Neurocognitive Functions of Kidney Transplant Children

Running title: Cognition of Transplant Children

Marta Molnar-Varga PhD[1,2]; Marta Novak MD, PhD[3,4]; Attila J Szabo MD, PhD, DSc[5,6]; Kata Kelen MD[5], Elani Streja, MPH, PhD[7]; Adam Remport MD, PhD[8], Istvan Mucsi MD, PhD[3,9], Miklos Z Molnar MD, PhD[10] and Gyorgy Reusz MD, PhD, DSc[5,6]

[1]Institute for the Psychology of Special Needs, Faculty of Special Education, ELTE University, Budapest, Hungary

[2]Special Education Institute of Atypical Behaviour and Cognition, Faculty of Special Education, ELTE University, Budapest, Hungary

[3]Institute of Behavioral Sciences, Semmelweis University, Budapest, Hungary

[4]Department of Psychiatry, University Health Network, University of Toronto, Toronto, Canada

[5]First Department of Pediatrics, Semmelweis University, Budapest, Hungary

[6]MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary

[7]Division of Nephrology, University of California, Irvine, CA, USA

[8]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary

[9]Division of Nephrology, University Health Network, University of Toronto, Toronto, Canada

[10]Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Corresponding author

Marta Molnar-Varga PhD

Senior lecturer, Institute for the Psychology of Special Needs

Faculty of Special Education, ELTE University

Budapest, Hungary 1097

Ecseri Street 3.

Tel.: (+ 36) 1-358-5572

E-mail: marta.molnar@barczi.elte.hu

Abstract word count: 199

Text word count: 3,114 (excluding cover page, abstract, references and tables)

Tables: 5

Abstract

Background: End-stage renal disease in children is associated with impaired neurocognitive function and development. However, data on factors associated with neurocognitive dysfunctions in children with kidney transplants are lacking.

Methods: We conducted a cross-sectional analysis comparing cognitive functions (using Woodcock-Johnson International Edition, WJIE) in 35 kidney transplant and 35 healthy control children. Data on laboratory measurements, comorbidities, social characteristics were collected.

Results: Transplant children had significantly worse scores on intelligence quotient (IQ) test compared to controls (Full Scale IQ score was 85 (26) versus 107 (10), $p<0.001$). Lower maternal education level was significantly associated with lower WJIE cognitive test scores; however, no association was found between laboratory values and WJIE. Among children with kidney transplants, those with co-morbid conditions had significantly lower Verbal Ability and Full Scale IQ scores. Earlier age of dialysis onset and a longer total time on dialysis (>9 months) was associated with lower test scores, while lifelong hospitalization time was inversely correlated with IQ ($r=-0.46$, $p<0.01$) as well as an independent significant predictor (Beta=-0.38, $p=0.02$) of IQ scores in these children.

Conclusions: Child kidney transplant recipients have relevant neurocognitive function impairments that are associated with markers of socioeconomic status and factors related to disease severity.

Keywords kidney transplant, intellectual functioning, hospitalization

Introduction

Children with end stage renal disease (ESRD) are at increased risk for atypical neurocognitive development (1) (2) (3) accompanied by documented impairments of the central nervous system (4). Recent studies suggested that pediatric patients with CKD have lower intellectual functioning, deficits in executive functions and problematic academic progress compared to normal controls or their sibling-controls. (5) (6) However, studies from the 2000s indicate that neuropsychological outcomes for children with CKD are more favorable (mean intelligent quotient (IQ) are within 1-2 standard deviation (SD) of the norms) than was detected in earlier reports. (7) (8) (6)

In children with CKD, poor neurocognitive functions were associated with anemia, hypertension, cardiovascular disease, malnutrition, seizures, earlier age of onset, longer disease duration and staging of kidney disease. (5) (6) In addition, it has also been shown that age at diagnosis, longer dialysis vintage as well as lower mother/caregiver's educational level may play a role in neurocognitive performance of kidney transplant recipient children. (1) However there are other risk factors which may contribute to poor cognitive function in CKD children (e.g. perinatal problems, underlying disease, long anesthesia). ESRD in childhood may also impact adult neurocognitive function. Groothoff et al. reported that adults with ESRD who also had more than four years of cumulative dialysis in childhood had a 3.4 times higher chance of having IQ scores one SD below the mean of the corresponding general population. (9)

