Cognitive functioning pre- to post-kidney transplantation—a prospective study

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Abstract

Background. Kidney transplantation (TX) may ameliorate the neuropsychological (NP) impairments in end-stage renal disease (ESRD). Previous studies have suffered from small sample sizes, lack of standardization of dialysis adequacy, and insufficiently sensitive NP tests.

Methods. Twenty-eight medically stable patients aged 44.04 (12.01) years with ESRD were investigated before and at 6 months after successful kidney TX using an NP test battery, which assessed attention–concentration, psychomotor ability and memory. Formal kinetic modelling of dialysis delivery ensured adequate renal replacement therapy. Transplant function was good on stable doses of immunosuppressive medication, without evidence of rejection at the time of testing.

Results. Within-subject comparisons showed statistically significant improvement in memory performance after kidney TX. Other NP measures (attention–concentration and psychomotor abilities) showed non-significant improvements. Normative comparisons showed NP impairments on dialysis, which were not apparent after TX.

Conclusion. These data demonstrate improvements in cognition following kidney TX and emphasize the reversibility of the memory problems evidenced in dialysis.

Keywords: cognition; dialysis; neuropsychological; transplantation

Introduction

Kidney transplantation (TX) is considered to be the preferred treatment for end-stage renal disease (ESRD). Studies on outcomes after TX have traditionally measured post-operative survival and complication rates. More recently, quality of life (QoL) issues have also gained importance as an area of study and there is now overwhelming evidence attesting the QoL advantages of TX over dialysis [1,2]. One area that has received less attention is the impact of dialysis and TX on neuropsychological (NP) functioning. This area deserves attention as cognitive capacity is intimately connected to outcomes such as activities of daily living [3] and social and vocational adjustments [4], and, in the Framingham study [5], has also been found to be an independent predictor of mortality.

The presence of cognitive impairment in ESRD is well recognized. Dialysis patients present with selective mild to moderate cognitive impairments [6,7] whereas normal or near normal NP performance has been found in transplant recipients [8]. While these data suggest that improved cognitive functioning should occur from dialysis to TX, most studies that have examined this question have performed cross sectional analysis. A clearer understanding of the cognitive consequences of kidney TX can be obtained by using a repeated measurement design with a pre-TX assessment, when patients are maintained on dialysis, followed by an assessment post-TX.

To date, there have been only two small prospective studies that have directly compared the NP performance pre- to post-kidney TX in adults. Teschan et al. [9] studied eight patients repeatedly during dialysis treatment and 4–23 months following kidney TX using NP tests of attention and memory along with electroencephalograms (EEG). They found a significant improvement in the EEG and choice reaction times following kidney TX but unfortunately failed to quantify the dialysis delivery. Kramer et al. [10] reported improved cognitive functioning as measured...
by the Trail Making Test (TMT) A and Mini Mental State Examination (MMSE) and also P300 event-related potentials in a group of 15 haemodialysis (HD) patients before and after TX as compared with age-matched healthy subjects. Prior to TX, the HD patients performed significantly worse than controls in both NP tests, but the performance between groups did not significantly differ following TX. Besides the small sample sizes, these studies had large variations in the timing of post-TX assessment and the NP tests used and the cognitive domains assessed were limited. For instance, the MMSE is a screening test and not considered sensitive enough to detect subtle cognitive impairment [11]. Tests such as the Trail Making Part A do not assess cognitive abilities found to be particularly impaired in ESRD patients such as complex attention [12,13]. Failure to control for other factors that could potentially confound NP performance, such as mood, also characterizes these studies and further complicates the interpretation and validity of these findings.

The present study was therefore designed:

(i) To prospectively evaluate and compare the NP functioning pre- to post-kidney TX using a larger number of NP tests to cover a range of cognitive domains.

(ii) To identify the predictors of NP changes pre- to post-TX.

Subjects and methods

Participants

Between October 1998 and October 2000, a sample of 145 patients established on either HD (n = 77) or peritoneal dialysis (PD) (n = 68) were consecutively recruited in a prospective investigation of QoL and cognitive functioning in ESRD. The project was approved by the respective hospital ethical committees, and all the participants gave written informed consent.

