Leveraging neuroimaging to understand the impact of chronic kidney disease on the brain

Ellen van der Plas¹ · Lyndsay Harshman²

Received: 3 October 2021 / Revised: 6 October 2021 / Accepted: 7 October 2021 / Published online: 3 November 2021
© The Author(s), under exclusive licence to International Pediatric Nephrology Association 2021

Introduction

In North America, children younger than 20 years of age account for less than 2% of the total chronic kidney disease (CKD) patient population; however, the prevalence of pediatric CKD within the population has increased by 32% since 1990 as pediatric CKD care improved [1, 2]. Approximately 50% of all pediatric CKD diagnoses are due to congenital, non-glomerular anomalies [3] and half of CKD patients with the congenital disease will need a kidney transplantation in their lifetime [2]. Cognitive deficits are known to emerge in parallel to CKD progression. Cross-sectional and meta-analytic data demonstrate that in contrast to advanced CKD, early-stage CKD patients have relatively intact IQ although with a general leftward skew of the distribution toward lower scores [4–6]. Furthermore, up to 35% of children with early CKD manifest impairment on measures of executive function (EF) [7]. More pervasive neurocognitive deficits have been well described in the pediatric CKD 5 population (e.g., dialysis, transplant, and/or post-transplant patients). There is greater variability in full-scale intelligence quotient (IQ) [8–11] with notable IQ deficits in advanced CKD/kidney failure, accompanied by poorer performance on neurocognitive assessment of EF, memory, attention, and academic achievement [10]. Furthermore, EF deficits are more pronounced with lower kidney function (e.g., disease progression) [4, 5, 7], longer duration of kidney disease [4, 12, 13], metabolic acidosis [14, 15], and hypertension [16]. These observations point to a potential relationship between pediatric CKD and abnormal neurodevelopment.

Magnetic resonance imaging (MRI) provides a valuable tool for assessing the neurobiological mechanism of the observed cognitive deficits in pediatric CKD.

Neuroimaging in CKD: what do we know?

Twenty neuroimaging studies that include pediatric CKD patients have been published in the literature between 1977 and today. Most early studies on the topic of neuroimaging in pediatric CKD utilized computerized tomography (CT) scans [17]. Less than five published studies have utilized quantitative, research-based MRI sequences to evaluate the brain in CKD [18–22]. Within more recently published data, Hartung and colleagues used MRI to examine brain structure in 85 patients aged 8–25 with CKD, encompassing a mix of pre- and post-transplanted patients [18]. They reported subtle cortical gray matter abnormalities in unadjusted models only. These differences were more prominent among kidney transplant recipients compared to those with pre-transplant CKD. More recently, our group showed reductions in cerebellar gray matter volume and unexpected increase in cortical (cerebral) gray matter volume among children ages 6–16 years old with early-stage CKD relative to controls [21]. Moreover, the degree of cerebellar volume reduction was associated with the estimated glomerular filtration rate. In addition to quantitative assessment of regional brain volume, white matter microstructural integrity can be evaluated using diffusion tensor imaging (DTI) sequences with MRI. Matsuda-Abedini et al. [20] used DTI to describe white matter in CKD patients and controls. They reported decreased white matter integrity—as measured by reduced white matter fractional anisotropy and increased mean diffusivity and radial diffusivity—specifically, within the anterior limb of the internal capsule.

In this issue of *Pediatric Nephrology*, Lijdsman and colleagues [23] report neuroimaging data from 24 patients between the ages of 8–30 years old with severe CKD

