Pediatr Transplantation 2010: 14: 887–890

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2010.01359.x

Cognitive improvement in children with CKD after transplant

Icard P, Hooper SR, Gipson DS, Ferris ME. Cognitive improvement in children with CKD after transplant.
Pediatr Transplantation 2010: 14: 887–890. © 2010 John Wiley & Sons A/S.

Abstract: The primary purpose of this paper was to examine the cognitive functioning of children with CKD receiving transplantation to children with CKD not receiving transplantation, and a healthy control group. The sample included six children with CKD receiving transplant, 28 children with CKD being treated conservatively, and 23 healthy controls. All participants were administered intellectual (IQ) or developmental assessments at baseline and at a one-yr follow-up. Results revealed that children with CKD who had received transplant showed a significant increase in their intellectual/developmental functioning post transplant compared to children with CKD not receiving transplant. Although their overall intellectual/developmental level was not fully normalized, when compared with the healthy control group, the change scores for the transplant group reflected over a 12 point increase, moving the group from the borderline range to the low average range of functioning. In this regard, pediatric transplantation appears to have a positive impact on the intellectual and developmental functioning of children with CKD.

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Accepted for publication 26 April 2010

Children with ESKD requiring dialysis and subsequent transplantation are at risk for neurodevelopmental delays and deficits. Lower scores on measures of IQ and academic achievement, as well as in specific cognitive domains of language, visual-spatial perception, attention, memory, and executive function have been documented by previous research (1, 2). These deficits have been corroborated with imaging and electrophysiologic investigations showing periventricular white matter lesions, cortical atrophy, slower peripheral nerve conduction, and delayed myelination of the somatosensory cortex (3). Slickers and colleagues found that younger age of onset, longer duration of kidney disease, and increased disease severity were associated with lower cognitive functioning (4). Although the relationship between kidney function and cognitive abilities is not linear, pediatric populations progressing to ESRD and dialysis dependence appear to be at increased risk for neurodevelopmental, intellectual, and related cognitive deficits (5).

Few studies have examined the impact of kidney transplant on cognitive function, and the available evidence is inconclusive. Lawry and colleagues (6) compared the IQ scores of nine children receiving dialysis, two children treated conservatively, and 13 transplant recipients. A higher mean IQ was found in the transplanted group compared to the dialysis group, although mean scores for both groups fell largely in the average range. Conversely, Brouhard et al. (7) conducted a cross-sectional study comparing 26 children with transplant to 26 dialysis-dependent children and found no overall differences in intellectual functioning. Even fewer studies have followed children with ESKD longitudinally to assess the cognitive impact of receiving a kidney transplant. Mendley and Zelko (8) found mental decision speed and sustained attention to be improved after transplant in a sample of nine children with ESKD. Despite the relatively limited evidence for neurocognitive improvement after pediatric kidney transplant, a neurobiologic model would suggest that improving kidney filtration should decrease the amount of

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Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; MSEL, Mullen Scales of Early Learning; WASI, Wechsler abbreviated scale of intelligence.

neurotoxic exposure to the brain which, in turn, may improve neuronal myelination and synaptic development as well as overall neurologic efficiency.

This study seeks to examine the pre- and post-transplant neurocognitive function in a small cohort of children with CKD. It was hypothesized that compared to a healthy control sample and pediatric CKD patients being treated conservatively, children receiving transplants would show significant increases in intellectual function during post-transplant follow-up.

