Vascular Disease Contributes to Cognitive Decline in Patients with Kidney Disease

By Bridget M. Kuehn

Until recently, nephrologists may have underappreciated the risks that acute kidney injury (AKI) poses to long-term kidney health. But a raft of clinical and epidemiological studies has shown that AKI greatly increases the risk of chronic kidney disease (CKD), end stage renal disease, and death (Coca SG, et al. Kidney Int 2012; 81:442–448).

"There has been a dramatic shift in our understanding of potential patient outcomes following AKI," said David P. Basile, PhD, associate professor of medicine at Indiana University in Indianapolis, during a symposium at Kidney Week 2016. A growing understanding of the molecular mechanisms underlying the continuum between AKI and CKD is helping nephrologists better understand why some patients with AKI never fully recover. The discoveries may one day help identify patients with AKI at risk of CKD and lead to kidney-protective AKI interventions.

**Capillary loss**

A rat model of what was thought to be "reversible AKI" first led Basile and his colleagues to discover permanent vascular damage that could lead to CKD. The rats undergo an ischemia reperfusion injury, and closer study revealed that not all the rats return to normal (Basile D, et al. Am J Physiol 2001; 281:F887–899).
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functioning, suggesting that albumin in the urine and changes in brain structure are likely both representations of the same vascular process, just in different organs,” said Weiner in a press release. “This manifests with worse brain function, particularly in domains linked to cerebrovascular disease.”

The fact that the results came from a large study of a nationally representative population of patients with kidney disease suggests the results may be relevant to “tens of millions of US adults,” said Weiner.

“It’s a great study to take advantage of to look at these relationships,” said Anne Murray, MD, MSc, professor of medicine and geriatrics at the Hennepin County Medical Center’s Berman Center for Clinical Research in Minneapolis.

The results confirm previous studies that show vascular disease contributes to cognitive decline in patients with chronic kidney disease, Murray said. She noted evidence that the brain and kidneys share many common anatomic and vasoregulatory features; they are low resistance end organs exposed to high-volume blood flow, which may make them especially vulnerable to microvascular damage (Bugnicourt JM, et al. J Am Soc Nephrol 2013; 24:353–363).

“The results also highlight that memory is impaired to a greater extent than executive function, in contrast to some other studies,” said Murray. She noted, however, that this result is consistent with results from the Brain in Kidney Disease Study (BRINK) (Murray AM, et al. Am J Kidney Dts 2016; 67:593–600).

One of the study’s strengths is that it looked at both ACR and eGFR, which showed that multiple mechanisms are likely involved, Murray said. One limitation is that the mean eGFR was high and the mean ACR was low in this patient population. Only a small percentage of patients had eGFRs below 30, a point at which the risk of cognitive impairment is high, and memory loss becomes more predominant, Murray explained.

“So, it’s difficult to interpret the ‘dose’ effect of lower ranges of eGFR and higher ACR on each outcome,” she said. In the meantime, it is important for clinicians to be aware that patients with eGFRs below 45, especially those with eGFRs below 30, and even somewhat elevated ACRs may be experiencing cognitive decline, Murray said.

“Clinicians should suspect significant cognitive impairment and manage their care accordingly,” she said. For example, the patient may not be able to be compliant with their medications so physicians might suggest having a caregiver or family member supervise medication administration. If there are decisions that need to be made regarding access, placement, dialysis initiation, or being placed on the transplant list those discussions should be held with family members present in case the patient’s judgment is impaired,” she stressed. This is particularly important for patients starting dialysis who are likely to experience further cognitive declines after 3-6 months of dialysis, she noted.

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“Renal blood vessels are permanently reduced following recovery,” he explained. “The vascular network is significantly compromised.”

Now, many investigators are studying vascular loss in AKI. Studies of tissue samples from patients with AKI have also revealed decreased peritubular vascular density and the development of fibrosis, Basile noted.

“We knew very little about what was going on with vessel loss,” Basile noted. But recent studies have shown that ischemia leads to the loss of endothelial cells then a gradual reduction of capillaries during the period after AKI when the kidney usually recovers (Ehling J, et al. J Am Soc Nephrol 2016; 27:520–532).

“While the rest of the kidney is putting itself back together, the vessels decline,” he said.

Animal studies now reveal that vascular damage contributes to the development of fibrosis, he said. This suggests there may be a window to intervene before permanent damage sets in.

“Intervention in early AKI might mitigate vascular loss,” he suggested.

Failed repair

Now, a growing body of evidence suggests that the kidney’s normal repair mechanisms may go awry and lead to an accelerated-aging like condition (Ferenbach DA and Bonventre JV. Nat Rev Nephrol 2015; 11:264–276).

Benjamin D. Humphreys, MD, PhD, chief of the division of nephrology at the Washington University School of Medicine, is one of the researchers at the cutting edge of this research. As part of the symposium, Humphreys delivered The Barry M. Brenner, MD, endowed lectureship, which recognizes the contributions of investigators like Brenner and Humphreys who have helped to nurture the careers of young nephrology investigators.

“We are interested in studying failed repair,” explained Humphreys, whose collaborator Monica Chang-Panesso, MD, presented an abstract (OR130) at Kidney Week tracing genetic factors that may inhibit kidney repair. She found that cells in the proximal tubule dedifferentiate to facilitate repair rather than relying on a population of progenitor cells.

Another collaborator, Rafael Kramann, MD, has developed a mouse model of AKI progressing to CKD. Like Basile’s rat model, Kramann’s model undergoes a loss of capillaries. The group has found that ablating kidney pericytes expressing Gli1+, which help to regulate vascular structure and stability in the kidneys, leads to capillary loss (Kramann R. J Am Soc Nephrol [published Sept. 13, 2016] pii:ASN.2016030297).

“The capillary dropout is permanent,” Humphreys said.

Already, Humphreys and his colleagues are studying experimental therapies that might prevent fibrosis. For example, they demonstrated that a small molecule that inhibits Gli2 reduces fibrosis by 60% in the AKI mouse model (Kramann R, et al. J Clin Invest 2015; 125:2935–2951).

“It is proof of principle that targeting pericytes might be a viable strategy,” said Humphreys.

Another gene of interest identified by the group is an enzyme that synthesizes retinoic acid that is up-regulated in the kidney during development. The retinoic acid may help kidney cells redifferentiate during the repair process, suggested Humphreys, and a lack of retinoic acid might contribute to failed kidney repair.

They are now studying the role of retinoic acid in human kidney organoids, which are created by coaxing stem cells into forming kidney-like structures in the laboratory. Treating the organoids with retinoic acid boosts markers of repair, but when it is absent there is capillary loss and fibrosis.

“Our data suggest that after AKI, about 80% of epithelia are able to undergo what we call successful repair, but about 20% of cells fail to repair,” said Humphreys.

In addition to highlighting his own laboratory’s research, Humphreys acknowledged the enormous contributions Brenner made to the field and urged other fellows to follow in his footsteps as a mentor. He noted that many future department heads, division chiefs, and deans trained in Brenner’s lab. These “bright minds” were attracted there by scientific innovations made in Brenner’s lab, he said.

“It behooves all of us to support our young people to make these scientific discoveries that will improve patient care and serve to reinvigorate the field,” Humphreys said.