hypotension and exacerbate cerebral hypoperfusion.

Creatinine clearance is a strong and independent determinant of arterial stiffness and dilatation in patients with CKD [7]. This literature has typically focused on changes in the internal carotid artery and carotid artery intima-medial thickness (cIMT). Briet et al.[9] prospectively evaluated patients with mild to moderate CKD in order to assess the association between arterial stiffness and remodeling as CKD progressed. After 3.5-year follow-up, aortic stiffness was unchanged; however, carotid stiffness increased significantly (adjusted slope, +0.28 + 0.05 m/s per year, $p < 0.0001$). Estimated GFR was independently related to increased arterial diameter, circumferential wall stress, and carotid artery stiffness. In a multivariate Cox analysis, carotid circumferential wall stress was an independent determinate of progression to ESKD (HR 2.48 [1.63–3.78]. Arterial dilatation results from the inability of a blood vessel's elastic fibers to sustain physiological pulsatile stress [13, 14]. In the setting of a low resistance organ, such as the brain, this may lead to increased blood flow and strain on the downstream cerebral vasculature. Kidney disease and stroke have common traditional cardiovascular risk factors, such as ageing, diabetes, hypertension, dyslipidaemia, obesity, and smoking;25 in other words, both the kidney and brain are target organs of arteriosclerotic insults. However, these factors do not seem to be sufficient to capture the extent of the risk for cardiovascular and cerebrovascular diseases in patients with chronic kidney disease.

CKD increases the risk of large vessel stroke via its effects on carotid artery stenosis, plaque size, and carotid intima-media thickness [1-3, 32-36]. In a series of prospective carotid ultrasound and CT imaging studies of patients after a stroke, those with CKD had significantly higher internal carotid artery stenosis and plaque size, including after adjustment for conventional CVD risk factors [33-35]. CKD was independently associated with carotid atherosclerosis in patients with hypertension [35]. Many patients in these studies were of Asian descent, limiting the generalizability of results; however, the effect of CKD on large vessel and intracranial hemodynamics in other patient populations is an area of active role.

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