Eligible participants were approached if they met the following inclusion criteria: (i) aged 18 years or more, (ii) no history or clinically evident cerebrovascular disease as reflected by new, transient or fixed neurological deficits, (iii) no major visual or hearing impairments, or other sensory or motor impairments that prohibit them from completing the scheduled assessments, (iv) absence of acute or chronic psychosis, evident depression, severe learning disabilities and/or dementia, (v) currently stable, defined as not being acutely ill or hospitalized at the time of the assessments, (vi) be fluent in written and spoken English and (vii) a minimum of 3 months on their respective mode of treatment and dialysis techniques (e.g. the same dialysate or dialyser if on HD).

Those patients of this cohort who received a kidney TX within the study period were assessed at ~6 months post operation (range 5–9 months). This interval was selected to ensure some distance from potential early post-operative complications and to allow some time for adjustment to the transplant and immunosuppressive regimen.

Measures

Sociodemographic characteristics. Demographic information including age, gender, ethnicity, education, marital and employment status, perceived work ability and household income was collected by means of a questionnaire.

As a patient’s mood may affect the NP performance, this was assessed prior to each NP assessment. The Beck Depression Inventory [14] was administered to measure depression. For the analyses presented here, a subset of 15 cognitive depression items, comprising the Cognitive Depression Index (CDI) was selected to control for the confounding contribution of somatic symptoms of physical illness [15]. This subset was selected because the somatic effects of depression such as loss of appetite and decreased sexual drive are also symptoms of ESRD.

Clinical Measures. A nephrologist familiar with the patient completed the End-Stage Renal Disease Severity Index (ESRD-SI) [16] for each patient. This provided a measure of comorbid illnesses and other complications of renal failure. The ESRD-SI measures the severity of illness as a function of 11 organic conditions.

Medical notes were also reviewed, and information regarding dialysis and TX history (e.g. time on dialysis, duration of functioning graft and rejection episodes) was recorded. Blood samples were taken after the completion of each NP testing session so as to avoid interference of any venupuncture pain with the participants’ NP performance. All blood samples were delivered to respective laboratories within 2 h of collection. Laboratory analyses consisted of the measurements of blood concentration of urea [blood urea nitrogen (BUN)], creatinine (Cr), haemoglobin (Hb) and albumin (Alb).

Dialysis adequacy was assessed by a calculated kinetic transfer/volume urea measurement (Kt/V) in both HD (single-pool determination) and PD patients (total weekly Kt/V urea). Only the measurements of adequacy made within 6 months of the study assessment were used for analysis purposes. Treatment was considered adequate when Kt/V met or exceeded the UK Renal Association Guidelines [17] as follows: for continuous ambulatory peritoneal dialysis (CAPD), a Kt/V of 1.70; for automated peritoneal dialysis (APD) (without a daytime dwell), of 2.0; for HD, of 1.20.

Glomerular filtration rate (GFR) was measured following the intravenous administration of 3 MBq 51Cr-EDTA diluted to 10 ml on 0.1% w/v excess EDTA solution [18]. Venous blood samples were taken from the opposite arm at 2, 3 and 4 h after injection. Following centrifugation, 3 ml aliquots were counted with standards and blanks in an automated gamma counter. GFR was calculated from the slow exponential of the bi-exponential plasma clearance curve and multiplied by a correlation factor of 0.87 because of underestimation of the plasma integral by this method.

Neuropsychological assessment. The NP test battery was designed to assess three cognitive domains: Attention and executive functions (Trail Making Tests A and B [19], Symbol Digit Modalities Test [20]), memory and learning (Rey Auditory Verbal Learning Test [21], Benton Visual Retention Test [22]) and psychomotor functions (Grooved Pegboard [23]).

Trail Making Test, forms A and B (TMT)[19]. This is a two-part measure of attention, visual scanning, motor
speed and planning ability. Part A (TMT-A) requires participants to connect 25 randomly arranged numbers in the proper order. Part B (TMT-B) requires participants to connect a series of numbers and letters in sequence (i.e. 1-A-2-B-3-C…13-L) as quickly as possible. Both parts of the test are timed (number of seconds) to completion with lower scores indicating better cognitive function.

