Cognitive outcome following kidney transplantation

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Abstract

Background. While a handful of studies have assessed cognition in kidney transplant (TX) recipients, the neuropsychological presentation of this population is not yet clear. Kidney transplantation typically leads to improvement of metabolic factors associated with chronic kidney disease (CKD). However, comorbid diseases independently linked with cognitive compromise often persist, and for this reason, cognitive difficulties may still be present following transplantation.

Methods. In this cross-sectional study, we assessed cognition in 42 kidney TX recipients, 45 outpatients with pre-dialysis CKD and 49 healthy controls using measures of verbal learning and memory and executive functioning.

Results. Findings indicated that TX and CKD patients demonstrated significantly worse verbal learning and memory in comparison to controls. While both CKD and TX patients exhibited significantly worse performance than controls on a response inhibition measure, only CKD patients performed significantly worse on a set-shifting task.

Conclusions. Results suggest that, in comparison to controls, verbal memory and executive functioning skills are worse in both CKD and TX patients. Further research is needed to determine the etiology and extent of cognitive compromise, as well as to assess the clinical implications of these findings.

Keywords: anxiety; chronic kidney disease; depression; kidney transplant; neuropsychological

Introduction

Although cognition following kidney transplantation has previously been assessed [1–5], the neuropsychological presentation of this population is not yet clear, with recent studies reporting conflicting findings [3–5]. Neuropsychological performance of kidney transplant (TX) recipients has primarily been described in relation to individuals on dialysis [1–4]. The cognitive limitations of persons on dialysis are well established (for a review, see [6]). Thus, comparisons to kidney TX recipients allow one to parcel out the effects of dialysis and renal failure on cognition. However, such comparisons do not address the question of whether cognition will approximate baseline pre-illness levels following successful kidney transplantation.

In fact, kidney TX recipients often present with several risk factors for diminished cognitive performance, including emotional distress [7] and a high prevalence of comorbid illnesses. Recent investigations of neuropsychological performance in persons with chronic kidney disease (CKD; i.e., prior to renal failure) suggest that comorbid cerebrovascular illnesses may underlie at least some of the cognitive difficulties associated with renal disease [8]. For instance, the two leading causes of CKD are diabetes and hypertension [9], and there is evidence for decrements in cognition in both conditions apart from CKD [10,11]. We have previously argued that the pattern of reduced cognitive performance observed in CKD (i.e., pre-dialysis) is most consistent with comorbid cerebrovascular illness [12], which is not likely to rescind following transplantation. Interestingly, previous research does not address to what extent reduced cognitive performance that presents in CKD may persist following kidney transplantation. Comparisons of kidney TX recipients to CKD patients allow for better elucidation of the role of metabolic derangements and other illness-related features.

While contrasting cognition in post-kidney TX recipients with that of CKD patients should allow one to better understand the etiology of cognitive difficulties, comparisons to within-study controls are also necessary for assessing whether cognitive performance post-kidney transplantation approximates baseline levels of functioning (i.e., pre-illness performance). While cognitive comparisons to normative databases have previously been made [3,5], no studies have compared kidney TX recipient’s memory and executive functioning performance to that of within-study controls.

It is within this context that we aimed to describe the neuropsychological capacities (specifically verbal memory and executive functioning) of TX recipients in relation to both healthy controls and persons with CKD. Taking into
consideration the resolution of metabolic factors and the neuropsychological presentation of persons with hypertension and diabetes \[10,11\], we predicted that both TX and CKD patients would perform worse than matched controls on neuropsychological measures. We chose to examine verbal memory and executive functioning given previous demonstrations of reductions in these functions in persons with CKD \[12,13\]. Our second objective was to assess for associations between cognition and a number of clinical factors (e.g., depression, immunosuppressants, GFR levels) that have been linked to cognition in previous research \[3,13\].

**Subjects and methods**

**Participants**

Neuropsychological tests and questionnaires were administered to 49 healthy controls, 45 CKD patients and 42 kidney TX recipients. The current study was, in part, based on data collected for a research project on cognitive functioning in persons with renal disease and matched healthy controls \[12\], and CKD patients and controls were selected from the existing data set to maximize matching on age and gender. Data were collected between March 2003 and October 2006. To be considered eligible for the current study, all participants met the following criteria: (1) capable of giving informed consent; (2) absence of visual impairments (corrected vision $\geq 20/50$) or hearing impairments; (3) fluency in the English language; (4) minimum of grade 6 education; (5) absence of psychosis, acute illness (e.g., metastatic cancer), neurological disease and other major organ failure (e.g., end-stage liver disease).

