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# Improvement in specific aspects of neurocognitive performance in children after renal transplantation

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**Improvement in specific aspects of neurocognitive performance in children after renal transplantation.**

*Background.* Chronic renal failure in childhood is considered to affect neurocognitive function adversely, and kidney transplantation may ameliorate the deficits. However, previous studies have suffered from the use of poorly matched control groups, comparison of transplant with uncorrected uremia, lack of standardization of dialysis, and insufficiently sensitive neuropsychological tests.

*Methods.* We studied nine medically stable children and adolescents age 14.2 ± 3.5 years with end-stage renal disease prior to and again one year after successful renal transplant. At baseline, the Wechsler Intelligence Scale for Children-III (WISC-III) or the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was performed. Repeatable tests used before and after transplant included the Paced Auditory Serial Addition Test (PASAT) or the Children's Paced Auditory Serial Addition Test (CHIPASAT), the Stroop Color-Word Naming Test, the Buschke Selective Reminding Test, the Meier Visual Discrimination Test, the Grooved Pegboard Test, the WISC-III or the WAIS-R Coding subtests and the Trailmaking Test. Computer-based measures of mental processing speed, reaction time, and discrimination sensitivity included the Cognitive Abilities Test (CAT) and the Connors Continuous Performance Test (CPT). Formal kinetic modeling of dialysis delivery ensured adequate renal replacement therapy. Transplant function was good on stable doses of immunosuppressives, without recent rejections at the time of testing.

*Results.* Within-subject comparison showed statistically significant improvement in mental processing speed by CAT, reaction time and discrimination sensitivity by CPT, and working memory by PASAT/CHIPASAT after renal transplant. Other measures were unchanged.

*Conclusion.* Mental processing speed and sustained attention improved in children after renal transplantation in a carefully controlled prospective cross-over study.

Chronic renal failure in childhood has been shown to be associated with deficits in neurocognitive performance, with the potential to limit cognitive development and long-term educational attainment [1]. Fennell et al found that children with renal disease in all stages of therapy (predialysis, dialysis, and transplant) performed worse than controls on a series of neuropsychological tests and that some differences increased over time [2]. There was no discernable effect of any particular therapy. This effect does not appear to fluctuate directly with changes in serum urea nitrogen, as Rasbury et al's study of children prehemodialysis and posthemodialysis sessions did not demonstrate improvement in performance on measures of attention, problem solving, and paired associate learning after individual hemodialysis (HD) treatments [3].

Renal transplantation is considered the optimal mode for therapy for children, allowing more normal growth than during dialysis, more consistent school attendance, and involvement in age-appropriate activities. A few studies suggest a beneficial effect of renal transplant on neuropsychological performance. Lawry, Brouhard, and Cunningham compared groups of dialysis and transplant patients and found the former to perform worse than the latter in mathematics, reading, and writing on the Woodcock-Johnson standardized achievement test [4]. However, the same subjects were not studied while receiving both forms of therapy. In another study, when children with advanced uremia were studied immediately prior to the initiation of HD and again after renal transplantation, IQ and mathematics improved with correction of uremia after renal transplant [5]. Past literature on neuropsychological functioning in renal failure has consistently shown deficits of mental efficiency, psychomotor speed, and attention in affected patients [1, 6]. Based on these observations, we hypothesized that the effects of advanced renal disease would be most apparent on tests of attention and mental processing speed, but we expected that motor speed indices would be more subject to other sources of variation and thus would be less sensitive to changes in renal function. Our protocol was tailored to sample skills previously considered abnormal in uremic subjects, including IQ, visual motor

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speed, motor dexterity, visuospatial ability, learning, and working memory, as well as measures of attention and mental processing speed, in a prospective, cross-over design.

We avoided the comparison of separate dialysis and transplant populations. We considered the two groups to be very different in medical, psychological, and socioeconomic status; thus, despite the presence of renal disease, they were imperfectly matched. Instead, we studied the same subjects both before and after renal transplant to define more precisely the difference in neurocognitive performance and to provide greater statistical power. In addition, earlier studies did not measure dialysis delivery by peritoneal dialysis (PD) or HD, or else used advanced uremia as a baseline. In this study, we were able to compare neurocognitive performance during a period of stable, adequate dialysis with results obtained with normalized renal function post-transplant.