The few studies which have examined the impact of kidney transplantation on cognitive functions in children have reported conflicting results regarding IQ differences between child transplant recipients and dialysis patients. (1) (10) (11) An early study by Fennell et al. showed that children with ESRD who received kidnely transplants showed significant improvement in full scale and performance IQ test scores one month after transplant, when

4

compared with healthy matched control children (12). Icard et al. also reported approximately a 12-point increase in intellectual functioning before and after transplantation; however, according to their results transplantation does not appear to normalize developmental or intellectual status in children with ESRD. (10)

We designed a cross-sectional study to compare the intellectual function of Hungarian transplant children with age and gender-matched healthy controls using standard and validated questionnaires. We also assessed the predictors of IQ in child transplant patients. Based on our previous findings, we hypothesized that cognitive functions are lower in transplant children than their healthy counterparts and that earlier dialysis onset and longer dialysis vintage are associated with poor achievement in intellectual skills.

Methods

Sample of patients and data collection

We collected data about all kidney transplant children between 6-18 years of age (n=40) who were regularly followed at the kidney transplant outpatient clinic at the First Department of Pediatrics and the Department of Transplantation and Surgery at the Semmelweis University, in Budapest between September 2007 and December 2008. Exclusion criteria were: current acute rejection (within the last 4 weeks), hospitalization, and transplantation in the previous 3 months. The baseline assessment was conducted between September of 2007 and December of 2008 (Psychosocial Problems and Cognition in Kidney Transplant Children (PPCKTC) Study). In addition, the children's parents were invited to participate personally in our case control study. Three (7%) of the eligible 40 children's parents refused to participate in the study and additional two (5%) children were excluded (one child was transplanted within the previous 3 months and one had had acute rejection within 4 weeks prior the study period). The control group was selected (1:1) by matching children from one elementary school and one high school in Budapest, Hungary based on gender and age (maximum 1 month difference). Children with any chronic illness were ineligible to be selected for the control group. The final cohort consisted of 35 kidney transplant children and their parents and 35 healthy children and their parents.

Demographic data and details of medical history were collected at enrollment and information on child kidney transplant recipient's use of immunosuppressive drugs was obtained. Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula: eGFR (mL/min/1.73 m^2) = k (Height) / Serum creatinine where k =0.45 in term infants to 1 year of age and 0.55 in children to 13 years of age. (13) We collected data on age at the time of first dialysis and cumulative time spent in the hospital over the course of their life.

Laboratory data and comorbidity

6

Laboratory data were extracted from the medical records and from the electronic laboratory database of the hospital. The following laboratory parameters were tabulated: blood hemoglobin, serum creatinine and serum albumin. We also collected information on the transplanted children's co-morbid conditions such as diabetes, hypertonia, osteoporosis, seizures and other diseases from the patients' charts.

Immunosuppressive therapy

Standard maintenance immunosuppressive therapy generally consisted of prednisolone/methylprednisolone, either cyclosporine A microemulsion formulation (Neoral) (CsA) or tacrolimus, combined with mycophenolate-mofetil (MMF) or azathioprine or sirolimus or everolimus.

Social characteristics

Data on psychosocial parameters were obtained for the enrolled children. Maternal education level was used as a marker of the socio-economic status (SES). "Learning problem" was a subjective indicator, where parents were asked to report if their child had a learning problem, which was independent of performance for other makers of achievement.

Woodcock-Johnson Cognitive Ability Test – International Edition (WJIE)

The adapted and validated Hungarian version of the Woodcock-Johnson Tests of Cognitive Abilities-Revised (WJIE) was used in this study. (14) The WJIE provides a comprehensive system for measuring general intellectual ability, specific cognitive abilities, language skills, and academic achievement. (14) It measures the cognitive abilities in populations between 2 to 90 years of age.

The WJIE battery consists of seven tests, each selected to serve as an indicator of at least one of the broad Cattell-Horn-Carroll (CHC) cognitive abilities. The General Intellectual Ability scale or Full Scale Intellectual Abilities consists of three parts: Verbal Ability, Thinking

Ability and Cognitive Efficiency. (14) The WJIE is standardized so the mean is 100 points and the standard deviation is 15; accordingly it can be compared with scores obtained on other IQ tests.