**Symbol Digit Modalities Test (SDMT)**[20]. This is a task that requires visual attention–concentration, scanning and visual shifting for successful completion. Occulomotor abilities and hand–eye coordination are also involved. It consists of matching numbers and symbols as fast as possible within a time frame of 90 s with the number of correct matches being the score. Both the written (SDMT-W) and oral (SDMT-O) administrations were used in this study.

**Rey Auditory Verbal Learning Test (RAVLT)**[21]. This widely used auditory verbal memory task assesses immediate memory as well as retrieval from verbal short-term memory storage. It consists of five presentations with a recall of a list of 15 words that are read out to the participants by the examiner, one presentation of a second 15-word list and a sixth recall trial of the original word list. The score used in this study was the total verbal recall from trials 1–5 (RAVLT-T) as it enabled comparison to be made with normative samples.

**Benton Visual Retention Test (BVRT)**[22]. This is a measure of visual perception, visual memory and visuconstructive abilities. Ten cards featuring 1–3 designs are sequentially presented to participants for 5–10 s, after which the participants are requested to reproduce or copy them depending on the administration method employed. For this study, administration A was used, which allows a 10 s exposure to each of the 10 cards with an immediate recall by drawing. The BVRT has three equivalent forms, which were used in this study in a counterbalanced order. The number of correct reproductions (BVRT-C) and number of errors (BVRT-E) were recorded.

**Grooved Pegboard (GP)**[23]. This test of fine motor coordination and manual dexterity involves placing 25 pegs as rapidly as possible into an equivalent number of similarly shaped holes, but varying in their orientation to the vertical. GP is a timed test; so the score is the time to completion, with higher scores demonstrating a slower and thus worse performance. Both dominant (GP-D) and non-dominant (GP-ND) hands were tested.

Alternate forms of the tests were used where available (TMT-A; TMT-B; RAVLT; BVRT), to minimize practice effects. All the tests were selected with regard to their sensitivity to measure specific cognitive deficits and the availability of normative data and extensive use [24].

**Procedure.** The NP test battery and study questionnaire were administered on two occasions: at dialysis and at ~6 months following successful kidney TX.

While on dialysis, the participants were assessed twice within a 24 h interval to ascertain acute NP changes from pre- to post-dialysis [25]. This procedure also resulted in obtaining a dual-baseline assessment that served to reduce the confounding influence of practice effects on the subsequent assessment post TX [26]. The NP scores from the second assessment (i.e. at 24 h post dialysis) were used as baseline measures for a comparison with the performance post-transplantation. Besides removing any learning effects, this measure would account for the improvements seen at 24 h post dialysis in HD patients [25,27]. In addition, even though reliance on these NP scores might have inflated the baseline results, it was considered that this comparison would constitute a much stronger test of the NP benefits of TX.

**Statistical analyses**

In order to judge the patients’ performance on NP tests relative to normative performance [28], individuals’ performances on each of the NP tests were compared with a normative sample. An individual’s NP performance was considered impaired on a particular test if it was >1 SD below the mean of the norms. This comparison was performed for all the NP tests except the BVRT scores where clinical cut-offs (indicative of NP impairments) were used [22]. Individual BVRT scores were classified as ‘impaired’ or ‘not impaired’ based on these clinical cut-offs and the frequency of NP impairments pre- to post-TX was computed.

Comparisons between the absolute NP scores pre- to post-TX were performed using repeated-measures analyses of covariance (ANCOVAs) with P-values corrected for multiple comparisons, considered significant if $P < 0.01$. Cognitive depression scores (at baseline and follow up) were included as covariates to control for mood variation and were also subject to a separate analysis to examine the change in depression pre- to post-TX.

To produce reliable change scores, baseline NP scores on (T1) were regressed on the respective NP score at the post-TX assessment (T2) resulting in residual change scores [29]. Pearson’s correlations were then computed to identify baseline sociodemographic and medical factors associated with change in NP performance pre- to post-TX.

**Results**

**Study sample**

Twenty-eight of the 145 dialysis patients assessed at baseline received a transplant during the study period. Of these, $n = 26$ had a cadaver transplant; $n = 2$ had a living related donor transplant. All of the transplanted patients consented to the study protocol (response rate of 100%) and were assessed at ~6 months post-TX (mean = 6.57; SD = 1.17) (Table 1).