Methods

Participants

Six children with transplant, 20 children with CKD (no transplant), and 23 healthy children were recruited as part of a larger investigation of neurocognitive function in pediatric CKD. Baseline neuropsychological functioning has been reported previously for this cohort (2, 4). Patients with CKD were recruited from a university nephrology clinic; healthy control subjects were recruited from the catchement area of the surrounding community. Inclusion criteria for CKD patients were (i) 0–18 yr of age; and (ii) Schwartz GFR <90 mL/min/1.73 m^2 or dialysis dependency for three months. Exclusion criteria were (i) no prior kidney transplant; and (ii) no history of comorbid conditions associated with CNS anomalies. The CKD group (no transplant) was comprised of children with moderate/severe CKD or dialysis dependency. Seven children were classified as having moderate kidney disease (GFR = 30–59 mL/min/1.73 m^2), four children were severe (GFR = 15–29 mL/min/1.73 m^2), and 15 children had progressed to end-stage kidney disease (GFR $<$ 15 mL/min/1.73 m^2) or were on dialysis. Inclusion criteria for the healthy control group were (i) birth to 18 yr of age; (ii) no history of chronic health conditions, developmental disorders, head trauma, neurologic illness, or medication usage other than multivitamins. Maternal education was obtained as a measure of socioeconomic status in children with CKD and the healthy control group. Maternal education was coded as follows: 1 – less than high school diploma; 2 – high school diploma or GED; 3 – two yr vocational degree; 4 – four yr college degree; and 5 – graduate or professional degree.

The CKD-transplant group was 10.7 yr of age (range 5.3–17.9) with an average time between visits of 12.8 months. Post-transplant evaluation occurred on average 6.3 months after transplant. The CKD-transplant group was 50% male, 33.3% Caucasian, and 75% right-handed. The average maternal education for the CKD-transplant group was 2.5. The CKD-no transplant group was 7.8 yr of age (range 0.2–16.2) with an average time between visits of 10.9 months. This group was 65.0% male, 40% Caucasian, and 83% right-handed. The average maternal education for the CKD-no transplant group was 2.8. The healthy control group was 10.3 yr of age (range 1.5–18.4) with an average time between visits of 11.0 months. This group was 52% male, 87% Caucasian, and 94% right-handed. The average maternal education for the healthy control group was 4.4. Upon entry to the study, the baseline assessment was considered Time 1; Time 2 was considered either the second visit for the CKD–no transplant and control groups, or the post-transplant visit for the CKD-transplant group.

Procedures

Patients and control subjects received IQ or developmental testing at baseline and approximately one yr after baseline. Post-transplant evaluation was given at a minimum three months post-transplant. The MSEL was administered to children five yr of age or younger (n = 17). The WASI was administered to children and adolescents 6–18 yr of age (n = 40). The MSEL and WASI provided measures of general developmental and intellectual functioning, respectively. IQ and composite scores have a mean of 100 and a standard deviation of 15. Across all of the groups, none of the participants moved from the Mullen at Time 1 to the WASI at Time 2, thus limiting possible variance secondary to changes in testing procedures. This study was reviewed and approved by the University of North Carolina Institutional Review Board.

Data analysis

Data were examined using SPSS 14.0 software (SPSS, Inc., Chicago, IL, USA). Any significant differences in demographic variables were covaried in subsequent analyses. Change in developmental and/or intellectual functioning over time was calculated as (Time 2/Post-transplant Visit – Time 1). An ANOVA was used to determine whether children receiving transplant showed a greater increase cognitive functioning over time compared to children with CKD not receiving transplant and healthy controls. An additional chi-square analysis examined the effect size magnitude of cognitive improvement from baseline measured via Cohen's *d*. Degree of improvement was classified as small (Cohen's $d \geq 0.2$), moderate (Cohen's $d \geq 0.5$), and large (Cohen's $d \geq 0.8$).

Results

Preliminary analyses

Children receiving transplant, children with CKD not receiving transplant, and the healthy control group did not differ on age, $F(2,46) = 1.39$, p = ns, gender ($\chi^2 = 0.86$, p = ns), handedness ($\chi^2 = 1.62$, p = ns), or time between visits $F(2,46) = 0.61$, p = ns. A significant difference was found for race ($\chi^2 = 15.93$, $p > 0.05$) and maternal education $F(2,40) = 19.03$, $p < 0.001$). Covarying race and maternal education did not change the outcome of the analysis and were, therefore, not covaried in the final analysis due loss of power from missing data.