Learning and intellectual disabilities

Learning disability (LD) was defined by applying the ability–achievement discrepancy approach as follows: academic standard score to be at least 1 SD (15 points, i.e. 70-85 IQ points) lower than a standard score according to the accepted routine clinical practice. (15)

For intellectual disability (ID), we used the definition and criteria provided in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): profound mental retardation (MR): IQ lower than 35; severe MR: IQ between 36-49 points; mild MR: IQ 50-69 points. (16)

Statistical Analysis

Statistical analyses were carried out using the IBM SPSS 20.0 software. The data were summarized using proportions, means (±standard deviation, SD) or median (interquartile range, (IQR)) as appropriate. Continuous variables were compared using Independent-Samples T-test, the Mann-Whitney U Test or One-Way ANOVA. Correlation analysis was performed using Pearson or Spearman correlation analysis as appropriate. To explore potential differences between short/long duration of dialysis for intellectual achievements, we divided the transplant group into two subgroups according to the transplant group's median dialysis duration. Linear regression analysis was used to determine the independent association between the presence of cognitive deficits (dependent variable) and the following correlated variables: age of dialysis onset, cumulative hospitalization and maternal education in transplant recipient children. Our multivariate model for cognitive deficit was constructed based on theoretical considerations. In all analysis, two-sided tests were used and p values <0.05 were considered significant.

Ethical permission

The studies were approved by the Ethics Committee of Semmelweis University (TUKEB number: 165/2007). Before enrollment, all patients and their parents received detailed written and verbal information regarding the aims and protocol of the study and parents were required to provide a signed informed consent.

Results

Demographics and baseline characteristics of the sample

Table 1 shows the main characteristics of the 35 participant child kidney transplant recipients (Tx) and 35 matched controls (Co). The cause of ESRD was Autosomal Recessive Polycystic Kidney Disease (ARPKD) in 8 patients (23%); seven patients (20%) had kidney/urinary tract abnormalities; 4 patients (11%) had chronic glomerulonephritis; 3 patients (9%) had congenital/hereditary kidney disease; two patients (6%) had chronic pyelonephritis/interstitial nephritis and 11 (31%) patients' cause of ESRD was unknown. Based on patients' chart 60% of transplant children had no known comorbidity. From the 14 patients with comorbidities, the prevalence of comorbidity was: hypertensive nephropathy (n=6, 43%); diabetic nephropathy (n=2, 14%); osteoporosis (n=1, 7%); and seizures (n=1, 7%). Fourteen percent of the patients had previous kidney transplantations and six percent (n=2) received a kidney from a live donor. The median and interquartile range (IQR) of ESRD vintage was 40 (57) months. The median age was 9 years in the beginning of dialysis treatment and 10 years when they had their first transplantation. The median of duration of dialysis therapy was 9 months (IQR: 14) and the time of the last transplantation was 28 months (IQR: 40). At the time of enrolment 40% of the patients were taking prednisolone or methylprednisolone and no one of them were taking cyclosporine A therapy. The percentage of patients taking MMF was 69%. 77% of the patients were taking tacrolimus, 3% were on azathioprine. Expectedly, cumulative lifetime spent in the hospital was significantly different between the groups, but the prevalence of learning problems was similar (**Table 1**).

Prevalence of cognitive deficits in transplant group

Transplant recipient children reported significantly worse scores on all sub-scales of the WJIE compared to controls (**Table 2**). Normal intellectual achievements (measured in IQ points) were shown in 60% of transplant children, while 17% were classified as having a

10

learning disability, and 23% were considered intellectual disabled (mental retardation groups) (**Table 3**).

Correlates of intellectual achievements in transplant group

Socio-demographic parameters

We analyzed the correlation between children's cognitive function and age, gender and maternal education. Chronological age had no correlation with intellectual achievements except Thinking Ability ($r=0.36$, $p<0.05$), and there was no difference between transplant males and females in any dimension of cognitive performances (not shown). No association was found between children's cognitive function and cause of ESRD.

All parts of WJIE cognitive test showed a linear direct relationship between higher maternal education level and higher test scores (**Table 4)**. Notably, in the assessment of Full Scale Intellectual Ability, children with mother's who only had an elementary school or less education had an average performance IQ score of 48 (±27), while their peers whose mothers' had a higher education had an average IQ score of 105 (±16).