✉ Lyndsay Harshman
lyndsay-harshman@uiowa.edu

¹ Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

² Department of Pediatrics, Division of Pediatric Nephrology, Dialysis, and Transplantation, University of Iowa Stead Family Children's Hospital, Iowa City, IA, USA

who were compared to 21 control subjects on measures of regional brain volume and white matter microstructure (diffusion tensor imaging, DTI). The primary regional brain volumetric finding was decreased gray matter volume within the nucleus accumbens among patients with CKD compared to controls. The nucleus accumbens refers to a small structure within the ventral striatum which is thought to mediate “reward signals” interfacing between the frontal and temporal lobes [24]. No other regional volumetric differences were noted; however, it is important to note that infratentorial brain regions (e.g., the cerebellum) were not evaluated in this paper. In evaluating white matter microstructure with radial diffusivity, Lijdsman et al. [23] noted more substantial group differences when evaluating voxel-wise group comparisons. The CKD group had higher radial diffusivity and decreased fractional anisotropy in a variety of voxel-based clusters relative to controls, potentially pointing to abnormalities in myelination (e.g., decreased myelin integrity) [25]. Due to the nature of the small sample, no correction for multiple comparisons was performed; however, Lijdsman’s observations are consistent with our own neuroimaging work in CKD that suggests globally decreased white matter integrity is present even in early CKD prior to dialysis or transplantation.

The study by Lijdsman et al. [23] included participants ranging from childhood to young adults. Importantly, the

brain continues to change throughout the human lifespan with dynamic changes occurring in childhood and adolescence. Given the age range of the sample, it is important to account for variation in head size, which Lijdsman and colleagues addressed using a linear model approach via volumetric scaling. Notably, brain regions do not necessarily scale linearly with head size, with many regions following power-law relationships [26]. Effective de-trending of the relationship between region of interest (ROI) and head size requires the utilization of methods that account for non-linear relationship (Fig. 1). As shown in Fig. 1B, failure to account for non-linear relationships can result in over- or underestimation of regional volumes.

Lastly, considering the evidence of continued white matter growth and gray matter reduction throughout childhood and adolescence [27, 28], it is also crucial to consider age as a variable of interest. This study by Lijdsman et al. matched subjects on age. While this method minimizes between-subject variations in age, the effect of normal, age-related changes in brain growth may be underestimated in this paper. Figure 2 shows published examples of age-related changes occurring throughout the human lifespan. Substantial changes in gray and white matter volume are notable between childhood and young adulthood, and these changes coincide with substantial neurocognitive and behavioral growth. It is critical to contextualize the observed

Fig. 1 The relationship between intracranial volume (ICV) and subcortical gray matter regions is non-linear. *Illustration of intracranial volume (ICV) scaling when the relationship between ICV and region of interest (ROI) is non-linear.* Panel A shows that the volume of the caudate (y-axis) scales non-linearly with ICV (x-axis). Panel B illustrates how failing to account for the non-linear relationship (by taking

the proportion of the caudate and ICV (y-axis)) overestimates caudate volume in people with small ICV and underestimates caudate volume in those with large ICV. The power proportion was used in panel C (y-axis). The adjustment was scaled non-linearly based on the power component (beta). As a result, there is effective de-trending of the relationship between ICV and caudate volume

Fig. 2 Effect of age on brain region of interest. Age-related volumetric changes in selected brain regions of interest are shown. Age data spanned 3–96 years of age. Composite brain volumes were obtained by combining single brain regions of interest into larger anatomical regions. Data were harmonized using the ComBat method [29, 30]. Figure reproduced with permission from Pomponio et al. [28]

neurocognitive deficits in pediatric and adult CKD within this dynamic framework.

Neuroimaging in CKD: challenges and opportunities

Systematic, quantitative neuroimaging studies in young children with CKD are still scarce, in part because of the known challenge of obtaining quality images from non-sedated, young children. The paper by Lijdsman and colleagues is an important contribution to the emerging field of neurocognition in CKD but also highlights opportunities for growth. The current neuroimaging literature in pediatric CKD is characterized by heterogeneous disease stage and etiology, making it difficult to pinpoint mechanisms of neurocognitive deficits. This is further compounded by a proclivity toward small sample sizes of individuals that span a wide age range; for example, our current understanding of brain development in pediatric CKD in children younger than 8 years old is predicated on one sample [21], highlighting a

critical opportunity for exploring early brain development in pediatric CKD.

