# Effect of Renal Transplantation on Cognitive Function in Hemodialysis Patients: A Longitudinal Study

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## Introduction

- ESKD patients as compared to age matched population have three folds higher impaired cognitive function (CF) [1]
- Higher prevalence of CF impairment is attributed to both [2]
  - Vascular causes (higher prevalence of hypertension, diabetes and stroke)
  - Uremic toxins associated neurodegeneration
- HD itself has been implicated as it causes episodic hypotension, osmotic shifts & micro IC bleeds[2]
- Single session of HD has shown to improve CF -?role of reversible soluble toxins [3]
- Renal Transplantation (RT) corrects *uremic milieu* and should improve CF
- The literature however notes inconsistent benefit in CF after RT

## CF Post-RT: Lacunae in Literature

- Most studies are from pediatric population with few well-conducted studies in adults
  - Associated co-morbidities like diabetes, cerebrovascular accidents and depressive disorders not accounted for
  - Small sample size
  - Used variable tools for assessment of cognitive function
  - Lack of age matched controls
  - Mostly cross-sectional studies
  - Longitudinal studies had variable timing of pre & post-transplant cognitive function evaluation
  - Variable graft function

## Cognitive Function Testing

- Neuropsychological tests
  - Trail making test
  - Symbol digit modality
- Neurophysiological tests
  - Prototype is P300 event related potential (ERP) which is evoked by oddball paradigm
  - Most positive peak occurring within a window of 250–480 ms
  - Latency represents speed and stimulus evaluation time
  - Amplitude represents conscious effort or attention given to task
- Increased P300 latency earliest sign in CF impairment due to metabolic encephalopathies [4]
- Is unaffected by educational status, negotiates the relearning curve
- Has low intra-individual and test-retest variability

## Aim of Study

- To evaluate cognitive function in ESKD patients on hemodialysis just prior to live renal transplantation using P300 ERP
- To evaluate its course approximately 3 months subsequent to successful renal transplantation

## Patients and Methods

- Single center, prospective study
- Consecutive, eligible & consenting adults undergoing first live RT enrolled
- Inclusion Criteria
  - Right handed, non-diabetic male subjects aged 18 to 50 years
  - On MHD >3 months
- Exclusion Criteria
  - History or clinically evident cerebrovascular disease
  - Auditory, visual and any other major sensory motor impairment
  - History of substance abuse
  - CLD, depression, dyselectrolytemia and haemoglobin <8 gm/dl
  - Post-transplantation: patients with eGFR <40 ml/min and history of acute rejection or infection 4 weeks prior
- 10 age/gender matched healthy controls satisfying all criteria also recruited

## Neurophysiological studies

- Study performed within 24 hours of HD in specialized Cognitive Neurophysiology Laboratory
- Computer generated programme (Neuropack 8, NEB4200K, Nihon and Koden Tokyo, Japan) used
- 20% were target stimuli (2000 Hertz) while 80% were non-target stimulus (1000 Hertz)
- 32 trials were recorded and subsequently averaged
- Signals recorded at 5 sites: Fz, Pz, Cz, C3 and C4 electrode sites (10-20 International System)

## Patient Enrollment Flow-chart

30 patients enrolled

- 2 - patient / Graft loss
- 3 - lack of follow-up
- 3 - eGFR <40
- 2 - recent admission

20 FU at 3 months

## Statistical analysis

- Data was calculated as mean ± standard deviation
- Means of two groups compared using paired t- test
- Pearson's correlation coefficient was calculated for various parameters

## Baseline Characterstics

- Mean age was 29.7±7.5 years (range 18-44 years)
- Mean dialysis vintage was 10.3±6.9 months
- Mean post-transplant period was 3.2±0.4 months
- Basic disease was unclassified in 80%
- All were on 3-drug immunosuppression of MMF, steroids & CNIs (18 Tacrolimus, 2 Cyclosporine)