Laboratory data and co-morbidity

None of the laboratory data (blood hemoglobin, serum creatinine, serum albumin) had significant correlations with intellectual performance scores. However, we found significant differences in performance scores between transplant children with and without co-morbid conditions. The transplant children with co-morbid conditions reported significantly lower points in Verbal Ability (85 ± 30 vs. 105 ± 17, $p=0.01$), Cognitive Efficiency (70 ± 23 vs 89 ± 24, $p=0.02$) and Full Scale IQ scores (74 ± 28 vs. 92 ± 23, $p=0.03$), but no differences were noted in Thinking Ability (79 ± 32 vs. 93 ± 23, $p=0.13$).

Estimated GFR, dialysis and hospitalization

11

Table 5 shows the correlations of intellectual achievements with medical parameters in transplanted children. Estimated GFR did not correlate with any intellectual function tests; however, age of dialysis onset was positively correlated with all composite scores of intellectual achievements (**Table 5**). Children with longer cumulative lifetime hospitalization duration had significantly lower IQs than those who spent less time in hospital (r=-0.46, p<0.01). This correlation remained the same after taking into account the patients' age (older patients have higher chance to be hospitalized) in the age standardized analyses (**Table 5**). In our cohort, median time on dialysis for transplant children was 9 months. When we compared transplanted patients according to total time on dialysis (less or more than 9 months), children with a shorter dialysis duration showed higher test scores in all intellectual performance evaluations: Verbal Ability (109 (26) vs. 90 (49), p=0.07), Thinking Ability (99 (22) vs. 86 (46), p=0.02), Cognitive Efficiency (93 (22) vs. 79 (45), p=0.01) and Full Scale Intellectual Abilities (99 (17) vs. 81 (53), p=0.01).

Multivariate analysis

In our multivariable linear regression model (Adjusted R Square: 0.50), examining predictors of Full Scale IQ (WJIE) scores in kidney transplant recipients, cumulative lifetime hospitalization duration (B=-63.47, Beta=-0.38, T=-239, p=0.02) was the only significant predictor. Maternal education (B=8.92, Beta=0.35, T=2.25, p=0.34) and age of dialysis onset (B=0.13, Beta=0.11, T=1.23, p=0.23) did not show any predictive roles.

<u>Discussion</u>

In this cross-sectional study we found two important new findings: 1, examined transplant children had 1 SD lower IQ scores compared to age and gender matched healthy controls; 2, cumulative lifetime hospitalization duration may have a predictive role in general intellectual function in children. In addition, our study confirmed that age of dialysis onset, cumulative time on dialysis as well as maternal education seems to be important factors of neurocognitive outcomes in children.

Compared to control children, nearly double the number of renal transplant recipient children had a diagnosis of a learning disorder. A few prior studies have shown that children with CKD or ESRD have a higher risk for grade retention and an increased risk for impairments on measures of academic skills and criteria for low school achievement (2) (1). However, another previous study showed that children with ESRD compared to their sibling matched controls showed no differences in learning problem prevalence (except in relation to motor skills), in spite of ESRD children having significantly lower IQ scores (8). Compared to normal controls, clinically significant differences were detected in school functioning in CKD patients in the recently published landmarked *Chronic Kidney Disease in Children* (CKiD) Study (17). In this study, school quality of life was diminished with age based on parents' assessments (18). Learning problems based on different neurodevelopmental disorders, therefore, probably have roots in preceding periods of development.

Similar to results of studies about general intellectual functions of CKD patients in the last decades, in our study, transplant recipient children in comparison to normal controls reported significantly lower intellectual achievements in all scales of IQ test at the time of school-age. (2) (11) The kidney transplanted children performed best in assessments of verbal abilities, while their most problematic area of measured general intellectual function

13

was cognitive efficiency; evaluated by sampling of two different factors of automatic cognitive processing: processing speed and short-term memory. Most of the kidney transplant patients belonged to the normal IQ range, but 40% of transplant children showed achievement of impaired intellectual functioning. These findings coincide with international reports of IQ measures in children with CKD (11) (17)

In our transplant patient group, maternal education was found to be a very strong predictor of general intellectual skills. The association of maternal education with children's IQ in the general population is well known. (19) However, maternal education may play an even more important role for intellectual development in children with chronic illnesses such as ESRD. Previous studies have shown that maternal education is strongly correlated with factors related to ESRD history and management such as age of dialysis onset and period of dialysis time (1) (20). In our study, cumulative dialysis duration and maternal education were the significant medical and social factors associated with IQ scores. Dialysis factors did not show a predictive role in the Brouhard et al. study (1). Based on these findings, we assume that parents' education level and the role of advocacy of ESRD children's parents could probably influence long-term outcomes of neurocognitive functions in the mentioned population. However, this question needs to be addressed in further studies.

