Chronic Kidney Disease and Stroke

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Chronic kidney disease (CKD) is associated with an increased risk of both ischemic and hemorrhagic stroke. In addition to shared risk factors, this higher cerebrovascular risk is mediated by several CKD-associated mechanisms including platelet dysfunction, coagulation disorders, endothelial dysfunction, inflammation, and increased risk of atrial fibrillation. CKD can also modify the effect of treatments used in acute stroke and in secondary stroke prevention. We review the epidemiology and pathophysiology that link CKD and stroke and the impact of CKD on stroke outcomes. Interdisciplinary collaboration between nephrologists, pharmacists, hematologists, nutrition therapists, primary care physicians, and neurologists in providing care to these subjects may potentially improve outcomes.

Key Words: Chronic kidney disease, Stroke, Thrombolysis, Alteplase, Stroke prevention

Introduction

CKD affects at least 20 million people in the United States, and the prevalence of CKD is particularly common among adults older than 70 years. Diabetes and hypertension further increase this risk, with nearly 1 of 3 adults with diabetes and 1 of 5 adults with hypertension having CKD.[1] This huge group of patients is burdened with a particularly high risk for both ischemic and hemorrhagic stroke. Reduced estimated glomerular filtration rate (eGFR) and elevated amounts of albuminuria are associated with an increased risk for incident stroke.[2] In the Reasons for Geographic and Racial Differences in Stroke study, among participants 45 years or older of age and with an eGFR less than 45 mL/min/1.73 m^2 who were free of a history of stroke or transient ischemic attack at baseline, the incidence of stroke symptoms over a median of 2.1 years was 20.7%.[2] In addition to the effect of common risk factors, stroke risk is increased through several CKD-associated mechanisms, such as hyperhomocysteinemia, inflammation, oxidative stress, anemia, endothelial dysfunction, arterial stiffness, and predisposition to atrial fibrillation. The management of stroke in the setting of CKD may be limited by a greater risk of treatment-related side effects because of impaired kidney drug clearance and increased bleeding tendencies. This quandary requires close collaboration among different clinical disciplines that manage the CKD population.

The Epidemiological Association Between Kidney Impairment and Stroke

Risk factors for stroke identified in the general population, including older age, hypertension, diabetes, obesity, and cigarette smoking, are also the risk factors for the genesis of CKD.[3] For this reason, an association between stroke risk and CKD is not surprising. The risk of stroke, however, increases incrementally with stages of CKD in a dose-like effect, a relationship that is independent of other vascular comorbidities. Proteinuria, which is an early marker of kidney disease, is associated with an increased risk of stroke. After adjusting for other vascular risk factors and independent of reduced eGFR, proteinuria confers a 71% increase in the risk of stroke (risk ratio [RR] 1.71; 95% confidence interval [CI] 1.39-2.10, $P = .008$).[4] If the GFR is diminished, the risk can be even greater. A meta-analysis incorporating data from 33 studies and 280,000 patients found that stroke risk increased by more than 43% (RR 1.43, 95% CI 1.30-1.57; $P < .001$) in patients with a GFR less than 60 mL/min compared with patients with normal eGFR, independent of other clinical factors.[5] The risk of stroke was also higher in those with a GFR less than 40 mL/min compared with those with a GFR of 40 to 60 mL/min, suggesting a dose-like effect. One prospective study found that the combination of CKD and anemia was associated with a substantial increase in stroke risk (hazard ratio [HR] 5.43, 95% CI 2.04-14.41), independent of other known risk factors.[6] Because of subclinical cerebrovascular disease, CKD is also associated with increased risk of cerebral microhemorrhages and cognitive impairment.[7,8] The situation is even more grave for patients with advanced CKD. The US Renal Data Systems reported that, in 2011, 3.1% of all deaths of dialysis patients were because of stroke, but cerebrovascular events may have also accounted for a portion of the 26.9% of deaths attributed to sudden cardiac death.[9]

Kidney Replacement Therapy and Stroke Risk

These prior studies confirm that with more advanced stages of CKD the risk of stroke increases; however, the risk of stroke seems disproportionally increased among individuals with ESRD undergoing dialysis.[10] For example, patients with ESRD receiving hemodialysis have about a 2 to 10 times greater incidence of stroke compared with the general population (RR 6.1, 95% CI 5.1-7.1 for Caucasian men; RR 4.4, 95% CI 3.3-5.5 for African American men; RR 9.7, 95% CI 8.2-11.2 for Caucasian women; RR 6.2, 95% CI 4.8-7.6 for African American women). Rates of stroke vary between 10 and 33 per 1000 patient-years depending on study population and design. Those with ESRD also have a higher

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prevalence of hemorrhagic strokes compared with the general population (HR 6.83, 95% CI 5.89-7.92).[11,12]