The CKD and TX groups were derived from outpatients seen at the Vancouver General Hospital (VGH) in Vancouver, B.C., Canada. Eligible CKD patients had less than half of normal kidney functioning (i.e., estimated GFR $<60$ ml/min/1.73 m$^2$ \[14\]) and none required dialysis treatment. TX recipients had maintained a successful kidney graft for at least 6 months. Consecutive patients who met these criteria were invited to participate during their regularly scheduled clinic visit. Additional TX patients were recruited through study information letters, which were followed up with phone calls as necessary. The overall recruitment success rates were approximately 70% for CKD patients and 60% for TX recipients. Lastly, controls were recruited through local community channels.

All participants signed letters of informed consent and received compensation for their time and travel expenses. The study protocol was approved by the University of British Columbia (UBC) and Simon Fraser University (SFU) research ethics boards.

**Measures**

**Clinical measures.** All participants filled out the Health Questionnaire, a self-report measure that assesses medical history and current health concerns (e.g., cerebrovascular risk factors). Additional information was collected from the CKD and TX patients’ medical records, including laboratory results [i.e., estimated GFRs (ml/min/1.73 m$^2$) and haemoglobin levels (g/l)], current medications and dosages, CKD etiology (usually determined by clinical diagnosis; typically, diagnoses were not biopsy-confirmed) and comorbid conditions. The modification of diet in renal disease (MDRD) prediction equation was used to estimate GFR \[15\]. Cognitive tests were administered within 4 weeks of the laboratory tests.

**Sociodemographic characteristics.** Demographic information included age, gender, ethnicity and education. Daily living skills were quantified using the Instrumental Activities of Daily Living questionnaire (IADL) \[16\], a questionnaire consisting of eight skills that are scored according to a hierarchical Guttman scoring format (i.e., less able versus more able to do a given task) with a dichotomous scale. Depressive symptoms were assessed using Center for Epidemiological Studies-Depression Scale (CES-D) \[17\] and anxiety symptoms were assessed using the Multidimensional Anxiety Questionnaire (MAQ) \[18\].

**Cognitive measures.** The cognitive measures utilized were selected because of their common application in the CKD literature (e.g., \[2,3,5,13\]) and documented psychometric properties \[19,20\]. According to standardized protocol, trained research assistants and graduate students individually administered and scored the tests. Healthy controls were tested at the SFU Human Neuropsychology Laboratory or at community sites (e.g., community centres). All TX and CKD patients were tested at VGH or SFU.

**California Verbal Learning Test–Second Edition (CVLT-II)** \[19\]. The CVLT-II is a measure of verbal learning and memory. Participants are read a list of words and, immediately following, are asked to recall as many items as they can and again, after a delay period. Trials 1–5 indicate the total number of items one is able to learn during five trials (i.e., learning), and Long Delay Free Recall provides an estimate of the amount of verbal information retained after a 20-min delay (i.e., memory) \[19\].

**Delis-Kaplan Executive Function System (D-KEFS)** \[20\]. The D-KEFS battery assesses executive functioning, which consists of complex tasks that require cognitive flexibility. The Trail Making Test and the Colour–Word Interference Test were selected from the D-KEFS battery, which assess flexibility of thinking and verbal inhibition of a dominant response, respectively \[20\].

