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Prevalence and Outcomes of Renal Transplantation in Children with Intellectual Disability

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Abstract

Objective—To describe the prevalence and outcomes of renal transplantation in children with intellectual disability (ID).

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Contributors Statement:

- Aaron Wightman – conceived the study, obtained the data, contributed to the design, performance, and interpretation of the analysis, wrote and revised the manuscript
- Bessie Young – contributed to the design of the study and analyses, interpretation of the analyses, and writing and revision of the manuscript
- Miranda Bradford – contributed to study design, performed the data analysis, contributed to interpretation of the analysis, writing, and revision of the manuscript
- Andre Dick – contributed to study design, interpretation of the analysis, writing and revision of the manuscript
- Patrick Healey – contributed to study design, interpretation of the analysis, writing and revision of the manuscript
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- Jodi Smith — conceived the study, contributed to design and interpretation of analysis and writing and revision of the manuscript

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Patients and Methods—We performed a retrospective cohort analysis of all children receiving a first kidney alone transplant in the UNOS dataset from 2008 to 2011. Recipients with definite, probable, and without ID were compared using chi-square. Kaplan Meier curves were constructed for patient and graft survival. Cox proportional hazard models were used to estimate the association between ID and graft failure and patient survival.

Results—Over the study period, 332 children with definite (117) or probable (215) ID underwent first renal transplant, accounting for 16% of all first pediatric renal transplants (n=2076). Children with definite ID were not significantly different from children without ID with respect to sex, ethnicity, or prevalence of acute rejection. ID was associated with increased likelihood of deceased donor source. ID was not significantly associated with decreased graft or patient survival.

Discussion—In this first large-scale study, up to 16% of first pediatric renal transplants were performed in children with ID. Short-term graft and patient survival after transplant were equivalent between children with and without ID. Further research is needed to examine long-term outcomes of transplant in this population.

Keywords

renal transplant; intellectual disability; ethics; nephrology; outcomes

Introduction

Renal transplantation in children with intellectual disability (ID) is a contentious issue.(1) Historically, children were denied access to transplantation due to intellectual disabilities.(2) Reasons for exclusion included belief of reduced life expectancy, lack of cognitive ability to understand transplantation and comply with the required post-transplant therapy, and a lack of improvement in quality of life. A 1993 survey of 411 transplant centers found that 54% of renal transplant centers considered IQ<70 as an absolute or relative contraindication and 76% of centers considered an IQ<50 as an absolute or relative contraindication for transplant candidacy.(3) In 1995, The American Society of Transplant Physicians released guidelines stating that cognitive impairment should only be considered a contraindication to transplantation when it is so severe to impair compliance with essential medication regimens and a caregiver was unavailable to compensate for the individual's limitations.(4) Despite these recommendations, a 2005 survey of pediatric transplant centers reported 56% of transplant centers would consider IQ <35 a relative contraindication to solid organ transplantation and 40% would consider it an absolute contraindication.(5) Some centers would only consider a child with intellectual disability for organ transplant if a parent or family member agreed to be a living donor rather than to list the child for a deceased donor transplant. (5, 6)

Limited data from small case series suggests that children with intellectual disability, including those with an IQ<35, who receive a kidney transplant have comparable graft and recipient survival outcomes when compared to children without intellectual disability.(7–10) Ohta et al reported improved quality of life among patients and their caregivers following

renal transplantation in 25 “multiply handicapped” patients at 8 Japanese centers over 7 years.(10)

In 2005, Richards et al found less than 20% of pediatric transplant centers required formal evaluation of neurodevelopmental status and there was considerable heterogeneity among the evaluation process and personnel.(5) In 2008, the United Network for Organ Sharing (UNOS) began collecting data on cognitive development and academic level in all pediatric transplant candidates. We sought to analyze these data to describe the prevalence and outcomes of renal transplantation in children with intellectual disabilities. We hypothesized that children with intellectual disability make up a significant percentage of children receiving renal transplants and that their early outcomes are equivalent to recipients without intellectual disability.