The heightened risk of stroke in advanced CKD, particularly those on dialysis, likely results from the interplay of the vascular comorbidities associated with kidney impairment and pathology resulting from uremia, such as accelerated vascular calcification and the malnutrition-inflammation-atherosclerosis syndrome. In subjects undergoing hemodialysis, stroke rates peak at 10 to 35 per 1000 patient-years with hemorrhagic stroke accounting for 20% to 30% of all events. Older age, hypertension, diabetes, and established cerebrovascular disease are additional risk factors for stroke. Dialysis initiation constitutes the highest risk period.[12] Advanced kidney disease is also associated with worse survival and functional outcome.[12]

The additional risk of stroke conferred by ESRD persists even among individuals who already have significant stroke risk because of conditions, such as atrial fibrillation.[10] This independent increased risk could be because of the impact of metabolic disturbances associated with reduced eGFR. In the setting of ESRD, however, the additional exposure to dialysis and dialysis-specific medications may also be contributing to cerebrovascular risk. In a study of 21,000 US dialysis patients aged 67 years or older, stroke rates began to rise about 3 months before the start of dialysis and peaked during the first 30 days of dialysis. Transient fluid shifts leading to hemodynamic instability are one potential mechanism underlying this risk.[13] In a study of a nationwide retrospective cohort in Taiwan, and after adjusting for all potential confounders and competing risk of death, patients receiving peritoneal dialysis had a lower risk of hemorrhagic stroke (HR 0.75; 95% CI 0.58-0.96) compared with those receiving hemodialysis, although the risk of ischemic stroke was similar.[11]

CLINICAL SUMMARY

- Independent of other vascular co-morbidities, the risk of stroke increases incrementally with worsening stages of CKD.
- CKD increases the risk of stroke-related neurological deficits, worse functional outcomes and mortality.
- Kidney impairment affects platelet and endothelial function, coagulation factors, arterial wall thickness, systemic inflammation, homocysteine levels, and risk of atrial fibrillation.
- Advanced CKD may modify the degree of therapeutic effect and side effects profile of medications commonly prescribed for stroke such as IV-tPA, anticoagulants, antiplatelet agents, and statins.

Stroke Subtype and CKD

Ischemic and hemorrhagic strokes occur through distinct pathophysiological mechanisms, and it is plausible that CKD might promote specific subtypes of stroke. Hemorrhagic strokes can be intraparenchymal or subarachnoid. Ischemic strokes can occur as a result of local large-vessel occlusion, small-vessel occlusion, and embolism from a proximal source, such as an abnormal heart valve or another cardiac source. One cohort study found that 76% of strokes in patients receiving dialysis were ischemic.[14] The largest proportion was because of cardiogenic embolism (28%), followed by small-vessel occlusion (20%) and large-artery atherothrombosis (11%), with 18% having multiple possible causes and 23% having undetermined causes. Advanced CKD (eGFR $<$ 30 mL/min) is also associated with a higher risk of hemorrhagic transformation of an initially ischemic stroke.[12] In 1 study, after adjusting for other risk factors, the risk of hemorrhagic transformation was nearly 3-fold higher (odds ratio [OR] 2.90; 95% CI 1.26-6.68, $P = .012$) in subjects with eGFR less than 30 mL/min.[15] Thus, the incidence of primary hemorrhagic stroke increases as GFR declines.[16] In addition, CKD is associated with an increase in the severity of hemorrhagic stroke. In 1 study comparing those with moderate-to-severe CKD (GFR $<$ 45 mL/min) with those with normal kidney function, hematoma volume was 2.3 times greater ($P = .04$) in those with CKD and was associated with more than 6-fold higher odds of lobar location (95% CI 1.59-24.02).[17] This evidence suggests that hemorrhagic strokes are more prevalent in patients with severe CKD.

CKD and Stroke Outcomes

Irrespective of stroke subtype, patients with CKD who had a stroke have greater neurologic deficits, worse functional outcomes, and higher mortality rates compared with those patients without CKD.[18] In-hospital mortality after stroke is increased among those with CKD with the risk higher in those with more severe kidney impairment. Similarly, patients receiving hemodialysis have a 3-fold higher risk of death after acute stroke compared with nonhemodialysis patients, an effect that is independent of other risk factors.[19,20] After stroke, a GFR of 15 to 44 mL/min was associated with 1-year mortality of 2.8% (95% CI 1.3-6.0).[20]

Pathophysiology

The multiple pathophysiological effects of kidney dysfunction contribute to stroke risk in patients with CKD (Fig 1). These include direct effects of kidney impairment on platelet and endothelial function, coagulation factors, arterial wall thickness, systemic inflammation, homocysteine levels, and risk of atrial fibrillation.

Platelet Dysfunction

Patients with CKD can manifest either bleeding diatheses or thrombotic tendencies. The risk of intracranial hemorrhage (ICH) is in part related to platelet dysfunction. In vitro studies with platelets from patients with kidney failure show diminished platelet degranulation, reductions in stored platelet adenosine diphosphate and serotonin, and decreased platelet synthesis of thromboxane.[21] There is also decreased activation of glycoprotein IIb-IIIa receptors on the platelet membrane leading to reduced binding of platelets to Von Willebrand factor and fibrinogen.[18] Uremia