



Clinical characteristics and complications of kidney transplantation among an Egyptian pediatric cohort

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ABSTRACT

Background: kidney transplantation is the treatment of choice in children with end stage kidney disease. Acute rejection represents a major complication with high risk of graft loss. Hence, the use of immunosuppressive therapy is inevitable to prevent allograft rejection. However, the excess use of immunosuppressive drugs can increase the risk of post-transplant infections with higher morbidity and mortality. The judicious use of the immunosuppressive drugs is crucial to enhance the transplant outcomes. Tacrolimus is the backbone of immunosuppressive therapy in the recent era of kidney transplantation. However, it is associated with many side effects. Close clinical and laboratory monitoring of tacrolimus trough level and serum creatinine are essential in all patients.

Methods: Analysis of the clinical data of 83 kidney transplant recipients with follow up data as graft function, post-transplant complications as acute rejection and infections were documented. Tacrolimus adverse effects were reported during at least 36 months of follow up post-transplant.

Results: Acute rejection was encountered in 43.4 % and post-transplant infections in 41 % of the included cases in the current study. In addition, tacrolimus side effects occurred in 32.5 % of the cases.

Conclusion: close follow up of kidney transplant recipients is essential for early detection and prompt management of graft rejection and infectious complications.

Keywords: *kidney transplantation, pediatric, complications*

INTRODUCTION

Kidney transplantation (KT) is the best treatment modality for children with end stage kidney disease (ESKD) (1). It provides them

with a better quality of life and long-term survival in comparison to dialysis (2). The variation in life expectancy may be up to 20 years (3).

The original kidney disease in pediatric population is often due to developmental renal anomalies as hypoplastic kidneys, obstructive uropathy, vesicoureteral reflux (VUR) and polycystic kidney disease in addition to glomerular diseases as focal segmental glomerular sclerosis (FSGS). It is completely different from adult population where hypertension, diabetes and glomerular disease are the predominant leading causes of renal failure (4).

In spite of the great advances in immunosuppressive (IS) therapy and post KT care, many complications still threaten both the graft and patient outcomes. Allograft rejection is a major complication with devastating effect on both patient and graft survival. The use of immunosuppressive drugs is crucial to prevent immune mediated graft damage. The standard protocol in pediatric KT is to give induction therapy as rabbit antithymocyte globulin (r ATG) or basiliximab, according to the patient immunological risk, followed by tacrolimus based triple maintenance therapy with MMF, and prednisone as being practiced in 55%–63% of all pediatric transplant centers in the United States (4).

Rejection can be either acute or chronic. Acute rejection was previously manifested as fever, oliguria, hypertension, proteinuria and graft tenderness. However, in the era of potent IS therapy, it mainly presented as asymptomatic rise of serum creatinine (5). Ultrasound (US) guided allograft biopsy remains the golden standard method for the diagnosis and staging of rejection according to the Banff pathology guidelines which was developed in the 1990s and has subsequently undergone frequent updating and revision. The last update was in 2019. AR can be classified according to the pathological criteria into T cell mediated rejection (TCMR), antibody mediated rejection (AMR) and mixed rejection (6,7).

Unique features of the immune system in children make the pendulum continuously swing between over and under IS. This urgently requires further research to find that balance as underuse is associated with rejection and overuse precipitate infections (8,9).

Post-transplant infections account for higher morbidity and mortality in pediatric KT recipients. They represent 33% of all mortalities according to the French registry during 70 months follow-up duration (10).

High index of suspicion and close monitoring of KT recipients for graft function and occurrence of any complications especially in pediatric age group are essential to improve the transplant outcomes, thus we conducted the current study to be aware of possible complications, how to diagnose and how to treat.

METHODS

In the current study, 83 children with living donor kidney transplantation (LDKT) following up at Kidney Transplantations Unit, Cairo University Children Hospital (Abo El Reesh) were included. The following data were collected from each transplant recipient's data sheet including demographic and clinical data including age, original renal disease, duration of dialysis, weight, height and body mass index. The follow up data as serial graft function, any complications as biopsy proven AR, infectious complications and tacrolimus related adverse effects were documented.