## METHODS

Nine subjects were recruited from the nephrology practice and dialysis unit at Children's Memorial Hospital and were studied in the Neuropsychology Laboratory of Children's Memorial Hospital by experienced psychometricians. Formal kinetic modeling of HD and PD delivery was performed at least every three months and within the month prior to neuropsychological testing.

Baseline testing was performed prior to kidney transplantation, and a series of repeatable measures was performed again one year after transplant, when patients had achieved stable renal function and were on maintenance doses of cyclosporine and prednisone. Subjects receiving HD were studied on a nondialysis day to avoid fatigue. Subjects were excluded if less than six years of age, medically unstable, or both verbal and performance IQ were less than 70. Each subject served as his own control in comparing pretransplant and post-transplant performance.

The cognitive tests chosen were established tasks widely used in diagnostic pediatric neuropsychology [7]. At first encounter, subjects were tested with the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) if less than 17 years of age or the Wechsler Adult Intelligence Scale-Revised (WAIS-R) if over age 17, and then with a series of measures that was considered repeatable because of the nature of the tasks or the possibility of varying the test on subsequent occasions. Repeatable measures were used at the one-year follow-up examination. The ability to hold discrete numbers in working memory and add them quickly was tested with the Paced Auditory Serial Addition Test (PASAT) for those over 17 and the Children's Paced Auditory Serial Addition Test (CHIPASAT) for those under 17. The Stroop Color-Word Naming Test was used as a measure of focal attention. Verbal learning was assessed with the Buschke Selective Reminding Test, and visuospatial ability was measured with the Meier Visual Discrimination Test. Motor dexterity and speed were tested with the Grooved Pegboard Test. The WISC-III Coding subtest (for those less than 17 years) or the WAIS-R Coding subtest (for those of more than 17 years) and the Trail-making Test were used to measure visual motor speed. Symptoms of depression were assessed with the Beck Depression Inventory, the Children's Depression Inventory, and interview by psychologist or psychometrician.

Computer-based neurocognitive testing was used extensively in this study, including the computerized Cognitive Abilities Tests (CATs) [8] and the Conners Continuous Performance Test (Conners CPT) [7]. The CATs are visual information-processing tasks, designed to measure elementary cognitive processes in a touch-screen administration format, and they have been previously tested in school-age children [9]. This format allows one to separate mental processing speed and motor response speed components of task performance. Three of the 11 available CAT subtests were selected for ease of administration and relevance to our hypothesis: the Stimulus Discrimination, Reaction Time, and Learning. For example, in the Stimulus Discrimination subtest, a row of small "checkerboard" patterns within rectangular windows is presented below a target pattern while the subject touches a finger bar on the touch screen monitor. This observation period (the interval for which the finger bar is touched and the patterns are visible) is recorded as the subject's *decision time* while searching for the choice pattern that matches the target. Once the target is located, the subject lifts his finger off the finger bar. The windows go blank, and the subject touches the window that contained the matching pattern. The time required to move from the finger bar to the choice window is recorded separately as the *movement time.* In the CAT Reaction Time task, the subject presses a finger bar and waits for one of an array of rectangular windows to light up and touches the lit window as quickly as possible. Decision and movement time are separately recorded as in Stimulus Discrimination. The CAT Learning task allows the measurement of speed and accuracy of responses while the subject learns a series of "checkerboard" patterns; however, decision and motor speed components are not separately measured on that task.

The Conners Continuous Performance Test (Conners CPT) is a computer-based test of sustained attention, consistency of performance, and the ability to suppress impulsive responses. In the Conners CPT, subjects observe letters that appear rapidly on a computer monitor, and they depress a mouse button for every target (letter that is not an *X*). This test measures accuracy (in total target hits), false positive responses, and discrimination ability, as well as reaction time.