**Statistical analysis**

One-way ANOVA and independent t-tests (for continuous data), and $\chi^2$ (for categorical data) were performed to compare groups according to cognitive, demographic, psychosocial and clinical variables. For the primary analysis, group membership (TX, CKD and controls) served as the independent variable and three cognitive scores served as the dependent variables. The cognitive scores included measures of learning and memory (composite score), and executive functioning (time to completion scores for the Trails and Colour-Word subtests). The learning and memory composite score was comprised of equally weighted t-scores for the CVLT-II Trials 1–5 and Long Delay tasks, which were highly correlated
Participant characteristics | CKD (n = 45) | Controls (n = 49) | Transplant (n = 42) | P-value
--- | --- | --- | --- | ---
Age (mean ± SD) | 59.67 ± 11.88 | 57.00 ± 13.59 | 55.24 ± 10.96 | 0.239
Female (n; %) | 23 (51.1%) | 30 (61.2%) | 20 (47.6%) | 0.394
Education (mean years ± SD) | 13.69 ± 3.02 | 14.41 ± 2.23 | 13.57 ± 2.55 | 0.248
Distress (mean t-score ± SD) | 55.79 ± 10.39 | 50.00 ± 9.45 | 56.68 ± 13.18 | 0.006
Smoke cigarettes (n; %) | 6 (13.3%) | 4 (8.2%) | 1 (2.4%) | 0.182
Hypertension (n; %) | 42 (93.3%) | 12 (24.5%) | 32 (76.2%) | <0.001
Diabetes mellitus (n; %) | 12 (26.7%) | 0 (0%) | 13 (31.0%) | <0.001
Hypercholesterolemia (n; %) | 19 (42.2%) | 5 (10.2%) | 13 (31.0%) | 0.002
Anti-depressants (n; %) | 3 (6.7%) | 5 (10.2%) | 12 (28.6%) | 0.006
Benzodiazepines (n; %) | 5 (11.1%) | 1 (2.0%) | 6 (14.3%) | 0.098
Opiates (n; %) | 3 (6.7%) | 0 (0%) | 0 (0%) | 0.045
Anti-cholesterol agents (n; %) | 20 (44.4%) | 4 (8.2%) | 16 (38.1%) | <0.001
Anti-hypertensives (n; %) | 44 (97.8%) | 11 (22.4%) | 31 (73.8%) | <0.001
Anti-diabetic medications (n; %) | 12 (26.7%) | 0 (0%) | 10 (23.8%) | 0.001
Estimated glomerular filtration rate (mean ± SD) | 23.66 ± 11.21 | N/A | 59.38 ± 19.42 | <0.001

P-values derived from one-way ANOVA for continuous data; P-values derived from $\chi^2$ for categorical data.

$r = 0.79, P < 0.001$). Similar to the learning and memory tasks, the measures of anxiety (MAQ) and depression (CES-D) were highly correlated ($r = 0.75, P < 0.001$), and a ‘distress’ measure was created, also by computing and equally weighting t-scores.

Planned comparisons were run using Tukey’s honestly significant difference test (Tukey’s HSD), which adjusts significance values for multiple comparisons. Estimates of effect sizes (Cohen’s $d$) were calculated with the Effect Size (ES) analysis software version 1.0 using a pooled SD. Pearson bivariate correlations were carried out in order to study the associations of various factors with cognition. We set the following criteria to assess for potential confounds. Variables would be adopted as covariates in the model (ANCOVA) if there were (1) significant group differences and (2) significant associations with cognition. All analyses were conducted using SPSS 14 software (SPSS Inc., Chicago, IL, USA) and all P's reflect two-tailed tests with a P-value <0.05 considered statistically significant.

**Results**

**Participant characteristics**

Participant characteristics, including means, frequencies and main effects for the three groups, are presented in Table 1. The three groups were matched in terms of age, education and gender (see Table 1). Table 1 also shows that levels of distress significantly differed by group, and planned comparisons revealed that both CKD and TX patients asserted significantly more symptoms of distress than controls ($P = 0.014; P = 0.016$, respectively). No main effects were found for scores on the IADL [$F(2, 128) = 1.90; P = 0.154$], with all participants scoring at least 6 out of 8.

**Medications**

Since antidepressants, benzodiazepines and opiates are all central nervous system-active medications [21], and could potentially have cognitive side effects, group differences in medication usage were assessed (see Table 1). *Post hoc* analyses revealed that more TX patients were taking antidepressants than both CKD patients and controls ($\chi^2 = 7.31, df = 1, P = 0.007; \chi^2 = 5.02, df = 1, P = 0.025$, respectively). In contrast, there was a trend for CKD patients to be taking more opiates than the controls and TX patients ($\chi^2 = 3.37, df = 1, P = 0.066; \chi^2 = 2.90, df = 1, P = 0.089$, respectively).

**Comorbidity**

Because a number of comorbid conditions (i.e., hypertension and diabetes) common to CKD are associated with compromised cognition apart from CKD, we assessed group differences in the prevalence rates of these conditions (see Table 1). *Post hoc* analyses revealed that in comparison to controls, both CKD and TX groups had significantly higher rates of hypertension ($\chi^2 = 45.48, df = 1, P < 0.001; \chi^2 = 24.21, df = 1, P < 0.001$, respectively), diabetes ($\chi^2 = 14.98, df = 1, P < 0.001; \chi^2 = 17.69, df = 1, P < 0.001$, respectively) and hypercholesterolemia ($\chi^2 = 12.65, df = 1, P < 0.001; \chi^2 = 6.136, df = 1, P = 0.013$, respectively). In addition, the CKD group had significantly higher rates of hypertension ($\chi^2 = 5.02, df = 1, P = 0.025$) than the TX group. Seven (16.7%) of the TX patients also received pancreas TXs that effectively reversed type 1 diabetes. When accounting for history of diabetes, there were significantly higher rates of diabetes within the TX group compared to the CKD group ($\chi^2 = 28.87, df = 1, P < 0.001$).