The patients who were transplanted were younger [$F(1, 144) = 7.29, P = 0.008$] and had a lower ESRD severity score [$F(1, 144) = 11.11, P = 0.001$] than those who were not transplanted. The lack of homogeneity of the transplanted vs non-transplanted subgroups was anticipated, as access to TX tends to favour the younger and fitter patients. All the study participants received adequate renal replacement therapy as indexed by formal kinetic modeling with mean HD, Kt/V of 1.78, and PD, weekly total Kt/V of 2.17, at baseline.

Following kidney TX, all the transplant recipients were on either ciclosporin or tacrolimus and steroids (prednisolone). Mycophenolic acid was prescribed...
NP performance pre- to post-transplantation

NP test scores prior to and post-TX are reported in Table 2. A series of repeated measures ANCOVAs (c covarying for cognitive depression) were performed to compare NP performance from pre- to post-TX. These indicated that the patients’ performance in verbal and non-verbal memory tasks improved significantly after TX compared with the dialysis NP scores (RAVLT-T \( F(3, 25) = 19.79, P = 0.0001 \), BVRT-C \( F(3, 25) = 9.07, P = 0.006 \). A trend in the same direction was also noted in BVRT-E \( F(3, 25) = 4.19, P = 0.051 \) and in SDMT-W \( F(3, 25) = 3.85, P = 0.061 \) but these did not reach significance. None of the remaining NP scores in attention and psychomotor abilities changed significantly pre- to post-TX (Table 2). A comparison between those on HD and PD revealed no significant differences (data not shown).

To evaluate patterns of intra-individual change before to after TX, the number of NP scores showing an improvement or deterioration for each individual was calculated. This showed that all patients improved in at least two of the NP tests. Twelve patients (43%) showed improvement in seven or more of the nine NP test scores 6 months post TX, 13 (46%) showed improvement in five to six NP scores and the remaining three (11%) improved with respect to at least two or three NP scores.

Patterns of change for each of the NP tests revealed similar findings. Relative to their respective dialysis NP performance, as many as 16 (57%) participants improved on the GP-ND; 20 (70%) improved on the GP-D; 19 (68%) on the TMT-A; 16 (57%) on the TMT-B; -22 (79%) on SDMT-W and 20 (71%) on SDMT-O when assessed 6 months after kidney TX. Twenty-six patients (96.9%) improved on the memory tests at the post-TX assessment (RAVLT-T; BVRT-C; BVRT-E).

Neuropsychological performance relative to norms

When the mean NP performance at dialysis and post-TX was compared with norms, the performances were all within 1 SD of the population mean, thereby indicating that cognitive functioning was not impaired in the group as a whole. However, the observed range and SDs of NP scores did indicate large individual differences in NP performance. Further inspection of individual NP scores indicated that NP impairments (as indexed by individual scores >1 SD lower than the expected age norms) were evident for a considerable number of patients, particularly at baseline/dialysis assessment. These data are displayed in Table 3.

However, at 6 months post-TX, the prevalence of NP impairments decreased substantially (Table 3). Post-TX, the proportion of scores 1 SD below the mean is similar to that which would be expected in a normal distribution (15.86%).

Table 1. Sociodemographic and medical characteristics of study sample at baseline