**Table 1.** Characteristics of patients, their dialysis delivery and renal function

| Characteristic | |
|---|---|
| Males/females | 5/4 |
| Pre-Tx therapy | 5 PD/3 HD/ 1 preemptive transplant |
| Age at pre-Tx testing: median, mean ± SD | 13.3 years, 14.2 ± 3.5 |
| Age at post-Tx testing: median, mean ± SD | 14.9 years, 15.8 ± 3.8 |
| Age at onset of ESRD: median, mean ± SD | 11.9 years, 11.7 ± 2.2 |
| Duration of ESRD prior to transplant | 2.5 years, 3.44 ± 2.9 |
| Mean Kt/V – hemodialysis | 1.8 ± 0.9 |
| Mean Kt/V – peritoneal dialysis (weekly) | 2.3 ± 0.5 |
| Post-transplant serum Cr: median, mean ± SD | 1.1 mg/dl, 1.3 ± 0.6 |

This protocol was reviewed and approved by the Institutional Review Board of Children's Memorial Hospital, and informed consent for participation was obtained from parents of the subjects. Assent was obtained from those age 12 and older.

### Statistical analysis

Pretransplant and post-transplant performance were compared within subjects by Wilcoxon signed rank test for paired samples ($P < 0.05$ significant). We performed further analysis of results from the Stimulus Discrimination subtest of the CAT to ensure that performance did not improve with practice, by comparing performance on the first half and second half of each task administration period. In addition, because of the wide age range of participants and the year interval between repeated testing, measures were converted to Z scores (number of standard deviations above or below mean for age) whenever age-adjusted normative data were available.

## RESULTS

Data on the nine subjects are shown in Table 1. Five were maintained on PD and three on HD prior to renal transplant. All subjects received adequate renal replacement therapy by formal kinetic modeling with mean HD Kt/V of 1.8 ± 0.9 and PD weekly total Kt/V of 2.3 ± 0.5. All subjects were medically and nutritionally stable at the time of neurocognitive testing. In particular, no subject had been hospitalized within the month prior to testing. Nutritional state was good, with mean serum albumin of 3.6 ± 0.4 mg/dl. Dietary protein intake was obtained by home diet record reviewed by a renal dietitian and averaged 1.4 ± 0.4 g/kg/day. Anemia was corrected with erythropoietin and iron to mean hematocrit of 30.5 ± 4.2%. Serum phosphorus control was fair, with a mean serum phosphorus of 5.9 mg/dl (range 2.8 to 10).

**Table 2.** IQ measurements of study subjects

| Variable | Median | Mean ± SD |
|---|---|---|
| Verbal IQ | 86.5 | 91.4 ± 18.9 |
| Performance IQ | 99 | 95.1 ± 15.7 |
| Full scale IQ | 93 | 91.6 ± 16.0 |

Compliance with the PD prescription was assured by regularly comparing drain volumes with expected values, and by measurement of actual urea and creatinine clearance from dialysate collection at least every three months and within the month of neurocognitive testing date. One subject had a preemptive renal transplant from a living related donor, but was tested at a time of renal insufficiency before his transplant (blood urea nitrogen 64 mg/dl, creatinine 5.5 mg/dl, estimated glomerular filtration rate 12 ml/min/1.73 $m^2$). He is not included in the calculation of duration of end-stage renal disease (ESRD) prior to transplant. The performance on neurocognitive testing did not appear to vary by dialysis modality, although the number of subjects is too small to test for heterogeneity.

The clinical course after transplant was typical of our pediatric patients. Two subjects had early acute tubular necrosis. Four subjects had a single acute rejection in the first three months post-transplant, and one subject had a rejection episode at seven months. No subject had more than one rejection episode. All rejection episodes were managed with intravenous methylprednisolone over three days; one subject received monoclonal antibody therapy. Post-transplant renal function was good (mean serum creatinine 1.3 ± 0.6 mg/dl, calculated glomerular filtration rate 76 ± 18 ml/min/1.73 $m^2$), and all subjects were on stable doses of prednisone (mean 0.16 ± 0.05 mg/kg/day) and cyclosporine (7.3 ± 4.2 mg/kg/day) without rejection episodes within four months of testing. The mean post-transplant hematocrit was improved at 34.4 ± 4.2%. Seven subjects required antihypertensive medication after transplant, although doses were modest and included lisinopril, atenolol, labetalol, and sustained-release nifedipine. All subjects attended school full-time with excellent attendance records. Three subjects were Hispanic. One was African American, and the remainder were Caucasian; this ethnic and racial mix is typical of our renal transplant population. The results of formal IQ testing are shown in Table 2. Mean IQs are similar to those reported by others in children with renal disease [5].