We found a lack of association between laboratory data such as eGFR, blood hemoglobin, serum creatinine and albumin with intellectual skills. These results are in contrast with the findings of Duquette et al., who found associations between renal function and intellectual function in CKD children (2). Conversely, other study results of long-term neurocognitive outcomes in ESRD children found questionable associations between kidney function at testing and intellectual skills (3). There are a couple of potential explanations for the discrepant results seen in our study and the study of Duquette et al. First, our cohort consisted of kidney transplant recipients, while Duquette et al. examined CKD patients. Since

14

all studies (including ours) used cross sectional baseline laboratory data and no time-dependent analysis was done, there has been no way to evaluate the association between progressive kidney function declined with change in intellectual functioning. Furthermore, since we are uncertain how kidney function abnormalities were treated in Duquette's study cohort, it is unknown what effect these factors may have had on examined associations.

In our cohort of Hungarian transplant children, more time spent on dialysis and earlier onset of ESRD (or age of dialysis start) was associated with lower IQ scores, which is consistent with findings in previous studies (3) (1) (11). One of the new findings of our study was the association between cumulative time spent in the hospital and IQ scores. Longer hospitalization record was strongly associated with lower IQ. In our multivariate model of 35 transplant children, standardized full time hospitalization was the independent and significant predictor of general intellectual functions. According to results of Gulleroglu et al. on neurocognitive functions in CKD children, showed that CKD children missed school much more frequently than their siblings and the time missed from school interfered with their academic achievements (20). Moreover it is known from the earlier psychological literature of the general population that hospitalizations have powerful influences on delayed development of children (21). This finding of the effect of hospitalization duration on neurocognitive function in transplant children may be important and relevant to clinical practice, as it may be a modifiable factor. However, it is unknown whether intervention aimed at shorter hospitalization has any impact for further neurocognitive development. Future well-designed studies are needed to answer this clinically relevant question.

There are a number of limitations of our study, which needs to be discussed. First, our sample size is limited. However the 35 transplant recipients represent the majority of the Hungarian transplant children population. Second, intellectual function was assessed based

on only IQ, however other methods such as relevant executive functions (memory, attention, visual-spatial abilities) and language could have been used (11). Finally, we could not analyze the association between intellectual function and perinatal events (22) effect of immunosuppressive therapy (23) as well as perioperative event such as type of anesthesia during transplantation (24).

Conclusions:

Here we have shown the results of a cross sectional study of kidney transplanted children and their healthy age and gender matched counterparts. We found that age of dialysis onset, cumulative time on dialysis, maternal education and a new potentially modifiable factor, cumulative time of hospitalization were predictors of neurocognitive outcomes in children. Further well-designed, larger, multicenter studies are needed to examine if shortened hospitalization duration may improve intellectual and executive skill development in kidney transplant recipient children.

References:

1. Brouhard BH, Lawry KW, McGowan KRB, Drotar D, Davis RS, Cohn RA, Tejani A (2000) Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplant 4: 261-267

2. Duquette PJ, Hooper SR, Wetherington CE, Icard PF, Gipson DS (2007) Brief Report: Intellectual and Academic Functioning in Pediatric Chronic Kidney Disease. J Pediatr Psychol nil:1-7

3. Johnson RJ, Warady BA (2013) Long-term neurocognitive outcomes of patients with end-stage renal disease during infancy. Pediatr Nephrol 28: 1283-1291

4. Gipson DS, Duquette PJ, Icard PF, Hooper SR (2007) The central nervous system in childhood chronic kidney disease Pediatr Nephrol 22:1703-1710