Cognitive improvement

Across the three groups, a significant difference was found between Time 1 and Time 2 assessments, $F(2,54) = 4.68$, $p < 0.05$. Means and standard deviations are presented in Table 1. Post-hoc analysis using a Bonferonni correction for multiple comparisons showed that children receiving transplants had a significant increase in intellectual functioning compared to children with CKD not receiving transplant ($p < 0.05$). The effect size for the difference between these

Table 1. Composite IQ/developmental scores over time (mean = 100, s.d. = 15)

Group	Time 1	Time 2
CKD – Transplant	72.83 (19.95)	85 (19.04)
CKD – No Transplant	87.15 (17.78)	83.55 (23.58)
Control	115.13 (16.49)	118.13 (15.13)

Scores represent a combination of the Mullen Early Learning Composite and the WASI Full-4 IQ.

two groups was large (Cohen's d = 1.12). Children receiving transplant had mean change in IQ of 12.17 points (s.d. = 12.02). Children with CKD not receiving transplant had a mean change in IQ of −3.45 points (s.d. = 15.53). The healthy control group had a mean change in IQ of 3.00 points (s.d. = 5.68). Although children receiving transplant had approximately a 10-point greater increase in IQ than the healthy control group, this difference was not significant; however, the effect size was large (Cohen's d = 0.98) and greater than would be expected given normal development.

Conversely, analysis of the magnitude of cognitive improvement (i.e., effect size) between the three groups was not significant ($\chi^2 = 6.99$, p = ns). However, for the CKD group receiving transplant, 33% had cognitive increases greater than or equal to two-thirds a standard deviation (≥12 points), 16.7% had a moderate increase (8–11 points), and 33.3% had a small increase (3–7 points). Comparatively, within the CKD group not receiving transplant, 15.0% had a small increase, 20.0% had a moderate increase, and 5.0% had an increase that would be considered large. For the healthy control group, 30.4% had a small change, 17.4% had a moderate change, and 8.7% had large changes in cognitive function.

Discussion

This study examined the impact of pediatric kidney transplantation on the cognitive and developmental functioning of children with CKD. Although a relatively small sample was examined, this is one of only a few studies that examined the impact of kidney transplant on developmental and intellectual functioning in children. In general, findings from this study suggest that children with CKD receiving transplant evidenced significant improvement in their overall cognitive function after transplant. Specifically, children with CKD receiving transplant showed approximately a 12-point increase in intellectual functioning, which descriptively went from the borderline range to the low average range. Although transplant did not appear to normalize developmental status or intellectual functioning, these findings support previous investigations espousing the overall benefits of pediatric kidney transplantation on cognitive abilities (8). Children with CKD not receiving transplants showed a mild decrease in intellectual function (three points) by their second visit, which may be related to environmental effects or, perhaps, worsening kidney function.

As previously mentioned, a neurobiological model of the relationship between kidney function and brain development would suggest that improving kidney filtration, and subsequently decreasing the amount of neurotoxins in the bloodstream, would be beneficial for brain growth and performance. Given that childhood and adolescence are important time periods for brain myelination and synaptic development, the potential neurocognitive impact of CKD and its associated symptoms (e.g., hypertension, anemia, uremia) is of great concern. The significant improvement seen in our small sample supports this model; however, it is important to note that other researchers have not found significant differences in cognitive performance between dialysis dependent and transplant cohorts (7). In addition, other research has suggested that cognitive improvements after transplant may be related to multiple factors including diminished aluminum burden and better nutritional regulation (9).

Over the past decades, we have acknowledged the burden of CKD and uremia on cognition, and we have provided pilot data that transplantation can reduce this burden. As we currently manage approximately 7000 children with ESRD in the USA, and much larger numbers globally (10), it will be important to continue to examine this issue, perhaps from a multidisciplinary, multicenter, prospective investigation in an effort to more definitively address this question.

Acknowledgments

This research was supported by grants from the Renal Research Institute, the Maternal Child Health Bureau (#MCJ379154A), the Administration on Developmental Disabilities (#90DD043003), and the General Clinical Research Centers program (RR00046) of the Division of Research Resources, National Institutes of Health.

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