The results of many repeated measures did not show statistically different performance before and after renal transplantation. Focal attention, as measured by the Stroop Color-Word Naming Test, did not differ between prerenal transplant and postrenal transplant testing dates. Verbal learning, as measured by the Buschke Selective Reminding Test, and visuospatial ability, as mea-

**Table 3.** Pre- and post-transplant performance on the Stimulus Discrimination, Reaction Time and Learning subtests of the Cognitive Abilities Test

| | | Pre-transplant | | Post-transplant | | |
|---|---|---|---|---|---|---|
| CAT-subtest | Parameter | Median | Mean ± SD | Median | Mean ± SD | *P* |
| Stimulus discrimination | Decision speed | 1.99 | 2.28 ± 0.72 | 1.57 | 1.64 ± 0.31 | 0.008 |
| | first half | 1.93 | 2.18 ± 0.70 | 1.58 | 1.67 ± 0.34 | 0.016 |
| | second half | 2.14 | 2.37 ± 0.74 | 1.51 | 1.62 ± 0.30 | 0.008 |
| | Motor speed | 0.20 | 0.23 ± 0.10 | 0.21 | 0.21 ± 0.04 | 0.742 |
| | first half | 0.18 | 0.23 ± 0.11 | 0.20 | 0.21 ± 0.03 | 0.844 |
| | second half | 0.22 | 0.23 ± 0.09 | 0.23 | 0.22 ± 0.06 | 0.742 |
| Reaction time | Decision speed | 0.44 | 0.48 ± 0.09 | 0.42 | 0.43 ± 0.05 | 0.016 |
| | Motor speed | 0.26 | 0.26 ± 0.06 | 0.23 | 0.25 ± 0.04 | 0.844 |
| Learning | Decision/motor | 1.42 | 1.53 ± 0.38 | 1.42 | 1.32 ± 0.50 | 0.164 |
| | accuracy | 37% | 40% ± 12 | 49% | 52% ± 15 | 0.012 |

sured by the Meier Visual Discrimination Test, did not change with renal transplantation. Performance on the Grooved Pegboard Test of motor dexterity and speed and the WISC-III/WAIS-R Coding subtest of visual motor speed did not change with improvement in renal function after transplantation. None of the subjects' scores on the Beck Depression Inventory and Children's Depression Inventory fell in the depressed range.

Significant differences were found in the results of computer-based testing. The results of computerized CAT are shown in Table 3. In the Stimulus Discrimination subtest, decision speed (mental processing speed) was significantly faster in the post-transplant evaluation compared with the pretransplant evaluation (median pretransplant vs. post-transplant, 1.99 vs. 1.57 seconds, $P = 0.008$), whereas there was no difference in motor speed (0.20 vs. 0.21 seconds, $P = 0.742$). To ensure that the improvement in decision speed was not the result of practice (albeit a year later), we compared performance in the first and second half of each test administration. In fact, decision speed slowed slightly in the second half of the testing period in the pretransplant evaluation (whereas motor speed was stable), suggesting that subjects were not becoming more proficient with practice. Decision and motor speed did not change during the post-transplant test administration. Furthermore, the standard deviation of the decision speed and the motor speed was smaller in the post-transplant evaluation, indicating less variable response times and more consistent performance.

The Reaction Time subtest of the CAT is also shown in Table 3 and, like the Stimulus Discrimination subtest, demonstrates a significant improvement in decision speed (0.44 vs. 0.42 seconds, $P = 0.016$) after renal transplant without a significant change in motor speed. The Learning subtest does not allow a distinction between decision speed and motor speed, and no difference in combined response speed was found. However, accuracy was greater in the post-transplant evaluation (37 vs. 49%, $P = 0.012$).