All the included cases were between 1-18 years old with minimum follow-up duration 36 months post transplantation. The original kidney disease was divided into Congenital anomalies of the kidney and the urinary tract (CAKUT) and non CAKUT. CAKUT include congenital obstruction of the urinary tract either lower obstruction as posterior urethral valve (PUV) or upper obstruction as pelviureteric junction obstruction (PUJO), developmental anomalies of the kidneys as aplasia, hypoplasia or dysplasia, VUR, polycystic and multicystic dysplastic kidneys (MCDK), hydronephrosis, duplex kidney, duplicated collecting system and megaureter (11). Need to do dialysis either hemodialysis (HD) or peritoneal dialysis (PD) prior to TX and their duration were documented.

All of the cases received induction therapy with either rabbit anti thymocyte globulin (r ATG) or basiliximab. All recipients were maintained on TAC based triple maintenance IS therapy with

steroids and MMF. Only one case received AZA rather than MMF due to development of intractable gastrointestinal side effects as adopted in the center protocol (12).

Tacrolimus was usually started at dose of 0.15 mg/kg/day, given in two divided doses and the dose was titrated according to the target trough level. Measurement of TAC trough level (ng/ml) was done at 9 am, 1 h before the next TAC dose. Concentration/dose (C/D) ratio was calculated by dividing the trough level (ng/ml) by the corresponding weight adjusted daily dose (mg/kg/day).

AR was defined as a rise in serum creatinine by 20-30% from baseline levels with or without clinical symptoms and signs of rejection and proven by allograft biopsy. AR can occur at any time after kidney transplantation, but commonly in early months with decreasing incidence thereafter (13).

In any case with AR, the time of onset post transplantation, pathological type according to the criteria of Banff classification, mean Tacrolimus dose (corrected to body weight) and mean trough Tacrolimus level (ng/dl) during AR episode, antirejection therapy and the response to treatment were documented.

Treatment of AR is usually started with 3-6 intravenous (IV) pulses of methylprednisolone, initiated even before graft biopsy. Allograft biopsy determines further treatment according to the severity of the pathological type. r ATG was started thereafter for steroid resistant TCMR (when serum creatinine does not return to the baseline level after 7-10 days of pulse steroid therapy). Treatment of acute ABMR includes plasma exchange (PEX), intravenous immunoglobulin (IVIG), anti-CD20 monoclonal antibody (rituximab), ATG or methylprednisolone. The response to antirejection therapy was assessed and classified according to the decrease in serum creatinine into: complete response when serum creatinine normalized to the basal level, partial response when creatinine level decreased but not reaching to the baseline value and no response when the creatine remained unchanged.

Patients with stable graft function (i.e. having serum creatinine < 1mg/dl or without change in graft function) without any documented AR episodes for at least one year after KT were considered (none rejection cases) (14). Patients receiving cyclosporine as maintenance IS or Patients with acute graft dysfunction due to causes rather than rejection as acute infection, dehydration episodes or surgical causes were excluded.

Risk stratification for cytomegalovirus (CMV) infection was defined according to the serological status of both donor and recipients prior to transplantation (15). High risk Tx is considered when the donor is positive for CMV IgG and recipient is negative (D+, R-), intermediate risk is defined when the recipient is seropositive, whatever the serological status of the donor, either (D+, R+) or (D-, R+) and low risk means both have negative serology (D-, R-) (16,17).

Tacrolimus induced side effects as nephrotoxicity, neurotoxicity, hypertension and metabolic complications (impaired glucose tolerance, dyslipidemia...etc.) were reported.

The baseline serum creatinine and follow up values were reported. The glomerular filtration rate (GFR) was estimated based on bed side Schwartz's formula: $GFR (mL/min/1.73 m^2) = K \times \text{height (cm)} / \text{serum creatinine (mg/dL)}$ (18). Values of serum creatinine and GFR were documented as basal levels and one year after KT for all recipients.

Statistical analysis

The analysis of the collected data was done by SPSS software (Statistical Package for the Social Sciences, version 25, SPSS Inc, Chicago, Ill, USA). Quantitative data were illustrated as mean and Standard Deviation (SD) or median and interquartile range (IQR). Qualitative data were presented as number (N) and percent (%). P value was considered statistically significant when it is ≤ 0.05 .