### Baseline Profile

| | Controls (N= 10) | ESKD (N=20) | Post-RT (N=20) | P value (Gp 1 vs Gp 2) | P value (Gp 1 vs Gp 3) | P value (G2 1 vs Gp 3) |
|---|---|---|---|---|---|---|
| Age (years) | 26.4±2.1 (23-29) | 29.7± 7.48 (18-44) | -- | 0.81 | -- | -- |
| Sex Ratio( M/F) | 10/0 | 20/0 | -- | - | -- | -- |
| Hemoglobin (gm/dL) | 13.96±0.4 (13.1-14.6) | 9.85±1.1 (8.4-11.0) | 12.56±2.32 (9.0-16.9) | 0.0001 | 0.07 | 0.001 |
| Albumin (gm/dL) | 4.95±0.25 (4.5-5.3) | 3.96±0.39 (2.9-4.7) | 4.49± 0.45 (3.6-5.2) | 0.0001 | 0.07 | 0.001 |
| Blood Urea (mg/dL) | 23.5±3.77 (16-28) | 136.7±36.9 (70-204) | 34.5±10.13 (20-62) | 0.0001 | 0.0001 | 0.001 |
| S. Creatinine (mg/dL) | 0.9±0.09 (0.8-1.1) | 8.95±2.61 (3.2-13.1) | 1.19±0.19 (0.9-1.7) | 0.0001 | 0.0001 | 0,001 |
| S Uric Acid (mg/dL) | 3.7±0.35 (3.2-4.2) | 7.32± 1.85 (3.7-9.8) | 5.50±1.57 (3.2-9.2) | <0.005 | 0.01 | 0.01 |

### P 300 latencies in all groups (ms)

| | Controls (N = 10) | ESKD (N=20) | Post-RT (n= 20) | P value (Gp 1 vs Gp 2) | P value (Gp 1 vs Gp 3) | P value (Gp 2 vs Gp 3) |
|---|---|---|---|---|---|---|
| Fz | 319.6± 33.6 | 348.6± 27.78 | 316.35± 33.68 | 0.018 | NS | 0.001 |
| Cz | 319.6± 33.6 | 347.7± 27.57 | 316.05± 27.4 | 0.021 | NS | 0.001 |
| Pz | 319.6± 33.6 | 347.0± 27.41 | 315.25± 29.16 | 0.024 | NS | 0.001 |
| C3 | 319.6± 33.6 | 349.9 ± 27.42 | 317.55± 28.87 | 0.013 | NS | 0001 |
| C4 | 319.6± 33.6 | 348.4± 27.89 | 317.55± 28.87 | 0.019 | NS | 0.0001 |

Fz, Pz, Cz, C3 and C4 EEG electrode sites (10-20 International System)

### P 300 Amplitude in all groups (μV)

| | Controls (N = 10) | ESKD (N=20) | Post-RT (n= 20) | P value (Gp 1 vs Gp 2) | P value (Gp 1 vs Gp 3) | P value (Gp 2 vs Gp 3) |
|---|---|---|---|---|---|---|
| Fz | 27.99±12.78 | 13.38±8.74 | 14.72±9.51 | <0.0001 | <0.001 | NS |
| Cz | 26.46±9.96 | 11.87±7.84 | 13.03±10.39 | <0.0001 | <0.001 | NS |
| Pz | 23.24±9.23 | 13.03±6.12 | 14.41±6.48 | <0.0001 | <0.001 | NS |
| C3 | 24.58±10.40 | 13.66±9.10 | 13.58±7.91 | <0.0001 | <0.001 | NS |
| C4 | 25.95±11.22 | 14.44±9.00 | 15.16±9.41 | <0.0001 | <0.001 | NS |

Fz, Pz, Cz, C3 and C4 EEG electrode sites (10-20 International System)

### Correlation of P300 latencies

| | | Fz | Cz | Pz | C3 | C4 |
|---|---|---|---|---|---|---|
| Hemoglobin | r | -.443* | -444* | -.438* | -.501** | -.468** |
| Albumin | r | -.357 | -.367* | -.425* | -.392* | -.400* |
| Blood Urea | r | .304 | .308 | .244 | .323 | .340 |
| S Creatinine | r | .369* | .368* | .331 | .414* | .398* |
| S Sodium | r | -.061 | -.066 | -.097 | -.054 | -.047 |
| Uric Acid | r | .265 | .245 | .277 | .294 | .296 |
| Duration of dialysis | *r* | -.091 | -.091 | -.040 | -.117 | -.138 |

r = * significant (p<0.05), ** highly significant (p <0.01)

## Strengths of present Study

- Recruitment of younger patients with no co-morbidities thus excluding other confounding factors
- Use of robust EPS testing of cognitive function
- Specified time of EPS studies pre & post RT
- EPS studies done within 24 hrs of HD
- Exclusion of patients requiring recent hospitalization & having eGFR < 40 ml/min post transplantation

## Limitations

- Small sample size & strict exclusion criteria limit generalizability of study

## Conclusions

- In our prospective cohort of young, well dialyzed ESKD patients with no significant co-morbidities we found
  - Impaired CF in ESKD patients as documented by prolonged P300 latencies
  - P300 latencies negatively correlated with haemoglobin & serum albumin levels
  - Significant improvement of CF, 3 months post-RT as documented by significant shortening of P300 latencies

## References

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