<table>
<thead>
<tr>
<th></th>
<th>Sample ( n = 28 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline</td>
<td>44.04 (12.01)</td>
</tr>
<tr>
<td>Education (age, years left school)</td>
<td>18.71 (6.44)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Black all</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Asian/Indian all</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Dialysis treatment</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
<td>30.96 (32.81)</td>
</tr>
<tr>
<td>Time on RRTs (months)</td>
<td>41.17 (51.06)</td>
</tr>
<tr>
<td>Time from baseline to TX (months)</td>
<td>14.88 (8.56)</td>
</tr>
<tr>
<td>Time from baseline to follow-up (months)</td>
<td>21.54 (9.02)</td>
</tr>
<tr>
<td>Kt/V (haemodialysis only)</td>
<td>1.78 (.158)</td>
</tr>
<tr>
<td>Kt/V (peritoneal dialysis)</td>
<td>2.17 (.454)</td>
</tr>
<tr>
<td>ESRD Severity Index</td>
<td>5.47 (6.84)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (82.1)</td>
</tr>
<tr>
<td>Heart conditions</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Primary kidney disease diagnoses</td>
<td></td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Adult polycystic kidneys</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>All other</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
</tr>
<tr>
<td>In a relationship</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>Married</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Work status (employed full time/ part time, student)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>Able to work (full time or part time)</td>
<td>18 (64.3)</td>
</tr>
<tr>
<td>Annual family income</td>
<td></td>
</tr>
<tr>
<td>£0–£10 000</td>
<td>15 (53.6)</td>
</tr>
<tr>
<td>£10 001–£20 000</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>£20 000–£30 000</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>&gt;£30 000</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Own home</td>
<td>17 (60.7)</td>
</tr>
</tbody>
</table>

Kt/V:K is defined as the total urea clearance rate, t represents the number of minutes of dialysis and V is the urea distribution within the patient.

only for highly sensitized patients and/or in the event of delayed function for the first 6 months post-TX operation \( n = 6 \). The post-TX renal function was adequate [mean calculated GFR 46.38 (15.89) ml/min/1.73 m²], ranging from 19 to 72 ml/min/1.73 m².

Depression pre- to post-transplantation

Repeated measures analysis of variances (ANOVA) showed that cognitive depression levels were significantly reduced from the baseline dialysis assessment (mean = 6.17; SD = 5.25) to post-TX follow-up (mean = 2.14; SD = 2.44) \( F(1, 27) = 52.98, P = .0001 \).
Biochemical data

Biochemical data are presented in Table 4. After TX, the biochemical markers of uraemia namely, urea and Cr, fell significantly \[ F(1, 27) = 48.35, P = 0.0001; F(1, 27) = 176.87, P = 0.0001, \] respectively. Hb and Alb levels also showed a significant increase from dialysis to TX.

Only a few significant, albeit weak correlations in the expected direction were found between the change in NP performance and the biochemical measures. Pearson’s correlations showed that, increases in Hb levels were significantly associated with improvements in SDMT-O \( R = 0.375, P = 0.050 \) and GP-D scores \( R = 0.416, P = 0.031 \) and that urea reduction pre- to post-TX correlated with more efficient performance in SDMT-O \( R = 0.453, P = 0.015 \). These were not consistently replicated across all NP scores and therefore the findings should be treated with caution.

None of the biochemistry changes correlated with changes in memory, whereas the function showed to improve significantly from dialysis to TX.

Baseline predictors of change in NP performance pre- to post-transplantation

Correlational analyses using Spearman’s correlation coefficient were performed to examine the associations between baseline sociodemographic (age; education) and medical variables [renal replacement therapy (RRT) duration; dialysis duration; ESRD severity] and NP change scores. Significant correlations were noted for age and dialysis duration albeit not consistently across all NP scores. These indicated that the older participants showed less improvement on TMT-B \( \rho = -0.443, P = 0.018 \) and SDMT-W \( \rho = -0.405, P = 0.032 \) post-TX. Time spent on dialysis was also inversely associated with improvement in one of the psychomotor tasks \( \rho = -0.386, P = 0.045 \). The longer the time patients spent on dialysis prior to receiving the transplant, the lower their improvement in GP-D task. All other correlations did not reach statistical significance. Finally, it is important to note that the time elapsed between baseline and follow-up assessments was unrelated to NP change scores.

Discussion

The current literature on the cognitive functioning after kidney TX is based predominantly on...
Cross-sectional data or prospective studies that assessed very small samples with brief NP assessments. Small samples in this area reflect the difficulty in identifying the time when patients will receive a transplant and the large numbers on many transplant lists. This prospective study succeeded in examining the cognitive functioning in 28 kidney transplant recipients tested before TX (while maintained on dialysis) and at ~6 months post-TX.