RESULTS

In the present study, the mean age at time of transplantation was 9.3 ± 2.9 years. CAKUT was the original kidney disease in 50.6% of cases. In addition, 7.2% of cases had positive family history of kidney disease. Unfortunately, 95.2% of cases required dialysis prior to KT for a median duration of 12 months. Native nephrectomy was performed in 48.2 % of cases due to many reasons. Heavy proteinuria was the most common indication in our cohort (42.5% of cases). Other causes for native nephrectomy as large polycystic kidney, Chronic pyelonephritis and marked hydronephrosis were found in 5 %, 15 % and 37.5 % of cases respectively.

The main complications found during follow up of our cases, were acute graft rejection, infections and tacrolimus related adverse effects as in table 1.

The clinical and pathological characteristics of acute rejection group are shown in table 2. AR

was documented in 36 cases (43%) of our cohort. Onset after transplantation was early in 25%, delayed in 41.7% and late in 33.3%. Pathological type of rejection was either ABMR, TCMR or mixed rejection in 50%, 11.1% and 38.9% of cases respectively. Empirical pulse steroids were initiated in all cases of AR, in addition to IVIG, PEX or ATG as indicated in 55.6 % of the cases. Fortunately, 52.8 % of cases achieved complete remission.

As regard the infections after KT, urinary tract infection (UTI) was the commonest infection and presented in 61.8% of cases as illustrated in table 3.

Although tacrolimus is a major component of IS regimen, it was associated with major adverse effects as illustrated in table 4. Nephrotoxicity was the most common encountered TAC adverse effects among our cases.

TABLE 1: Post-transplant complications documented among KT recipients.

Complication		KT recipients N=83
Acute rejection	N (%)	36 (43.4 %)
Post-transplant infections	N (%)	34 (41%)
Tacrolimus related side effects	N (%)	27 (32.5 %)

KT; kidney transplant, N; number

TABLE 2: Clinical, pathological criteria and treatment of AR cases.

Character			AR (n=36)
Original kidney disease	CAKUT	No (%)	19 (52.8%)
	None KACUT	No (%)	17 (47.2%)
CMV risk	Low	No (%)	5 (13.9%)
	Intermediate	No (%)	30 (83.3%)
	High	No (%)	1 (2.8%)
HLA mismatch	3/6 mm	No (%)	22 (61.1%)
	2/6 mm	No (%)	12 (33.3%)
	1/6 mm	No (%)	2 (5.6%)
Onset of rejection post transplantation	Early (in 1st 3 months)	No (%)	9 (25%)
	Delayed (between 3 m-1y)	No (%)	15 (41.7%)
	Late (after 1 year)	No (%)	12 (33.3%)
Pathological type	ABMR	No (%)	14 (38.9%)
	C4d positive	No (%)	11 (30.6 %)
	TCMR	No (%)	18 (50%)
	Mixed rejection	No (%)	4 (11.1%)
Antibody induction	Basiliximab	No (%)	15 (41.7%)
	ATG	No (%)	21 (58.3%)

Maintenance therapy with TAC	MMF	No (%)	36 (100%)
Preemptive PEX		No (%)	4 (11.1%)
Trough level at time of AR (ng/ml)		median (min-max)	5 (3-8)
TAC dose at time of AR (mg/kg/day)		median (min-max)	0.14 (0.08-0.22)
C/D ratio at time of AR (ng/ml/mg/kg/day)		median (min-max)	38 (18-78.6)
Antirejection therapy	Pulse steroids only.	No (%)	16 (44.4%)
	Pulse steroids plus:	No (%)	20 (55.6%)
	PEX and RTX	No (%)	4 (11.1%)
	PEX and IVIG	No (%)	5 (13.9%)
	RTX and IVIG	No (%)	5 (13.9%)
	PEX, IVIG and ATG	No (%)	2 (5.6%)
	ATG	No (%)	1 (2.8%)
Response to antirejection therapy	RTX	No (%)	3 (8.3%)
	No response	No (%)	3 (8.3%)
	Partial response	No (%)	14 (38.9%)
	Complete response	No (%)	19 (52.8%)

N; number, SD; standard deviation, CAKUT; congenital anomalies of kidney and urinary tract, CMV; cytomegalo virus, HLA; human leukocytic antigen, ABMR; antibody mediated rejection, C4; complement 4, TCMR; T cell mediated rejection, TAC; tacrolimus, MMF; mycophenolic mofetil, C/D: concentration/dose of TAC, PEX; plasma exchange, RTX; rituximab, IVIG; intra venous immunoglobulins, ATG: anti thymocyte globulin.