Patients and Methods

We performed a retrospective cohort analysis of all children receiving a first kidney-alone transplant in the UNOS dataset from January 1st 2008 to October 31, 2011. Children who underwent a second transplant or multi-organ transplant were excluded. Children were scored by their transplant center on Likert scales for cognitive development (1: definitely cognitive delay/impairment, 2: probable cognitive delay/impairment, 3: questionable cognitive delay/impairment, 4: no cognitive delay/impairment, 5: not assessed), academic progress (1: full academic load, 2: reduced academic load, 3: no participation due to disease or condition, 4: not applicable [less than 5 years old, high school diploma or certificate of high school equivalency GED], 5: Status unknown), and academic level (1: within one grade level of peers, 2: delayed grade level, 3: special education, 4: not applicable [less than 5 years old, high school diploma or GED], 5: Status unknown).

We categorized recipients as definite intellectual disability if they were identified as “definitely cognitive delay/impairment” by their center. We categorized recipients as probable intellectual disability if they met two out of three criteria: “probable” or “questionable” cognitive delay/impairment, “reduced academic load/nonparticipation,” or “delayed grade level/special education”. Children under 5yrs of age with “probable” or “questionable cognitive delay/impairment” were included in the probable intellectual disability group, although they had not yet entered school.

The primary outcomes of interest were patient and death-censored graft survival following transplant. Demographic and transplant-related characteristics of recipients with definite or probable intellectual disability were compared to those without intellectual disability using chi-square tests. Kaplan Meier curves and log-rank tests stratified by intellectual disability status were constructed for patient and graft survival.

Cox proportional hazard models were used to estimate unadjusted and adjusted hazard ratios to determine the associations between intellectual disability and graft failure and intellectual disability and patient survival.(11) The adjusted models included, a priori, age in years (<5, 5–12, 13–18), male sex, nonwhite race, etiology of end-stage kidney disease (ESKD) (structural, focal segmental glomerulosclerosis [FSGS], glomerulonephritis [GN], other),

living donor, cold ischemia time > 24 hrs, HLA match, and PRA/CPRA(<10%, 10–<80%, 80–100%).

Secondary analysis was performed to compare the demographic and transplant-related characteristics of transplant recipients without information entered about intellectual disability status to those recipients included in our analysis.

Results

Of the 2292 children who underwent transplantation during the study period and for whom both waitlist and follow-up data were available, cognitive and educational information were available on 2076 (91%) transplant recipients. Table 1 illustrates the distribution of cognitive and academic scores among this subgroup. One hundred seventeen children (5.6%) were categorized as having definite intellectual disability and an additional 215 (10.3%) were categorized as having probable intellectual disability.

Patient characteristics are summarized in Table 2. Recipients with definite and probable intellectual disability tended to be younger than children without intellectual disability. A greater proportion of children with probable intellectual disability were male when compared to children without intellectual disability. The distribution of ethnicity was similar across disability groups. Compared with patients without intellectual disability, patients with definite or probable intellectual disability tended to have different etiologies of ESKD. Specifically, patients with definite and probable intellectual disability had higher rates of structural ESKD and lower rates of glomerulonephritis (GN) and focal segmental glomerulosclerosis (FSGS). Recipients with definite and probable intellectual disability were more likely to have a public payer as a primary source of insurance than those without intellectual disability.

Recipients with definite and probable intellectual disability underwent a greater percentage of deceased donor renal transplants compared to those with no intellectual disability (definite 74%, probable 73%, none 59%, $p<.01$ [definite vs. none] $p<.001$ [probable ID vs. none]). The proportion of recipients with definite intellectual disability who received a preemptive transplant was similar to that of recipients with no intellectual disability (Table 2). A lower proportion of recipients with probable intellectual disability received a preemptive renal transplant (20%) compared to those with no intellectual disability (30%).

Kaplan Meier curves and log-rank tests did not suggest significant differences in patient or graft survival during the first three years following renal transplantation (Figures 1 and 2).

In unadjusted Cox regression, intellectual disability was not significantly associated with graft or patient survival; this lack of association remained after adjusting for covariates (Tables 3 and 4).

Compared with the children included in our analysis, the 216 children without cognitive and intellectual information tended to be younger, more likely male, and more likely to have an “other” diagnosis of ESKD (results not shown). They did not differ by ethnicity or proportion of preemptive or deceased donor transplants. There was no difference in any

measured outcomes between those with cognitive and intellectual information and those without.

