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COMMENTARY

Is CKD a surrogate marker for predicting cognitive impairment?

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Because medical approaches to cognitive impairment (CI) in its progressive state are limited, it is expected that early detection of CI may be the key to preventing worsening of quality of life and reducing the profound disease burden, morbidity and mortality. However, there are few markers for evaluating the future risk of CI in subjects. Recently, impaired kidney function was reported to be associated with dementia and CI. For example, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study showed an association between reduced kidney function and CI.[1] Other studies have also indicated that patients with more severe chronic kidney disease (CKD) have a higher risk of CI.[2–4] In a recent study in Japan, Yano *et al.*[5] found that hypertensives with CKD experience more stroke events compared with hypertensives without CKD, indicating that CKD is an independent predictor of stroke in Japanese patients.

The clinical interaction between the brain and the kidney has been referred to as the 'cerebro-renal connection,' as we previously reported.[6] Unlike most organs, the kidney and brain are low-resistance end organs that are exposed to high-volume blood flow throughout the cardiac cycle. These hemodynamic similarities are observed in the vascular beds of both the organs.[7] Ito *et al.*,[8] in their 'strain vessel hypothesis,' proposed that this similar condition, in which high blood flow leads to disturbances may be a mechanism for cerebro-cardio-renal interactions. Because the small vessels in the brain are similar to those in the kidney, small-vessel disease (SVD) in the kidney may alert us to the presence of SVD in the brain. Recently, changes in the vascular system in the brain have been shown to contribute to the onset and progression of CI and dementia.[9] Impairment of the so-called 'neurovascular unit' is linked to many common human CNS pathological conditions, including dementia. Although multiple mechanisms are involved in CI and dementia associated with CKD, cerebrovascular disease in the brain is considered to have a key role in dysfunction of the neurovascular unit and result in CI and dementia.

In a study reported in this issue, Yamamoto *et al.*[10] clearly demonstrated that brain SVD, such as lacunar infarction and white matter lesions, is associated not only with CI, but also with CKD in Japanese subjects. The authors followed 245 consecutive patients with lacunar infarction assessed by magnetic resonance imaging and ambulatory blood pressure monitoring. They found an independent association between CKD and CI, which was defined as a Mini-Mental State Examination (MMSE) score of 24 or less. Even moderately reduced kidney function (estimated glomerular filtration rate (eGFR)= 30–60: stage 3) has a higher odds ratio (OR) for mild CI (MCI), which was defined as an MMSE score of 25–27 (OR: 1.77) and CI (OR: 3.69), indicating that patients with eGFR $\leqslant 60\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$ may have CI. The results lead to the important suggestion that it is sometimes advisable for clinicians to administer the MMSE to patients with moderate CKD. However, given the cross-sectional study design (which was similar to that of the REGARDS study), these findings do not prove that CKD actually predicts CI. To explore additional enhancement factors for CI in CKD patients, and to address the effect of CKD progression, a longitudinal study focusing on the relationship between CI and CKD is needed.

Yamamoto *et al.*[10] also showed that not only the mean blood pressure, but also the proportion of dippers and risers as identified via 24-h ambulatory blood pressure monitoring is higher among patients with SVD, including lacunar infarction and white matter lesions, and CI, indicating that controlling blood pressure throughout the day (known as perfect control of blood pressure) is important to prevent brain SVD and CI.

Ischemic stroke due to SVD is thus far considered to have a better outcome compared with ischemic stroke due to large artery atherosclerosis and cardioembolism. However, in a very recent report, ultra-long follow-up (12 years) of patients with ischemic stroke due to SVD revealed poor long-term survival and an increase in risk of cardiac death compared with other types of stroke,[11] indicating that patients with this type of stroke may have a high risk of cardiovascular disorders, as well as of cerebrovascular disorders. Common risk factors for SVD, such as high arterial blood pressure and diabetes mellitus, are thought to lead to progression of SVD; therefore, clinicians should provide systematic care to patients who have markers for SVD (in even one organ) to help prevent multiple-organ failure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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