The cerebro-renal interaction in stroke neurology

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Chronic kidney disease (CKD), defined as a reduced glomerular filtration rate (GFR) or albuminuria, is a known, strong risk factor for stroke. Meta-analyses of cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71%–92%, and estimated GFR (eGFR) <60 mL/min/1.73 m^2 increases the risk by 43%.[1,2] CKD is also predictive of poor outcomes after stroke; reduced eGFR is independently associated with increased 1- and 10-year mortalities.[3,4] Since end-stage renal disease (ESRD) is another established predictor of stroke risk and poor stroke outcomes,[5] stroke neurologists should fully understand the interaction between stroke and CKD/ESRD.

In this issue of *Neurology*®, Kumai et al.[6] studied 3,778 patients admitted within 24 hours of onset of their first-ever ischemic stroke from a large-cohort multicenter stroke registry; of these, 1,320 (34.9%) had CKD defined as proteinuria or reduced eGFR on admission. They found that CKD patients had a 49% greater risk of neurologic deterioration, defined as a ≥2-point increase in the NIH Stroke Scale, during hospitalization; a 138% greater risk of in-hospital mortality; and a 25% greater risk of a modified Rankin Scale score (mRS) ≥2 at discharge than non-CKD patients after adjustment for potential confounding factors, including initial stroke severity. As a component of CKD, proteinuria showed a much stronger association with unfavorable outcomes than reduced eGFR; for example, patients with mild proteinuria, with an estimated amount of urine protein of 30–100 mg/mL, had a 69% greater risk of an mRS ≥2 than patients without proteinuria. In contrast, reduced eGFR was not associated with stroke outcomes in the study by Kumai et al.[6] Albuminuria and reduced eGFR may involve separate pathologic processes. Kumai et al. did not measure filtration function prior to stroke onset but only on admission, when it may have been affected by acute stroke damage. Measurement of eGFR and urine protein in the chronic stage of stroke might show different associations.

Other potential limitations include use of semiquantitative measurement of urine protein using dipstick testing, which may result in frequent false-positive and false-negative results. However, it is meaningful that such a handy and economical measurement can predict stroke outcomes. Also, outcomes were measured after only a short interval. Vital and functional outcomes were assessed at hospital discharge (median, 23 days after stroke onset). Because their registry has a plan to perform yearly follow-up for enrolled patients, this limitation will eventually be resolved.

Renal dysfunction is a bystander of stroke, since both conditions are associated with hypertension and several traditional vascular risk factors. Additionally, albuminuria is an indicator of cephalocervical and systemic vascular dysfunction via nontraditional vascular risk factors, including endothelial dysfunction, maladaptive carotid arterial remodeling, homocystinemia, coagulation disorders, impaired endothelial release of tissue plasminogen activator, extravascular coagulation, and higher levels of inflammatory cytokines and oxidative stress. An association between albuminuria and hemorrhagic transformation of infarcts has also been noted.[7] Such factors might cause both initial severity and unfavorable outcomes of stroke in patients with proteinuria.

These data underscore the fact that one can no longer manage and care for stroke patients while disregarding their renal condition. CKD/ESRD is not only predictive of unfavorable outcomes after general stroke, but also of stroke outcomes after specific therapies. In our multicenter observational studies (the SAMURAI rt-PA Registry), reduced eGFR was associated with early symptomatic hemorrhagic conversion, mortality, and an mRS ≥4 at 3 months after IV recombinant tissue plasminogen activator therapy.[8] Although thrombolysis is generally not considered safe for stroke patients undergoing hemodialysis, most experts who responded to an international survey favored its use.[9] Patients with stages 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) have a high 30-day mortality when

See page 1909

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undergoing carotid endarterectomy or carotid angioplasty and stenting.[10] Dabigatran, a new oral anticoagulant for stroke prevention, is mainly excreted by the kidneys, and should be used cautiously even in patients with moderate renal damage.

Another essential issue that must be resolved is whether active treatment to reduce albuminuria and improve filtration dysfunction can decrease stroke risk and improve stroke outcomes. CKD is also associated with subclinical brain abnormalities, including white matter changes, microbleeds, mild cognitive disorders, and intima-medial thickening of carotid arteries. The cerebro-renal interaction is an understudied and underused concept at present, but it has as great a clinical significance as the cardio-renal interaction and should be studied more extensively and in great detail.

Finally, the Fukuoka Stroke Registry that Kumai et al.[6] used as a study cohort merits specific comment. This multicenter registry for acute stroke patients in the Fukuoka metropolitan area, in western Japan, has several strengths, since the database includes extensive underlying patient information, image data principally from MRI/magnetic resonance angiography, long-term follow-up of vital and functional conditions for many years, and the results of serologic and genome genetic analyses for most participants. This systematic stroke registry will help resolve several problems in stroke neurology, in particular in relation to stroke in the Asian population, in whom the stroke burden is increasing.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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