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Acute Kidney Injury and Brain Outcomes in Preterm Neonates—The Two Most Intelligent Organs Collide

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Acute kidney injury (AKI) occurs in nearly 30% of neonates admitted to the neonatal intensive care unit and is similar to AKI rates observed in other pediatric intensive care units. The landmark Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) study revealed that neonatal AKI is independently associated with increased risk of morbidity and mortality.[1] In the last decade, long-term outcomes for AKI survivors (including neonates) have become a focus significant epidemiologic interest, yet most studies assess for potential associations between AKI and chronic kidney disease.[2] Although some studies have observed that AKI is associated with increased risk of cerebrovascular events in adult AKI survivors[3] and provide evidence for a brain-kidney axis in children with AKI and malaria,[4] assessment of neurodevelopmental outcomes and brain growth is lacking in the preterm neonatal AKI population.

In a recent issue of the *Kidney International Reports*, Chen *et al.*[5] assessed associations between AKI and neurodevelopmental outcomes in 732 preterm infants less than 31 weeks of gestational age. They used both the serum creatinine and urine output Kidney Disease: Improving Global Outcomes criteria with validated neonatal modifications. Outcome measures included head circumference Z-scores at 6-, 12-, and 24-month term equivalent age, neurodevelopmental assessments at 24 months, and mortality. The investigators observed a 21% AKI rate (11% non-oliguric AKI and 10% with oliguric AKI). Patients with AKI exhibited higher rates of co-morbidities and risk factors for poor outcomes including lower Apgar scores and gestational age and maternal pre-eclampsia. Long-term follow-up revealed decreased head circumference Z-scores, higher prevalence of microcephaly, and worse neurodevelopmental outcomes in AKI survivors versus controls in unadjusted analysis. Nevertheless, some associations were maintained only with the oliguric AKI group when adjusted for gestational age, sex, and other covariates.

The authors should be commended on this well-designed long-term follow-up of preterm survivors. Their insight to separate out oliguric and non-oliguric AKI to assess for a differential in outcomes was extremely novel. The authors also interpret their findings with appropriate caution given the inherent limitations of the study design.

This manuscript raises questions regarding mechanisms of immature brain growth and development in

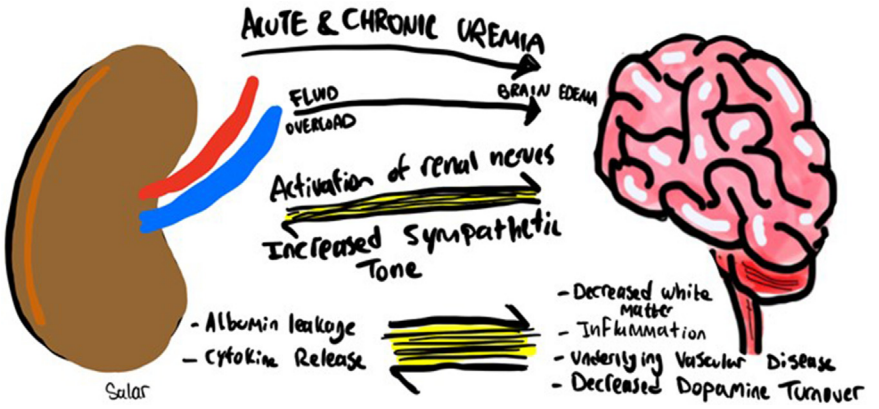

Figure 1. Some potential mechanisms of how kidney injury may hinder brain growth and development.

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kidney injury. Although this remains unclear, our understanding of kidney-brain crosstalk in the setting of chronic kidney disease has long held that acute and chronic uremia causes decreased dopamine turnover in certain parts of the brain[6] and subclinical vascular disease with white matter inflammation (Figure 1).[7] Interestingly, the stronger relationship between oliguric AKI (and no non-oliguric AKI) and poor outcomes requires further investigation. The pediatric literature is replete with data regarding associations with increasing degrees of volume accumulation and poor outcomes,[8] and obviously oliguria will increase the likelihood of poor outcomes. Could it be the case that volume overload is associated with brain edema or ischemia? Could it be that volume restriction in the setting of oliguria could lead to decreased nutrition administration which leads to poor brain growth and development? Because survival rates are increasing for the neonatal population with development and application of new dialysis platforms, the important work by Chen *et al.*[5] should galvanize the neonatal AKI community to make the kidney-brain axis a fertile area of research.[9]

DISCLOSURE

The authors declared no competing interests.

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