TABLE 3: Infectious complications among pediatric KT recipients

Post-transplant infections		KT recipients
		N=83
Any	N (%)	34 (41%)
Urinary tract infection	N (%)	21 (61.8%)
Gastroenteritis	N (%)	3 (8.8%)
Pneumonia	N (%)	2 (5.9%)
UTI and pneumonia	N (%)	6 (17.6%)
UTI and gastroenteritis	N (%)	2 (5.9%)

N; number, UTI; urinary tract infection.

TABLE 4: Documented tacrolimus adverse effects among KTRs.

Variables		KT recipients	
		N=83	
Tacrolimus adverse effects	Nephrotoxicity	N (%)	20 (24%)
	Neurotoxicity	N (%)	7 (8.4%)
	NODAT	N (%)	1 (1.2%)
	Dyslipidemia	N (%)	4 (4.8%)
	Hirsutism	N (%)	1 (1.2%)

KTRs; kidney transplant recipients, AR; acute rejection, N; number, NODAT; new onset diabetes after transplantation.

TABLE 5: Serum creatinine at baseline and after 1 year follow up post-transplant.

Variables			KT recipients
			N=83
Serum creatinine	Baseline (mg/dl)	Mean ± SD	0.6 ± 0.16
	at 1 year (mg/dl)	Mean ± SD	0.8 ± 0.2

KT; kidney transplant, N; number, mg/dl; Milligrams per deciliter.

DISCUSSION

KT is the best available renal replacement therapy in ESKD. In the current study, we describe the clinical criteria and post-transplant complications among 83 KTRs. The mean age at time of KT was 9 years and all of our cases received LDKT. CAKUT is the most common cause of original kidney disease among our cohort (50.6%). This is quite similar to previously reported data from North America, where CAKUT was represented in 48% of cases (19) and slightly lower than that reported in other studies as ranging from 58-60% of cases (20,21).

Unfortunately, most of the cases (95.2 %) required dialysis before proceeding to KT. Hemodialysis (HD) was the only modality used among our cases for a median duration of 12 months. Although peritoneal dialysis (PD) is more physiological than HD, its use has been limited by unavailability of required solutions, adequate aseptic condition at home and the limited capability of caregiver to provide service by his own. PD has been described to lower the risk of delayed graft function (DGF). However, it is associated with higher risk of infections, graft vessel thrombosis and graft loss (22, 23).

Only 5 % of cases underwent preemptive KT. This is similar to previous study from our center (24), but it is contradictory to that reported from the United States (US) that preemptive KT was performed in 32.8% of children. It is proved that dialysis avoidance in pediatric KT patients decreases the mortality and enhances the graft survival. This great difference is mostly linked to higher socioeconomic state, better orientation and transplant centers availability (25).

Need to perform native nephrectomy was required in about 48.2 % of the cases, 12 cases underwent unilateral and 28 cases underwent bilateral nephrectomy. Unilateral nephrectomy was performed in the same setting with KT

surgery. However, in case of bilateral nephrectomy, one kidney was removed before KT and the other was removed at time of transplant operation. The main indication was to control heavy proteinuria as in FSGS (42.5% of nephrectomy cases), marked hydro-uretronephrosis in 37.5 % of cases, pyelonephritic kidney in 15 % and to allow room for graft in case of huge kidneys as in ARPKD in 5% of cases.

This was higher than that reported in another study, when native nephrectomy was performed in 39% of cases either unilateral or bilateral. The main clinical indications of nephrectomy were to control polyuria, heavy proteinuria and recurrent UTI (26). Polyuria was defined as sustained urine output more than 2.5 ml/kg/h and heavy proteinuria was determined by quantitative method as more than 40 mg/m² per hour (27).

Although KT is the best treatment modality for ESRD, it has many complications. AR was encountered in 43.4 % of cases, post-transplant infections in 41 % and tacrolimus related adverse effects in 32.5 % of cases.