5. Gipson DS, Hooper SR, Duquette PJ, Wetherington CE, Stellwagen KK, Jenkins TL, Ferris ME (2006) Memory and executive functions in pediatric chronic kidney disease. Child Neuropsychol, 12: 391-405

6. Slickers J, Duquette P, Hooper SR, Gipson DS (2007) Clinical predictors of neurocognitive deficits in children with chronic kidney disease. Pediatr Nephrol 22: 565-572

7. Madden SJ, Guerrero-Blanco M, Bruce M, Trompeter RS (2003) Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev 29(1): 55-61

8. Bawden PA, Carter J, Lirenman D, MacDonald GW, McAllister M, McDonnell MC, Shea S, Crocker J (2004) Neuropsychological functioning in end-stage renal disease. Arch Dis Child 89: 644-647

9. Groothoff JW, Dommerholt A, Gruppen MP, Offringa M, Heymans H (2002) Impaired cognition and schooling in adults with end stage renal disease since childhood. Arch Dis Child 87: 380-385

10. Icard P, Hooper SR, Gipson DS, de Ferris ME (2010) Cognitive improvement in children with CKD after transplant. Pediatr Transplant 14(7): 887-890

11. Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB, Mendley SR, Warady BA, Furth SL, Hooper SR (2006) Neurocognitive outcomes in children with chronic kidney disease: current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev 12: 208-215

12. Fennell RS 3rd, Rasbury WC, Fennell EB, Morris MK (1984) Effects of kidney transplantation on cognitive preformance in pediatric population. Pediatrics 74(2): 273-278

13. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58: 259-263

14. Schrank FA, McGrew KS, Woodcock RW (2001) Technical Manual. Woodcock-Johnson III. Itasca, Illinois, USA

15. Fletcher JM, Denton C, Francis DJ (2005) Validity of alternative approaches for the identification of learning disabilities: Operationalizing unexpected underachievement. 2005., J Learn Disabil 38: 545-552

16. APA (American Psychiatric Association) (1994) Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR.

17. Copelovitch L, Warady BA, Furth SL (2011) Insights from the Chronic Kidney Disease in Children (CKiD) Study. Clin J Am Nephrol 6: 2047-2053

18. Gerson AA, Wntz MA, Abraham AG, Mendley SR, Hooper SR, Butler RW, Gipson DS, Lande MB, Shinnar S, Moxey-Mims M, Warady BA, Furth SL (2010) Health-related quality of life of children with mild to moderate chronic kidney disease. Pediatrics 125: e349-e357

19. Carneiro P, Meghir C, Parey M (2013) Maternal education, home environments, and the development of children and adolescents. J Euro Econ Association 11: 123-160

20. Gulleroglu K, Baskin E, Bayrakci US, Aydogan M, Alehan F, Kantar A, Karakayali F, Moray G, Haberal M (2013) Neurocognitive functions in pediatric renal transplant recipients. Transplant Proc 45: 3511-3513

21. Van der Horst FCP, Van der Veer R (2008) Loneliness in Infancy: Harry Harlow, John Bowlby and Issues of Separation. Integr Psych Behav 42: 325–335

22. Van Handel M, Swaab H, De Vries LS, Jongmans MJ (2007) Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. Eur J Pediatr 166(7): 645–654

23. Martínez-Sanchis S, Bernal MC, Montagud JV, Candela G, Crespo J, Sancho A, Pallardó LM (2011) Effects of immunosuppressive drugs on the cognitive functioning of renal transplant recipients: a pilot study. J Clin Exp Neuropsychol 33(9): 1016-1024

24. Backeljauw B, Holland SK, Altaye M, Loepke AW (2015) Cognition and Brain Structure Following Early Childhood Surgery With Anesthesia. Pediatrics 136(1): e1-12

25. Wechsler D (2003) Wechsler Intelligence Scale for Children - Four Edition The Psychological Corporation, Harcourt Assessment Company, San Antonio, Texas, USA

26. Wechsler D (2008) Wechsler Adult Intelligence Scale - Fourth Edition Edition The Psychological Corporation, Harcourt Assessment Company, San Antonio, Texas, USA

27. Crocker JFS, Acott PD, Carter JEJ, Lirenman DS, MacDonald GW, McAllister M, McDonnel MC, Shea S, Bawden HN (2002) Neuropsychological outcome in children with acquired or congenital renal disease. Pediatr Nephrol 17: 908–912