Table 2 presents the clinical characteristics of the CKD and TX patients. As can be seen, similar proportions of both types of donor recipients received dialysis (i.e., either haemodialysis or peritoneal dialysis) prior to receiving a TX ($\chi^2 = 0.266, df = 1, P = 0.606$). However, living donor recipients were on dialysis for significantly less time ($M = 1.69$ years; $SD = 1.53$) than deceased donor recipients ($M = 3.62$ years; $SD = 2.71; t(40) = 5.62, P = 0.023$).

**Cognitive performance**

Results from ANOVA and planned comparisons are reported in Figures 1–3, and, as can be seen, there were
Table 2. CKD and TX patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>CKD (n = 45)</th>
<th>Transplant (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient diagnoses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>11 (24.4%)</td>
<td>13 (31.0%)</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis/ischaemic nephropathy</td>
<td>5 (11.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GN* (e.g., IgA, FS, FSGS)</td>
<td>17 (37.8%)</td>
<td>17 (40.5%)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>6 (13.3%)</td>
<td>7 (16.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (13.3%)</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td><strong>Transplant characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since transplant (years; M ± SD)</td>
<td>5.24 (4.98)</td>
<td></td>
</tr>
<tr>
<td>Time spent on dialysis (years; M ± SD)</td>
<td>2.88 (2.50)</td>
<td></td>
</tr>
<tr>
<td>Kidney and pancreas transplant</td>
<td>7 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>15 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>27 (64.3%)</td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>26 (61.9%)</td>
<td></td>
</tr>
<tr>
<td>Previously on dialysis</td>
<td>24 (92.3%)</td>
<td></td>
</tr>
<tr>
<td>Living donor</td>
<td>16 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>Previously on dialysis</td>
<td>14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Number of kidney transplants received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Transplant</td>
<td>37 (88.1%)</td>
<td></td>
</tr>
<tr>
<td>2 Transplants</td>
<td>5 (11.9%)</td>
<td></td>
</tr>
</tbody>
</table>

* GN = Glomerulonephritis, IgA = IgA nephritis, FS = focal sclerosis, FSGS = focal and segmental glomerulosclerosis.

main effects for group for all cognitive measures under consideration. As predicted, planned comparisons revealed that both CKD and TX patients performed more poorly than controls on one of the executive functioning measures (Colour–Word Interference) and on the learning and memory task (CVLT-II).

However, only CKD patients performed significantly worse than controls for the other measure (Trails Letter–Number Sequencing). Effect sizes between CKD patients and controls were large for Learning and Memory ($d = -0.95$), large for Colour–Word Inhibition ($d = -0.68$) and medium for Trails Letter–Number Switching ($d = -0.59$). Effect sizes between TX patients and controls were large for Learning and Memory ($d = -0.74$), medium for Colour–Word Inhibition ($d = -0.56$) and medium for Trails Letter–Number Switching ($d = -0.44$). TX and CKD patients did not significantly differ on any of the measures.
Clinical correlates of cognition

Pearson bivariate correlations were run between cognitive measures and patient characteristics thought to be of potential importance (Table 3). No significant associations were found between cognitive performance and distress or measures of illness severity (GFR and haemoglobin levels, duration of dialysis, time since TX). However, there were significant associations between age and all the measures of cognition, indicating that older individuals tend to perform more poorly on each of these tasks.
Table 3. Intercorrelations for the full sample (n = 136)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distress</th>
<th>Learning and Memory</th>
<th>Trails Letter–Number Sequencing</th>
<th>Colour–Word Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.10</td>
<td>−0.36**</td>
<td>0.48**</td>
<td>0.55**</td>
</tr>
<tr>
<td>Education</td>
<td>0.06</td>
<td>0.23**</td>
<td>−0.21*</td>
<td>−0.12</td>
</tr>
<tr>
<td>Distress</td>
<td>−0.15</td>
<td>0.08</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>GFR</td>
<td>0.04</td>
<td>0.13</td>
<td>−0.21</td>
<td>−0.10</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>0.01</td>
<td>−0.01</td>
<td>−0.21</td>
<td>0.01</td>
</tr>
<tr>
<td>Duration of CKD (years)</td>
<td>0.05</td>
<td>−0.14</td>
<td>−0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>Time on dialysis (years)</td>
<td>0.02</td>
<td>0.14</td>
<td>−0.03</td>
<td>−0.07</td>
</tr>
<tr>
<td>Time since transplant (years)</td>
<td>−0.48**</td>
<td>0.10</td>
<td>0.14</td>
<td>−0.05</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01 (two-tailed).