AR has detrimental effects on both patient and graft survival. Unfortunately, it occurred in 43.4 % of the studied KT recipients. Similarly, it was reported in the USA, that 45.6% of Pediatric KD recipients developed at least one AR episode and about 50% of them suffered from more than one episode (28). Other studies reported AR in 15 to 39% of KT recipients (29, 30) This difference may be related to the timing of biopsies and sampling of study population.

AR can occur at any time post-transplant, but the peak occurs in first year post transplant. According to the onset of AR, it can be classified as early (in 1st 3-months), delayed (between 3 months and 1year) and late (after 1year) in 25%, 41.7% and 33.3 % respectively as done in another

study (31). Human leukocyte antigen (HLA) mismatch was 3/6 in 61.1 % with no cases with either 6/6, 5/6 or 4/6 mismatches.

The pathological type of AR is classified according to the Banff classification. AMR was diagnosed in 38.9%, C4d was positive in 78.6% of AMR cases, TCMR was found in 50% and Mixed rejection in 11.1% of cases. Acute rejection cases received r ATG as an induction therapy in 58.3 % of cases and basiliximab in 41.7 % of cases. Only 4 cases underwent preemptive PEX to prevent recurrence of FSGS.

The adopted protocol is to give pulse steroids in any case of presumed AR, even before performing graft biopsy. Actually, 44.4 % of cases did not require further anti-rejection therapy. However, 55.6 % of cases required additional PEX, RTX, IVIG and ATG either alone or in combination. Adjustment of maintenance IS therapy as increase dose of tacrolimus to achieve trough level and advice patients about strict adherence to IS treatment were done in all cases as indicated.

After treatment, 52.8 of the cases achieved complete response, 39.9 % achieved partial response and 8.3 % had no response to antirejection therapy. Complete response was defined as return of serum creatinine after treatment to 25 % or less above the basal creatinine, partial remission was considered if creatinine remains 25-75 % above basal level and no response if none of the above-mentioned definitions is fulfilled (32,33).

As regard post transplantation infections, UTI was the most common infection followed by pneumonia in the studied cases. UTI was reported in 61.8 % of our cases. However, it was reported to occur in 15 to 33% of transplant cases, in another pediatric study (34). In the current study, most of the infectious complications occurred between 1-6 months post transplantation and this was quiet similar to that reported in the literature due to the maximum immunosuppressive effect of IS therapy (35).

Tacrolimus remains one of the essential components of IS therapy in pediatric KT. However, it is associated with many adverse

effects as nephrotoxicity, neurotoxicity and new onset diabetes after transplantation as documented in the current study in 24%, 8.4 % and 1.2 % respectively.

CONCLUSION

KT is the best option in children with ESKD. However, it is still associated with many complications as rejection and increased risk of infections. Close follow up of the cases and judicious use of IS therapy is crucial to improve both the graft and patient outcomes.

List of abbreviations

AR, Acute rejection; AMR, antibody mediated rejection; r ATG, rabbit anti-thymocyte globulin; C/D, concentration/dose; CAKUT, Congenital anomalies of the kidney and the urinary tract; CMV; cytomegalo virus, D, donor; ESKD, end stage kidney disease; FSGS, focal segmental glomerular sclerosis; HLA, human leukocytic antigen; IV, intravenous; IVIG, intra venous immunoglobulins; IS ,immunosuppressive; KT ,Kidney transplantation; MMF, Mycophenolate mofetil; N; number; P, P value; PEX, plasma exchange; PUJO, pelvi-ureteric junction obstruction; PUV,posterior urethral valve; R, recipient; RTX, rituximab; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; TCMR, T cell mediated rejection; TAC, tacrolimus; US, Ultrasound; UTI, urinary tract infection, VUR, vesicoureteral reflux;

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not applicable.

Competing interests

The authors declare that they have no competing interest

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Statement of ethical approval

The study was reviewed and approved by Mansoura Faculty of Medicine Institutional Research Board (MD.20.02.283) and by Pediatric Nephrology Unit, Department of Pediatrics, Faculty of Medicine, Cairo University. Informed consent was obtained for all patients. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for participation

Written informed consent was obtained from children care givers prior to inclusion in the study.

Consent for publication

Not applicable (no identifying information about participants is available in the article)

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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