The hypothesis that kidney TX would uniformly improve NP performance received modest support. The findings suggest that significant pre- to post-TX improvements occur only in certain NP tests and not across all the cognitive domains assessed. The one area where clear evidence of NP improvement was found was memory. For example, on the verbal learning task (RAVLT-T), the participants recalled an average of 10 words more across the five trials after TX compared with the pre-transplant assessment. Most importantly, the observed memory improvements cannot be attributed to the changes in mood, as depression was assessed on both occasions and controlled for in all comparative analyses. Analysis of individual scores indicated that improvement in memory function was evident in all but two of the participants. Normative comparisons also indicated an improvement in memory following the TX. While a number of patients \( (n=11; \ 39\%) \) performed worse than their age respective norms on the verbal memory task at dialysis (more than double of what expected in a normal distribution), only four patients \( (14\%) \) performed worse than their age norms at the post-TX assessment.

In contrast, there were no significant changes in measures of attention, visual planning, mental processing speed (TMT-A; TMT-B; SDMT-W; SDMT-O) and motor abilities (GP-D; GP-ND). Mean scores in these NP tests showed some improvement from dialysis to TX, but none reached levels of statistical significance. This is at odds with previous findings of small studies [9] and contrasts with commonly held views that TX, by improving the organ-system functioning and restoring kidney function, should result in the amelioration of NP functioning.

These findings of differences in NP changes are open to a number of different interpretations. One is that memory is an area of functioning particularly sensitive to the improvement of renal function, or sensitive to the improvement in GFR of kidney TX. These findings are in line with the reports of impaired memory function in dialysis [30–32] and substantiate our previous cross sectional findings of memory differences between dialysis and transplant patients [8]. Most importantly, the observed changes seem to imply that even though memory appears to be vulnerable to the effect of dialysis, these effects are reversible with kidney TX. The comparison of individual scores to normative data also indicated that memory functions are particularly vulnerable at the time of dialysis. Conversely, attention and mental processing speed functions may be less susceptible to ESRD and hence to the improvement that occurs with TX. Previous studies did indicate that ‘adequately dialysed’ HD patients do not manifest NP deficits in tests of attention and concentration [33,34].

An alternative interpretation for the differential pattern of improvement may relate to differences in the relative sensitivity of NP tests of attention and memory. It may be that the memory tests used in this study are more stringent and sensitive than those to assess attention and concentration and perceptuo-motor abilities.

It is also possible that other aspects of kidney TX may have reduced the likelihood of finding more widespread NP improvements pre- to post-TX. These include the neurotoxic effects of immunosuppressive medications such that the beneficial effects of improved GFR may have been attenuated by an adverse effect of cyclosporin, tacrolimus or prednisolone on motor skills or cognitive function. There is evidence on neurotoxic effects and brain imaging changes with both cyclosporin and tacrolimus [35]. It is also possible that particular medication side effects might have also directly affected the NP performance. Many of the NP tests with the exception of memory task involved a timed response coupled with motor activity. Slowness in execution might be related to other factors such as tremor, common in some TX patients. This is however unlikely as none of the TX recipients presented with visible evidence of tremor. Furthermore, the SDMT-W which involves a motor response showed no change in performance, as did the SDMT-O in which no manual activity is involved.

Other methodological considerations might have undermined the detection of significant cognitive improvements pre- to post-TX. It is possible that the use of a double baseline might have inflated

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Time 1 Dialysis M (SD)</th>
<th>Time 2 Transplantation M (SD)</th>
<th>F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>20.23 (1.44)</td>
<td>10.47 (0.72)</td>
<td>48.35</td>
<td>0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>793.75 (33.38)</td>
<td>135.43 (8.33)</td>
<td>176.87</td>
<td>0.0001</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>11.10 (1.24)</td>
<td>13.12 (1.65)</td>
<td>32.12</td>
<td>0.0001</td>
</tr>
<tr>
<td>Albumin</td>
<td>39.22 (5.00)</td>
<td>44.0 (2.45)</td>
<td>21.18</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

M, mean; SD, standard deviation.
baseline results and diminished the effect of transplant. This conservative approach was purposefully preferred to provide a stronger test of TX-related improvements. This is unlikely as the data analyses were repeated using the first baseline (i.e. the first baseline scores obtained immediate prior the HD session or the PD clinic visit) and revealed a similar pattern of results. Significant improvements were evident in the two memory scores (RAVLT; BVRT-C) and in only one of the six remaining attention and psychomotor abilities scores, namely the SDMT-O. The consistency in the observed findings with both baselines attests to the robustness of the findings.