For transplant and CKD patients only (n = 87).

For transplant patients only (n = 42).

Discussion

To our knowledge, no previous research has compared the neuropsychological performance of kidney TX recipients to that of pre-dialysis CKD patients. In addition, this is the first study to use multiple measures of executive functioning and include within-study controls in the assessment of memory and executive functioning post-kidney transplantation. The results from this study suggest that both TX and CKD patients, in comparison to controls, exhibit greater difficulty on measures of learning and memory and response inhibition. The CKD and TX groups did not significantly differ from each other on any of the cognitive measures. Furthermore, the estimated effect sizes (i.e., between medical groups and controls) ranged from medium to large.

Our hypotheses regarding neuropsychological functioning were supported for both groups on the response inhibition measure (Colour–Word Inhibition) and verbal learning and memory measure. However, only CKD patients performed more poorly than controls on the set-switching task (Trails Letter–Number Sequencing). Given the fact that both CKD and TX patients exhibited poorer cognitive performance than controls, important questions remain: what factors may be accounting for these differences, and are the etiologies similar in both illness groups? We took into consideration several potential explanations for these findings. Importantly, a number of illness and socio-emotional variables (e.g., distress, haemoglobin and GFR levels, time since TX, duration of dialysis and kidney disease) were not significantly correlated with cognitive performance. Our analyses further suggest that metabolic factors and distress were not related to cognitive performance in either CKD or TX patients. Given the close association of hypertension and diabetes with renal disease, and the fact that both conditions have been independently associated with decrements in cognition [10,11], it seems likely that a history of or the presence of these illnesses contributes to cognitive performance in CKD and TX patients. This argument is bolstered by recent MRI evidence of greater prevalence of silent cerebral white matter lesions amongst pre-dialysis CKD patients in comparison to normotensive controls [8]. Nonetheless, it is also possible that the mechanisms of reduced cognition in the TX and CKD groups may differ. For instance, a recent study suggests that lower memory performance in TX patients is associated with the immunosuppressant prednisone, a glucocorticosteroid, which may have degenerative effects on the hippocampus [4].

These findings should be considered in light of certain limitations. Since we used a cross-sectional design, case mix differences between the TX and CKD groups may have added additional variability to the study. The sample size in the current study limits our ability to assess the role of potential factors such as use of psychotropics and comorbidity in the cognitive differences observed. In addition, only a portion of the individuals in the CKD group will go on to receive a kidney TX or even be accepted onto the kidney TX waitlist for a variety of reasons (e.g., age of CKD onset, lifestyle choices), and consequently, a number of group differences other than those addressed in this study may be present. Furthermore, it is important to note that while this study is useful in identifying between-group differences in cognitive performance, changes in cognition across the course of the disease can only be inferred from a longitudinal design. Also, the exclusionary criteria of the present study may limit the generalizability of the results to the kidney TX population at large (i.e., individuals with psychosis, acute illness, neurological disease and other major organ failure were not included in this study). In fact, it is likely that we would have observed even greater cognitive differences if such individuals had been included.

While set-switching effects (i.e., Trails Letter–Number Sequencing) were not present for TX patients, it is important to note that the estimated effect size for this comparison was medium. According to Cohen’s recommendations, at least 64 subjects would be necessary to provide enough power (0.80) to detect effect sizes of this magnitude [22]. Since the sample sizes in our study were smaller than this, power limitations are evident, thereby highlighting the importance of revisiting these issues with larger samples. In the future, studies that include other medical populations as comparison groups (e.g., diabetic patients without CKD), compile cumulative dosages of central nervous system-active medications, and use longitudinal designs could aid in further clarification of the origins of compromised cognition in CKD and kidney TX populations. The impetus for such research is readily apparent as the prevalence of CKD, and consequently, the demand for kidney transplantation, continues to grow (see [9]).
In summary, the current findings suggest that memory and executive functioning difficulties may be present following successful kidney transplantation. Given the fact that reduced cognitive performance has been identified in kidney TX recipients, it will be paramount to elucidate the consequences in terms of medication adherence, ability to return to work and other functional outcomes. Such research may prove invaluable in assessing the relevance of neuropsychological findings to everyday living, and further highlight the potential benefits of formal evaluation of cognition to develop and implement treatment strategies throughout the course of kidney disease.

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Conflict of interest statement. Portions of this work were presented at the Annual International Neuropsychological Society’s 34th Annual Meeting.

References


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