Results from the Conners Continuous Performance Test are shown in Table 4, and although there was no difference in the absolute number of target hits or false alarms (commission errors), target hit reaction time improved after transplantation (0.47 vs. 0.36 seconds, $P = 0.039$). Furthermore, the signal detection index for target versus nontarget discrimination sensitivity (expressed as the difference between the Z score for commission errors and the Z score for target hits) improved in the post-transplant evaluation (2.46 vs. 3.67, $P = 0.039$). Table 4 also includes the results of the PASAT/CHIPASAT (testing the ability to hold discrete numbers in working memory and add them quickly), which are shown as a Z score for performance at each testing date. Performance significantly improved after renal transplant (−0.41, vs. 0.46, $P = 0.016$).

## DISCUSSION

We hypothesized that measures of mental processing speed and sustained attention would be particularly sensitive to improvements in renal function after renal transplantation, whereas motor or movement speed would be less affected. Thus, our test protocol included tasks that separate decision and motor speeds (that is, the CAT Stimulus Discrimination and Reaction Time subtests). Our data largely support this hypothesis. Pre–post-transplant comparisons clearly indicated improvement in "motor-free" decision speed (faster and less variable) on these tasks, whereas the actual motor response speed did not change. Not surprisingly, other tests that depend exclusively on motor speed (Grooved Pegboard Test) or combined motor and mental processing speed (WISC/WAIS-R Coding, Trailmaking Test) showed no change with the improvement in glomerular filtration rate of renal transplantation.

Subjects also demonstrated improved performance in

**Table 4.** Pre- and post-transplant performance on the Conners Continuous Performance Test and the Paced Auditory Serial Addition Tests/Children's Paced Auditory Serial Addition Test

| | | Pre-transplant | | Post-transplant | | |
|---|---|---|---|---|---|---|
| Test | Parameter | Median | Mean ± SD | Median | Mean ± SD | *P* |
| Conners CPT | Correct hits | 314 | 293 ± 44 | 322 | 311 ± 22 | 0.156 |
| | False alarms | 10 | 14 ± 9 | 10 | 13 ± 9 | 0.734 |
| | Reaction time | 0.47 | 0.47 ± 0.10 | 0.36 | 0.38 ± 0.72 | 0.039 |
| | Discrimination sensitivity | 2.46 | 2.19 ± 1.29 | 3.67 | 2.95 ± 1.33 | 0.039 |
| PASAT | Z-score | −0.41 | −0.07 ± 1.42 | 0.46 | 0.62 ± 1.55 | 0.016 |

target hit reaction time on the Conners CPT, a test of sustained visual attention with a minimal motor response component (pressing a mouse button), which largely taps decision speed. In addition, the CPT also showed improved stimulus discrimination sensitivity (that is, the ability to distinguish between target and nontarget letters) after transplantation.

Performance on the PASAT/CHIPASAT tests of speeded working memory also improved after renal transplant. Because the results for this task were normalized for age, a change in performance over a one-year measurement period cannot merely be ascribed to practice. Nonetheless, because this test draws on arithmetic skills as well as on working memory, more consistent school attendance could have resulted in improvement in computational ability. Our study was not designed to look at school attendance, so we cannot rule out this possible confounding effect.

Although the tasks that improved after renal transplantation are heavily dependent on mental processing speed, they do not appear to be modality specific. The CAT tasks and the Conners CPT are primarily visual, but the PASAT and CHIPASAT are primarily auditory tasks. Our subjects' overall improvement in mental processing speed is consistent with Kramer et al's findings of post-transplant improvement in P300 latency, a motor-free event-related potential (ERP) that appears to be a sensitive electroencephalogram (EEG) index of mental processing speed [10]. Others have shown correction of anemia with erythropoietin to affect P300 latencies or amplitude [11]. However, our subjects did not have profound anemia during dialysis, and the change in hematocrit post-transplant was not large enough to account for the improvement in mental processing speed.