Discussion

This study provides the first large-scale description of 332 children with intellectual disability who underwent renal transplantation. Historically, children with intellectual disabilities have been denied access to transplantation. Changes in professional guidelines in the last 20 years have made many of these children eligible for solid organ transplant; however, the reported practice of individual transplant centers has been markedly heterogeneous.⁽⁵⁾ Our analysis of the UNOS dataset revealed that 16% of all first pediatric renal transplant recipients were children identified as having definite or probable intellectual disability. Short-term graft and patient survival were similar between children with definite or probable intellectual disability and without intellectual disability.

Recipients with definite or probable intellectual disability did not differ significantly from other recipients on the basis of ethnicity, but tended to be younger and have higher rates of structural kidney disease and lower rates of glomerulonephritis. Previous studies have been unable to compare age of transplant recipients due to use of age-matched controls. These findings may reflect a higher number of syndromic causes of ESKD among the intellectual disabled population.

It has been reported that some centers would only consider a child with intellectual disability for organ transplant if a parent or family member agreed to be a living donor rather than to list the child for a deceased donor transplant.⁽⁵⁾ Our results do not support this practice. We observed that recipients with definite and probable intellectual disability had a lower proportion of living donor renal transplants than children without intellectual disability. It is possible that these results indicate a shift in the attitudes of the pediatric kidney transplant community toward children with intellectual disabilities.

Our results demonstrate that early survival of recipient and graft are equivalent between children with and without intellectual disability at 3 years of follow-up. These findings provide further validation of previously published case series. Combined, Galante, Benedetti, and Ohta reported 100% 1 and 5 year graft survival and 96% patient survival. The 2 deaths among 49 recipients were described as related to infectious complications.^(7, 8, 10)

This study has a number of limitations. Our study only analyzed children who received a kidney transplant. We did not assess children listed for transplant who remain on the wait list, those who were refused listing by a transplant center, those with ESKD not referred to a transplant center, or with intellectual disability but needing a different solid organ transplant. In this context, our findings underestimate the number of children with intellectual disabilities eligible for consideration for kidney transplant. Data from dialysis registries does not exist to describe the number of children with intellectual disability who receive dialysis but are not considered for renal transplant. We were also unable to assess the prevalence or outcomes of adult transplant recipients with intellectual disability, as data on cognitive delay/impairment is not collected in the UNOS dataset for adults. For the purpose of this

study, we created a definition of intellectual disability based on information available in the UNOS dataset. Previous studies have used definitions based upon American Psychological Association (APA) criteria(8–10) or formal intellectual quotient (IQ) or developmental quotient (DQ) testing.(5, 8, 10) Currently, there are no standardized mechanisms for transplant centers to assess cognitive development, academic level, or academic activity.(5) It is possible that our definition of intellectual disability does not reflect true assessments by transplant centers. Richards et al found considerable heterogeneity among centers regarding which team member assesses intellectual function and how.(5) Finally, although this is the largest study conducted in a pediatric population, there were only 3 years of potential follow-up and the number of recipients with intellectual disability was small. We may not have enough power to show a significant difference by cognitive categories.

Conclusion

In this first, large-scale cohort study, up to 16% of first pediatric renal transplant recipients were identified as having intellectual disability and there was no difference in survival of the graft or the patient when compared to other pediatric recipients. While we cannot exclude the possible impact of selection bias, we have demonstrated that for children with intellectual disability whose family and providers have pursued renal transplant, early outcomes are comparable to those of other children without intellectual disability. Further research is needed on long-term outcomes and quality of life effects, including the possibility of catch-up in intellectual function, of transplant in this population and in those with intellectual disabilities requiring a different solid organ transplant.

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Abbreviations

ID intellectual disability

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Figure 1.
KM graft survival for definite intellectual disability (ID), probable ID, and no ID
Log-rank test: P-value = 0.920

Figure 2.
KM patient survival for definite intellectual disability (ID), probable ID, and no ID
Log-rank test: P-value = 0.342