It is also plausible that improved pre-TX treatment in our study sample, as evidenced by the high Hb levels and indices of dialysis adequacy compared with previous investigations [e.g. 10], may have limited the extent of the NP improvements post TX in this study.

Inspection of mean NP scores showed that on all measures of cognitive function, patients assessed post TX fared no worse than the respective age-reference population. These formal observations accord with previous studies [9,10]. That normal or near normal NP functioning can be expected following renal TX will be reassuring to patients. Many are aware of the possibility of cognitive difficulties in the wake of the ESRD, and some might have experienced such problems while on dialysis. It is possible that other NP tests might have detected differences relative to norms or pre- to post-TX. However, the NP tests performed in this study are widely used, sensitive, well standardized and covered a range of cognitive areas [24].

Study findings indicated that age was associated with NP functioning changes. The effects of age on absolute NP performance are well known but this study suggests that it is also important in the recovery of function [28]. The significant changes in urea, Cr, Alb and Hb were consistent with the impact of TX. The links, however, between changes in biochemical markers of renal function and NP performance were weak and inconsistent, albeit in the anticipated direction. It is notable though, that none of the biochemical assays were found to be associated with memory, the only function that significantly improved pre- to post-TX. This may be related to the small sample size. Alternatively, the absence of significant associations may reflect lack of sufficient value range. The mean biochemical values at baseline fell within the normal physiological range for adequately dialysed patients. Significant associations may only become evident when biochemical levels fall below a certain threshold and these minimal levels were exceeded in this study. For example, several studies have consistently demonstrated that uncorrected anaemia is associated with cognitive deficits and that erythropoietin treatment leads to NP improvements [36,37]. Mean Hb levels in our sample while at dialysis, for instance, were adequate (>10 g/dl) and those patients who were previously anaemic were on erythropoietin in order to obtain an Hb concentration of not <10–11 g/dl. It is likely that this explains the absence of significant associations between NP improvements and Hb. Further studies are needed to elucidate the biological mechanism underlying improvements in cognitive functioning pre- to post-TX and to elucidate the optimal Hb levels for cognitive functioning.

Several limitations to this study must be considered. Foremost of these is that although the sample size was significantly larger than other published studies, it still had relatively low power to detect anything other than major NP changes pre- to post-TX. It is important that the observed changes in attention and motor tasks were in the same directions as those observed in memory scores, but failed to reach significance. This may have been due to the small numbers.

It is important to note that the sample in this study consisted of relatively healthy, clinically stable and well-dialysed patients. The patients in this study were also fairly young and had low prevalence of diabetes in contrast to the transplant cohorts in other countries [38]. This may raise issues of the generalizability from this study to other cohorts with different demographic characteristics.

Another limitation of this study is that NP assessments were based solely on paper and pencil NP tests and it was not feasible to undertake NP assessments such as the P300 event-related potentials to assess the possible underlying physiological change [10]. This would potentially have been interesting in this study as the P300 has been found to be associated with memory problems [39]. Related to that is the lack of a control group for practice effects resulting from repeated NP test administration. Practice effects could artificially inflate test scores. However, having a double baseline, using of alternate forms as well as the performing of follow-up assessments at ~6 months post-TX would all serve to minimize learning effects [26].

Finally, follow-up assessments were taken only at 6 months post-TX. It is plausible that further improvement might be expected at longer post-operative follow ups as patients continue to recover both medically and functionally and are put on lower dosages of immunosuppressive medication.

Acknowledgements. This research was supported by a grant from Alexandros Onassis Foundation to K.G., and the R.L. Weston Institute for Neurological Studies of the UCL Medical School, both of which are gratefully acknowledged.

The authors also thank the renal staff for participating in the CAPD-haemodialysis (Trish Greenacre, Sunita Hansraj and Chris Lewis), the transplantation units (Sue Woods) for their support and the patients for giving us their time to complete the research protocol.

Conflict of interest statement. None declared.

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Received for publication: 2.2.06
Accepted in revised form: 8.6.06