Incorporating neuroscience research principles in parallel with pediatric CKD research provides the clinical-translational tools to identify potential neurobiological mechanisms that bring about neurocognitive deficits in this population. This means moving beyond the use of clinical scans to describe brain structure in pediatric CKD, as the nature of these scans highlights only a limited range of potential neurobiological mechanisms. Rather, applying a multitude of high-resolution imaging modalities will enable detailed exploration of brain development in pediatric CKD. Multisite collaborations are necessary to address limitations related to small sample sizes and heterogeneity of neuroimaging research in pediatric CKD. There are a growing number of methods available that account for variation induced by multiple different scanners. For instance, existing brain processing tools for volumetric segmentations have been demonstrated to produce robust results in a multisite setting [31]. Post-processing correction tools are also available for methods that are prone to scanner-induced variation, such as diffusion tensor imaging [29] and cortical reconstruction

[30]. Collaboration between nephrologists and neuroscientists is necessary to effectively utilize these tools to embark on multisite neuroimaging initiatives.

Lastly, research on this topic must move beyond neuroimaging assessment as an isolated entity. Concurrent neuroimaging, neurocognitive assessment, and collection of kidney disease biomarkers are necessary to improve our ability to identify patients who are at risk for neurocognitive deficits to inform early brain changes in parallel with CKD progression. Neurocognitive difficulties emerge in early childhood, during early CKD, and signal a need for greater understanding of the developing brain amid a life-long, chronic disease process. In parallel to this, longitudinal assessment into adulthood is essential with crossover into the dialysis and transplant progression of CKD. Future neuroimaging research in this field is required to further delineate the neurobiological underpinnings of cognitive deficits in CKD with the goal of earliest detection, intervention, and ultimately prevention of poor neurodevelopmental outcomes.