Table 1: Main characteristics of the transplant (Tx) versus the control (Co) groups (n=70)

	Tx (n=35)	Co (n=35)	p value
Age (months) (mean±SD)	161 (±29)	161 (±30)	0.95
Male (%)	60	60	1.00
Maternal education (%)			0.36
Primary education or less	15	0	
Skilled workers	44	51	
High school or equivalent	18	29	
University diploma	23	20	
Age at dialysis onset (months) (mean±SD)	108 (±38)*	N/A	N/A
Duration of dialysis (months) (median; IQR)	9 (16)	N/A	N/A
Blood hemoglobin (g/l) (mean±SD)	128 (±14)	N/A	N/A
Serum albumin (g/l) (mean±SD)	47 (±3)	N/A	N/A
Estimated GFR (Schwartz) (ml/min/1.73 m^2) (median; IQR)	94 (44)	N/A	N/A
Learning problems (%)	33	17	0.12
Cumulative Lifetime Hospitalization Duration (months) (median; IQR)	6 (16)	0.3 (0.8)	<0.001

*Four (11%) children had never been on dialysis in transplant group

Abbreviations: Tx = Transplant group, Co = Control group, SD = Standard Deviation, IQR = Interquartile Range, GFR = Glomerular Filtration Rate, N/A = Not Applicable

Table 2: Performances of Woodcock-Johnson Cognitive Ability Test (WJIE) (n=70)

	Transplant (n=35)		Control (n=35)	
		Mean (SD)	Mean (SD)	Level of significance (p-value)
WJIE – Verbal Ability		97 (25)	110 (13)	<0.01
WJIE – Thinking Ability		88 (28)	107 (10)	<0.001
WJIE – Cognitive Efficiency		82 (25)	103 (13)	<0.001
WJIE – Full Scale Intellectual Abilities		85 (26)	107 (10)	<0.001

Abbreviations: WJIE = Woodcock-Johnson Cognitive Ability Test – International Edition, SD = Standard Deviation

Table 3: Distribution of intellectual achievements in transplant children (n=35)

IQ scores	Frequency (Percent)
Normal range IQ>85	21 (60%)
Learning disability IQ 70-85	6 (17%)
Mild mental retardation IQ 69-50	4 (11.5%)
Severe mental retardation IQ 49-35	0 (0%)
Profound mental retardation IQ 34 or lower	4 (11.5%)
Total	*35 (100%)*

Abbreviations: IQ = Intelligence Quotient

Table 4: Maternal education levels and intellectual functioning

	Elementary school or less (n=5)	General Certificate of Secondary Education (GCSE) (n=15)	More than secondary school (n=6)	Higher educated/ graduated (n=8)	p-value
WJIE – Verbal Ability	57 (±21)	99 (±19)	105 (±21)	109 (±14)	<0.001
WJIE – Thinking Ability	48 (±33)	91 (±22)	90 (±20)	104 (±17)	<0.001
WJIE – Cognitive Efficiency	56 (±26)	79 (±19)	77 (±21)	104 (±20)	<0.001
WJIE – Full Scale Intellectual Abilities	48 (±27)	85 (±20)	85 (±22)	105 (±16)	<0.001

Values are mean ± standard deviation (analysis of variance)

Abbreviations: WJIE = Woodcock-Johnson Cognitive Ability Test – International Edition, SD = Standard Deviation, GCSE = General Certificate of Secondary

Education

Table 5: Correlations of intellectual achievements and medical parameters in transplant

group (n=35)

	WJIE Verbal Ability	WJIE Thinking Ability	WJIE Cognitive Efficiency	WJIE Full Scale Intellectual Abilities	GFR (Schwartz)	Age of dialysis onset	Full hospital stay
Estimated GFR (Schwartz)	0.076	0.093	0.088	0.095	-		
Age of dialysis onset (months)	0.462#	0.629#	0.366*	0.526#	0.423*	-	
Full hospital stay in life (months)	-0.213	-0.333	-0.561#	-0.468#	-0.208	-0.322	-

*: p<0.05

#: p<0.01

Abbreviations: WJIE = Woodcock-Johnson Cognitive Ability Test – International Edition, GFR = Glomerular Filtration Rate