Brain Imaging and Cognition after Kidney Transplantation

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A growing body of evidence points towards cognitive deficits among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1–3]. Often-times these deficits are best uncovered by specialized neuropsychologic testing, unaccompanied by any overt motor or sensory deficits or conventional brain imaging findings that explain the burden of cognitive deficit [4]. The etiology of these cognitive deficits has been attributed predominantly to hypertensive vascular disease, diabetic vasculopathy, embolic phenomena, disease-related changes such as systemic lupus and the hemodynamic stress attendant to hemodialysis and ultrafiltration [3, 5]. Studies have described immediate and continued improvement in cognition after successful kidney transplantation [4, 6]. However, these studies did not attempt to establish any correlation between structural substrates in the brain centers and tracts underlying the noted improvement in cognitive function.

The advent of MRI and quantitative approaches to analyzing brain imaging highlighted the presence of brain white matter defects (leukoaraiosis) among patients with CKD and ESRD [3]. However, the correlation between leukoaraiosis on imaging and observed deficits in cognitive function remained imperfect [3]. One postulation to explain this disconnect is that conventional imaging and clinical examination examine slices of the brain and focus on the evaluation on gross neurologic deficits and ignore connections between functional connections of anatomic substrates in the brain that subserve cognition [7].

A newer brain imaging technique, diffusion tensor imaging (DTI), allows mapping of the anatomy and function of white matter tracts [8].

Tensors are geometric constructs that describe linear relationships between geometric vectors and scalars [8]. Thus, the diffusion of water molecules in tissues can be mapped both in terms of magnitude and direction in tissues and the resulting image can reveal information as to the integrity of various tracts in the brain and the connections between brain regions that subserve cognition. The promise of DTI lies in its ability to detect subtle yet functionally significant ultrastructural abnormalities in highly organized tissues such as white matter, where, in the intact axon, water molecules diffuse more freely along an axonal fiber tract than across it [8]. This differential directional behavior of water molecules can be expressed by the DTI metrics of fractional anisotropy (FA), which measures directionality of diffusion and, mean diffusivity (MD), a measure of overall diffusivity [8]. In general, a higher FA and lower MD correlate with the integrity of tract structure and function across diverse disease states [8].

In this issue of the Journal, Gupta et al. [9] describe structure-function relationships underlying cognition, pre and post-transplantation, among a small group of kidney transplant recipients on conventional calcineurin inhibitor-based immunosuppression. In their study, neuropsychologic tests of executive function and memory and DTI were evaluated before and 90 days after

transplantation. Despite a small number of patients ($n = 11$) studied, the findings merit serious consideration. Neuropsychologic parameters of memory and executive function improved significantly post-transplantation. These improvements in neuropsychologic tests were paralleled by significant improvements in the DTI metrics, FA and MD in tracts connecting areas associated with memory and executive function, that is, the corpus callosum, cingulate gyrus, forceps minor and forceps major [9]. Notably, this measured improvement in cognition was sustained at 1 year although not exceeding the improvements noted at 3 months post-transplant [9]. Furthermore, the findings noted on DTI could not have been explained by conventional MRI findings [9]. The reader is also directed to a recent study on kidney transplant recipients reported by Zhang et al. [10] where the authors examined brain imaging and the default mode network (DMN) that subserves core processes of human cognition such as cognitive and emotional processing, monitoring of the surrounding environment and mind wandering. In this study by Zhang et al. [10] improvement in DMN function correlated with improvements in functional MRI measures as well as in anatomic substrates of cognition, namely, fiber bundles connecting the posterior cingulate cortex and precuneus to the left parahippocampal gyri and the right inferior parietal lobule. These improvements, which were noted post-transplantation, were significant in that tract function approached that observed among normal controls [10]. An interesting correlation that these authors observed was that the improvement in hemoglobin levels post-transplantation correlated positively as improvements in the tract function. These 2 studies differ in several respects. Zhang et al. [10] included healthy controls and yet only chose to examine 4 tracts that were chosen for convenience, whereas, Gupta et al. [9] examined 13 tracts. The patients in the Zhang study were younger averaging 32 years of age, whereas the patients in the Gupta study were older averaging 56 years of age [9, 10].

These findings prompt cautious optimism despite their small sample sizes and attendant limitations. Notably, these studies do not inform us as to whether patients with systemic lupus erythematosus or diabetes differ or for that matter whether the elderly transplant differs from the younger recipient. A further limitation is that the studies obtained measurements only at discrete time points early post-transplantation, as appropriate for preliminary inquiries. Taken together, the studies of Gupta et al. [9] and Zhang et al. [10] add to a consistent body of knowledge that informs us about how the brain function

changes as we traverse the continuum from health to CKD through ESRD and successful renal transplantation. Most importantly, these studies usher in a new way with which we can begin to image the brain and better understand the mechanistic underpinnings of cognition in kidney disease and transplantation. Also, these studies point towards potential biomarkers of cognitive function that need to be validated in larger studies. These studies also demonstrate that relatively young patients exhibit significant decline in cognition with ESRD that improves after transplantation. Despite hemodynamic stresses attendant to surgery and expected neurotoxic effects of immunosuppression, cognitive improvement occurred with successful transplantation. These results are biologically plausible in that one would expect robust improvement in most body systems after kidney transplantation over and above what is expected even with increasing intensity of dialysis. Such an effect has been noted with regard to the progression of cardiovascular disease after transplantation [11]. Transplantation confers synthetic functions attendant to normal kidney function, such as erythropoietin production and other less well understood mechanisms that could confer advantages beyond the restoration of diffusive clearance. While most of these findings could reflect the resolution of the uremic state, the correlation with hemoglobin levels could point to improvements in tissue-level oxygenation as an additional mechanism [10].

These small studies also demonstrate an important and elegant aspect of patient centered clinical investigation in small groups of patients that often is lost in our current obsession with trials that seek to enroll thousands of patients across the world, or inquiry into large databases that involve tens of thousands of patients. Large [8] studies often leave us uncertain about the clinical significance of the small but statistically significant differences that they often uncover. Good clinical investigation with a novel technique in the context of a well-directed design can often uncover insights that have far-reaching consequences.

The promise shown by DTI in understanding cognition in patients with kidney disease and kidney transplants obviously needs further study. If DTI turns out to be a robust biomarker of cognitive dysfunction in kidney disease, the field is opened up for studies that examine DTI parameters in the context of the continuum of kidney disease from those at risk such as hypertensives and diabetics all the way through CKD, ESRD and transplant patients both in observational and interventional studies.

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