With our sample size, we did not demonstrate an effect of renal transplant on neuropsychological tasks which depend on motor speed (or on tasks that combine mental processing and motor response components into a single performance index), memory, or learning; however, it is possible that a larger sample would permit detection of such an effect. On the other hand, the neurotoxic effects of immunosuppressives [12] may have confounded our observations in the post-transplant period, and the beneficial effect of improved glomerular filtration rate may have been attenuated by an adverse effect of cyclosporine or prednisone on motor skills or cognitive function.

Depression can clearly affect performance on some neurocognitive tests, and studies in adult dialysis patients indicate a high prevalence of depression [13]. We sought to account for this with the Beck Depression Inventory and the Children's Depression Inventory, as well as the observations of the psychologist and psychometrician. We did not find evidence of depression in these subjects either before or after their transplant; thus, we cannot ascribe improved performance to improvement in affect.

Advanced uremia in the absence of dialysis is not an appropriate baseline from which to compare intellectual performance, yet several studies of adults and children have done exactly that, yielding convincing, but clinically less relevant, differences between the uncorrected uremic state and that of dialysis or transplant [2, 4, 5]. Other researchers have studied dialysis patients without rigorously assuring that adequate HD or PD was provided [14, 15]. In this study, we provided adequate dialysis, as assessed by routine measurement of dialysis delivery, for months prior to neurocognitive testing.

Our findings of improved neurocognitive performance after transplantation are conclusive because of the strength of within-subject comparisons. Had we relied on group means rather than within-subject comparisons, as previous studies have done [4, 5, 14], nearly all neuropsychological measures would have failed to demonstrate significant improvement after transplantation. Only the CAT Stimulus Discrimination task distinguished between pretransplantation and post-transplantation performance when unpaired comparisons were used. Furthermore, the use of "matched" controls in various disease states must be approached cautiously, as the use of a particular control group can confound the assessment of cognitive function. Fennell et al determined significant baseline differences between "healthy" children and those with chronic renal failure, despite matching for age, race, and sex [2]. However, Pliskin et al compared well-dialyzed adults to age- and education-matched controls with a similar burden of chronic disease, absent renal insufficiency, and found no difference in performance on a battery of neuropsychological tests [16].

There are a few studies that compare neurocognitive function after renal transplant with that observed during dialysis. Teschan et al compared EEG power spectrum analysis and found significant improvement from chronic HD to the transplanted state [17]. Kramer et al studied P300 ERPs, the Trailmaking Test, and the Mini-Mental Status Exam in chronic HD patients and "healthy" controls [9]. Following renal transplant, P300 latencies decreased, whereas performance on the Trailmaking test did not differ from controls. These findings are consistent with our current data that show improvement in tests that depend on mental processing speed (as the P300 latency does), but not on those that combine motor and mental processing speed, such as the Trailmaking Test. The Mini-Mental Status Exam appears not to have been sensitive enough to demonstrate an effect of renal transplantation.

Dialysis delivery, determined by measured Kt/V, was very good in our subjects; none would be considered inadequately dialyzed by current standards. This raises the possibility that even the most intensive dialysis regimens would fail to correct deficits in neurocognitive function. Further, post-transplant renal function in this group was good, with an average estimated glomerular filtration rate of 76 ml/min/1.73 $m^2$. The neurocognitive tests used in this study may be sensitive enough to detect subtle changes in "pre-ESRD" patients without clinically evident uremia.

We used a novel series of sensitive, yet repeatable, neurocognitive tasks with an emphasis on computer-based testing. Because our patients frequently entertain themselves during HD sessions with video games (and our PD and preemptive patients are familiar with them, as well), the subjects in our study found this a very comfortable medium for testing. Older adult HD and transplant patients may not be as comfortable with computers, yet they are increasingly used in clinical neuropsychological assessment in children. Although previous studies of children with chronic renal failure used older tests that did not allow discrimination of specific mental and motor processes, we have used more specific tasks that measure discrete components of information processing that appear particularly sensitive to the effects of uremia and respond favorably to the effects of renal transplantation. We expect these tests will be applicable to other protocols studying the effects of various therapies in children and adults with chronic renal failure.

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