Table 1

Academic and cognitive characteristics of pediatric kidney transplant recipients

		N=2292	
		n	%
Cognitive Development	Definite cognitive delay/impairment	117	5.1
	Probable cognitive delay/impairment	67	2.9
	Questionable cognitive delay/impairment	92	4.0
	No cognitive delay/impairment	1286	56.1
	Missing or unknown	730	31.8
Academic Progress	Full academic load	1400	61.1
	Reduced academic load	78	3.4
	No participation due to disease/condition	130	5.7
	N/A: <5 or High school graduate	369	16.1
	Missing or unknown	315	13.7
Academic Level	Within 1 grade level of peers	1274	55.6
	Delayed grade level	117	5.1
	Special Education	30	1.3
	N/A: <5 or High school graduate	299	13.0
	Missing or unknown	572	25.0
Definite Intellectual Disability		117	5.6
Probable Intellectual Disability		215	10.3
No intellectual Disability		1744	84.1

Table 2

Patient characteristics

	Definite intellectual delay (ID) N = 117			Probable ID N = 215			No ID N = 1744		
	n	%	Chi square P value Def. ID vs. No ID	n	%	Chi square P value Prob. ID vs. No ID	N	%	
Age:			<0.001			<0.001			
<5yrs	23	19.7		47	21.9		140	8.0	
5–12 yrs	41	35.0		68	31.6		532	30.5	
13–18 yrs	53	45.3		100	46.5		1072	61.5	
Male gender	67	57.3	0.756	142	66.0	0.004	973	55.8	
Ethnicity:			0.579			0.482			
White	62	53.0		111	51.6		855	49.0	
Black	27	23.1		42	19.5		323	18.5	
Hispanic	24	20.5		58	27.0		472	27.1	
Asian	2	1.7		2	0.9		54	3.1	
American Indian/Alaska Native	1	0.9		1	0.5		12	0.7	
Native Hawaiian/Other	0	0.0		0	0		9	0.5	
Multiracial	1	0.9		1	0.5		19	1.1	
Preemptive	36	30.8	0.933	43	20.0	0.002	529	30.3	
Donor Type			0.002			<0.001			
Living	31	26.5		59	27.4		712	40.8	
Deceased	86	73.5		156	72.6		1032	59.2	
Etiology of end stage kidney disease:			0.025			0.008			
Structural	53	45.3		90	41.9		616	35.3	
FSGS	13	11.1		20	9.3		270	15.5	
GN	8	6.8		21	9.8		256	14.7	
Other	42	35.9		82	38.1		576	33.0	
Missing	1	0.9		2	0.9		26	1.5	

	Definite intellectual delay (ID)			Probable ID			No ID		
	n	%	Chi square P value Def. ID vs. No ID	n	%	Chi square P value Prob. ID vs. No ID	N	%	N = 1744
Primary Insurance Payer Public	83	66.6	0.001	160	68.4	<0.001	956	50.7	
Acute rejection episode in 1 st 6 months	9	7.7	0.454	16	7.4	0.259	170	9.7	
Acute rejection episode between 6–12 months	12	10.3	0.562	21	9.8	0.315	209	12.0	

FSGS: Focal Segmental Glomerulosclerosis
GN: glomerulonephritis

Table 3

Hazard ratios for graft survival, comparing definite or probable ID to no ID

	Unadjusted model (N=2075) (# of total graft failures= 129)			P Value	Adjusted model* (N=1562) (# of total graft failures=89)			P value
		HR	95%CI		HR	95% CI		
Definite ID		1.0	0.5–2.3		1.1	0.5–2.5		
Probable ID		0.9	0.5–1.7		0.5	0.3–2.0		

* Includes age in years (<5, 5–12, 13–18), male gender, race (white/nonwhite), etiology (structural, FSGS, GN, other), deceased donor (Y/N), cold ischemia time >24 hrs (Y/N), HLA match, PRA/CPRA (<10%, 10–<80%, 80–100%).

Table 4

Hazard ratios for recipient survival, comparing definite or probable ID to no ID

Unadjusted model (N=2076) (# of total deaths= 19)	Adjusted model* (N=1563) (# of total deaths= 14)		P value
	HR	95% CI	
Definite ID	2.4	0.5–10.5	0.939
Probable ID	1.9	0.6–6.8	0.752

* Includes age in years (<5, 5–12, 13–18), male gender, race (white/nonwhite), etiology (structural, FSGS, GN, other), deceased donor (Y/N), cold ischemia time >24 hrs (Y/N), HLA match, PRA/CPRA (<10%, 10–80%, 80–100%).