Chronic kidney disease and cerebral small vessel disease: A casual or causal cerebrorenal relationship?

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Recent studies show that individuals with progressive chronic kidney disease have a greater risk of cardiovascular events, hospitalization and death [1]. Chronic kidney disease (CKD) is prevalent in acute stroke patients with rates varying from 20–35% in ischemic stroke and from 20–46% in intracerebral hemorrhage [2, 3]. Previously, a higher four to ten times, prevalence of stroke in dialysis patients have been reported [3]. It can therefore be concluded that CKD is an established and emergent risk factor for cardiovascular disease in general and for cerebrovascular disease in particular.

Chronic kidney disease is defined either by a decrease in the estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m$^2$ or by the presence of albuminuria as a marker of an increased glomerular permeability [4]. It represents also a poor prognosis factor in patients with acute stroke and its presence has been associated with stroke severity and poor outcomes in ischemic and hemorrhagic stroke. A study reported that patients with CKD had a 49% greater risk of neurological deterioration during hospital stay and in-hospital mortality, and higher degree of disability at discharge according to the modified Rankin scale score of 2 or more than patients without CKD [5]. Greater risk of recurrence of non-cardioembolic stroke in CKD patients has also been reported [3].

Worse neurological prognosis may be caused by the presence in these patients of proteinuria and albuminuria, and both conditions are significantly associated with high levels of inflammatory cytokines and oxidative stress, inflammation and conditions promoting coagulation, potentially causing excessive vascular damage at stroke onset. These factors are also associated with accelerated atherosclerosis and endothelial dysfunction. Albuminuria is also predictive of hemorrhagic transformation of stroke [2].

We must also point out that CKD patients have both high thromboembolic and high bleeding risks and this has implications for deciding the optimal therapeutic strategy for primary or secondary prevention in these clinical conditions. Thus, non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants) seem to be safer and more effective for patients with nonvalvular atrial fibrillation than warfarin, but cannot be given to patients with advanced CKD because the activity of these drugs is greatly affected by renal function [2, 6]. Intravenous thrombolysis is not contraindicated for patients with CKD but experts have limited experience with this treatment in these patients [6].

It is worth mentioning that kidney impairment is strongly associated with cerebral small vessel diseases (SVDs), which occur as asymptomatic lacunar infarcts (Figure 1) often resulting in classical lacunar syndromes (pure motor hemiparesis, pure sensory syndrome, sensorimotor stroke, ataxic hemiparesis or dysarthria-clumsy hand) or, less frequently, in atypical lacunar syndromes [7,8]. They also result in leukoaraiosis or white matter hyperintensities, silent lacunes, prominent or enlarged perivascular spaces and cerebral microbleeds [9].

One study reported that the volume of white matter lesions increased when eGFR decreased [10], and another showed that proteinuria had strong relation with both the presence and number of microbleeds [11].

This special relationship between CKD and cerebral SVDs is still unclear and warrant further investigation but is probably due to the fact that the vasoregulation of the microvasculature of the two organs (kidney and
brain) is similar anatomically and functionally [12]. Afferent glomerular arterioles of the juxtamedullary nephrons and the cerebral perforating small vessels share common anatomical and functional characteristics. They are short arterioles arising directly from large high-pressure arteries and so they are exposed to high pressure and they have to maintain a strong vascular tone. These would be “strain vessels” together with the coronary microcirculation and retinal arteries [13, 14]. Distinctively hypertensive vascular damage occurs first and severely in such strain vessels. Kidney impairment is, therefore, characterized by glomerular endothelial dysfunction and lipohyalinosis both of which are features of cerebral small-artery diseases (Figure 2) [13–15]. Cerebral SVDs and white matter hyperintensities are mediated by ischemic arteriolosclerosis, low perfusion, endothelial dysfunction and blood-brain barrier damage [9].

Other relevant clinical observations reaffirm this causal association. For example, albuminuria—component of CKD that reflects glomerular damage distal to the juxtamedullary glomerular arterioles—also seems to reflect an early stage of damage of cerebral SVDs [16–18]. In a meta-analysis, the presence of proteinuria was associated with a 71% increased risk for stroke compared with those without proteinuria [17], and another study also reported albuminuria as an independent predictor of ischemic stroke recurrence [18].

It should finally be pointed out that patients with CKD have a higher risk of developing cognitive impairment and dementia than the general population, which might be explained by a triple mechanism: first, by direct neuronal toxicity by uremic toxins; second, by the effects of vascular risk factors on cerebral parenchyma (mainly chronic hypertension); and third, by the high prevalence of silent lacunar infarcts, white matter hyperintensities and cerebral microbleeds. In short, CKD, retinopathy, and cognitive impairment, share common vascular pathology with cerebral SVDs [19–22]. Patients with CKD may probably develop more cerebral cortical atrophy, as observed in patients with ischemic lacunar stroke subtype (Figure 3), but we do not yet have data on this subject in the CKD patients’ subgroup, aspect that should be considered as a promising and exciting future research area [23].
CONCLUSION

Chronic kidney disease (CKD) and stroke have a strong relationship. CKD is a predictor of stroke, subclinical cerebrovascular abnormalities and cognitive impairment. Cerebrorenal main interaction is between CKD and SVD. They share arteriolar anatomy, and traditional cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, and smoking) including age, are commons to CKD and stroke promoting its pathological association. Research should be dedicated to increasing the awareness and understanding of the cerebrorenal interaction in order to reduce the risk of stroke in patients with CKD and improve health care management.

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