References

- Warady BA, Chadha V (2007) Chronic kidney disease in children: the global perspective. *Pediatr Nephrol* 22:1999–2009
- Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A (2003) Chronic renal insufficiency in children: the 2001 Annual Report of the NAPRTCS. *Pediatr Nephrol* 18:796–804
- North American Pediatric Renal Trials and Collaborative Studies (2014) North American Pediatric Renal Transplant Cooperative Study Annual Report
- Hooper SR, Gerson AC, Butler RW, Gipson DS, Mendley SR, Lande MB et al (2011) Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. *Clin J Am Soc Nephrol* 6:1824–1830
- Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB et al (2006) Neurocognitive outcomes in children with chronic kidney disease: current findings and contemporary endeavors. *Ment Retard Dev Disabil Res Rev* 12:208–215
- Chen K, Didsbury M, van Zwieten A, Howell M, Kim S, Tong A et al (2018) Neurocognitive and educational outcomes in children and adolescents with CKD: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 13:387–397
- Mendley SR, Matheson MB, Shinnar S, Lande MB, Gerson AC, Butler RW et al (2015) Duration of chronic kidney disease reduces attention and executive function in pediatric patients. *Kidney Int* 87:800–806
- Warady BA, Belden B, Kohaut E (1999) Neurodevelopmental outcome of children initiating peritoneal dialysis in early infancy. *Pediatr Nephrol* 13:759–765
- Qvist E, Pihko H, Fagerudd P, Valanne L, Lamminranta S, Karikoski J et al (2002) Neurodevelopmental outcome in high-risk patients after renal transplantation in early childhood. *Pediatr Transplant* 6:53–62
- Slickers J, Duquette P, Hooper S, Gipson D (2007) Clinical predictors of neurocognitive deficits in children with chronic kidney disease. *Pediatr Nephrol* 22:565–572
- Lawry KW, Brouhard BH, Cunningham RJ (1994) Cognitive functioning and school performance in children with renal failure. *Pediatr Nephrol* 8:326–329
- Hooper SR, Gerson AC, Johnson RJ, Mendley SR, Shinnar S, Lande MB et al (2016) Neurocognitive, social-behavioral, and adaptive functioning in preschool children with mild to moderate kidney disease. *J Dev Behav Pediatr* 37:231–238
- Hooper SR, Laney N, Radcliffe J, Moodalbail D, Hartung EA, Ruebner RL et al (2015) Executive functioning in children, adolescents, and young adults with chronic kidney disease. *J Dev Behav Pediatr* 36:734–742
- Dobre M, Gaussoin SA, Bates JT, Chonchol MB, Cohen DL, Hostetter TH et al (2018) Serum bicarbonate concentration and cognitive function in hypertensive adults. *Clin J Am Soc Nephrol* 13:596–603
- Harshman LA, Kogon AJ, Matheson MB, Johnson RJ, Shinnar S, Gerson AC, Warady BA, Furth SL, Hooper SR, Lande MB (2020) Bicarbonate, blood pressure, and executive function in pediatric CKD—is there a link? *Pediatr Nephrol* 35:1323–1330
- Lande MB, Mendley SR, Matheson MB, Shinnar S, Gerson AC, Samuels JA et al (2016) Association of blood pressure variability and neurocognition in children with chronic kidney disease. *Pediatr Nephrol* 31:2137–2144
- Moodalbail DG, Reiser KA, Detre JA, Schultz RT, Herrington JD, Davatzikos C et al (2013) Systematic review of structural and functional neuroimaging findings in children and adults with CKD. *Clin J Am Soc Nephrol* 8:1429–1448
- Hartung EA, Erus G, Jawad AF, Laney N, Doshi JJ, Hooper SR et al (2018) Brain magnetic resonance imaging findings in children and young adults with CKD. *Am J Kidney Dis* 72:349–359
- Liu HS, Hartung EA, Jawad AF, Ware JB, Laney N, Port AM et al (2018) Regional cerebral blood flow in children and young adults with chronic kidney disease. *Radiology* 288:849–858
- Matsuda-Abedini M, Fitzpatrick K, Harrell WR, Gipson DS, Hooper SR, Beiger A et al (2018) Brain abnormalities in children and adolescents with chronic kidney disease. *Pediatr Res* 84:387–392
- Solomon MA, van der Plas E, Langbehn KE, Novak M, Schultz JL, Kosciak TR et al (2021) Early pediatric chronic kidney disease is associated with brain volumetric gray matter abnormalities. *Pediatr Res* 89:526–532
- van der Plas E, Lullmann O, Hopkins L, Schultz JL, Nopoulos PC, Harshman LA (2021) Associations between neurofilament light-chain protein, brain structure, and chronic kidney disease. *Pediatr Res*. <https://doi.org/10.1038/s41390-021-01649-6>
- Lijdsman S, Konigs M, van Sandwijk MS, Bouts AH, van Hoeck K, de Jong H et al (2021) Structural brain abnormalities in children and young adults with severe chronic kidney disease. *Pediatr Nephrol*. <https://doi.org/10.1007/s00467-021-05276-5>
- Floresco SB (2015) The nucleus accumbens: an interface between cognition, emotion, and action. *Ann Rev Psychol* 66:25–52
- Winkowski PJ, Sabisz A, Naumczyk P, Jodzio K, Szurowska E, Szarmach A (2018) Understanding the physiopathology behind axial and radial diffusivity changes—what do we know? *Front Neurol* 9:92
- Liu D, Johnson HJ, Long JD, Magnotta VA, Paulsen JS (2014) The power-proportion method for intracranial volume correction in volumetric imaging analysis. *Front Neurosci* 8:356
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A et al (1999) Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci* 2:861–863
- Pomponio R, Erus G, Habes M, Doshi J, Srinivasan D, Mamourian E et al (2020) Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. *Neuroimage* 208:116450
- Fortin JP, Parker D, Tunc B, Watanabe T, Elliott MA, Ruparel K et al (2017) Harmonization of multi-site diffusion tensor imaging data. *Neuroimage* 161:149–170

30. Fortin JP, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA et al (2018) Harmonization of cortical thickness measurements across scanners and sites. *Neuroimage* 167:104–120
31. Kim EY, Johnson HJ (2013) Robust multi-site MR data processing: iterative optimization of bias correction, tissue classification, and registration. *Front Neuroinform* 7:29

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.