

Renal transplantation in patients with congenital abnormalities of the lower urinary tract

Transplante renal em doentes com alterações genitourinárias congénitas

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■ ABSTRACT

Introduction: Renal transplantation in adults with congenital abnormalities of the lower urinary tract (CALUT) carries particular complications. Careful urologic evaluation of abnormal bladders, due to neuropathy or outlet obstruction, may indicate the need for surgical correction before transplantation. This population is also at increased risk for urinary tract infections. **Purpose:** We assessed the outcome of renal transplantation in patients with CALUT at our Transplant Unit. Patients with primary vesicoureteral reflux (VUR) were excluded from our analysis. **Materials and Methods:** A total of eight patients with CALUT, 13 to 39 years old, were evaluated. End-stage renal disease was caused by secondary VUR and recurrent urinary tract infections in patients with myelomeningocele (three cases), posterior urethral valves (one case), neurogenic bladder associated with imperforate anus (one case), congenital megaureter (two cases) and idiopathic neuropathic bladder and sphincter dyssynergia (one case). **Results:** All patients underwent surgical interventions before transplantation: ureteronephrectomy of the native kidneys (two cases), ablation of posterior urethral valves (one case), augmentation cystoplasty (six cases) and construction of an ileal conduit (one case). Seven patients remained continent, six were able to empty the bladder by clean intermittent self-catheterization and the remaining by using the Valsalva maneuver. A rate of 31 episodes per 100 patient-years of graft pyelonephritis was found, much higher when compared to other transplant recipients, although graft survival was not affected. After a mean follow-up of 104 ± 11.8 months, five patients have kept functioning grafts with mean serum creatinine of 1.17 ± 0.40 mg/dl. **Conclusion:** Renal transplant in patients with CALUT has good outcomes after preparatory urologic surgical corrections although graft pyelonephritis remains a frequent complication.

Key-Words: Congenital abnormalities; graft survival; kidney transplantation; pyelonephritis; urinary tract.

RESUMO

Introdução: O transplante renal em adultos com alterações congénitas do trato urinário inferior (ACTUI) apresenta complicações específicas. O estudo urológico de bexigas com baixa capacidade e pouco complacentes pode determinar a necessidade de cirurgia vesical reconstrutiva e soluções derivativas. Além disso, esta população apresenta maior risco de infeções do trato urinário (ITUs). **Objetivo:** Caracterizar os doentes com ACTUI seguidos na Unidade de Transplante Renal do Centro Hospitalar de São João e avaliar complicações pós-transplante renal. Os doentes com refluxo vesicoureteral (RVU) primário foram excluídos da análise. **Materiais e Métodos:** Foram avaliados 8 doentes com ACTUI com idades entre 13 e 39 anos. A doença renal crónica estabeleceu-se por RVU secundário e ITUs de repetição em contexto de mielomeninogocelo (3 casos), válvulas da uretra posterior (1 caso), bexiga neurogénica com ânus imperfurado (1 caso), megaureter congénito (2 casos) e bexiga neurogénica idiopática com dissenergia vesicoesfincteriana (1 caso). **Resultados:** Todos os doentes foram submetidos a intervenções cirúrgicas antes do transplante: nefrectomia dos rins nativos (2 casos), ablação das válvulas da uretra posterior (1 caso), cistoplastia de aumento (6 casos) e ureteroileostomia (1 caso). Sete doentes mantiveram-se continentes, 6 praticando auto-algália intermitente para esvaziamento vesical e 1 usando a manobra de Valsalva. Verificou-se uma taxa de pielonefrites agudas do enxerto renal com necessidade de internamento de 31 episódios por 100 doentes-ano, bastante superior à descrita para transplantados renais por qualquer causa, apesar da sobrevida do enxerto não ter sido afetada. Após um seguimento médio de 104 ± 11.8 meses, 5 doentes mantêm enxertos funcionantes com creatinina sérica média de 1.17 ± 0.40 mg/dl. **Conclusão:** O transplante renal em doentes com ACTUI apresenta bons resultados após cirurgia prévia para correção das alterações urológicas, apesar da frequência elevada de pielonefrites do enxerto.

Palavras-Chave: Alterações congénitas; pielonefrite; sobrevida do enxerto; transplante renal; trato urinário.

INTRODUCTION

Congenital abnormalities of the lower urinary tract (CALUT) cause 8-20% of paediatric end-stage renal disease (ESRD) and are one of the most frequent primary diagnoses among children subject to transplant¹. The spectrum of CALUT includes primary vesicoureteral reflux (VUR), neurogenic bladder, posterior urethral valves and other causes of bladder obstruction. Such conditions are occasionally associated with other congenital abnormalities outside the urinary tract². These children may progress to ESRD in adulthood and will be referred to adult nephrologists and urologists. Although they account for only a small proportion of adult renal transplant patients (about 6.5%)³, individuals with renal tract malformations represent a population with particular problems for which few long-term follow-up studies are available⁴.

In patients with CALUT requiring renal transplantation, the aim is to achieve continence and to establish

low-pressure voiding with no VUR. A bladder capacity of less than 100ml or voiding pressures above 100 cm H₂O may predispose to complications after transplantation⁵. Many of these patients may need augmentation cystoplasty. After reconstructive surgery, voiding mechanisms can remain intact or clean intermittent self-catheterization (CISC) can be used to drain urine. Transplantation draining into a urinary diversion is another option, although it requires a stoma and an external collecting device⁶.

Transplantation is achievable in most cases of CALUT, but there are questions regarding the indication for surgical procedures, as well as the frequency of complications, especially urinary tract infections (UTI) and their prophylaxis⁴.

We report our experience with renal transplant patients with secondary VUR and aim at describing the surgical management of malformations, graft survival, function and complications following transplantation.

MATERIAL AND METHODS

Between 2001 and 2015, 825 renal transplants were performed at the Transplant Unit of São João Hospital Centre in Porto. The records of all patients with CALUT followed at our institution were reviewed. We considered only secondary VUR and excluded primary VUR from our analysis because in the latter the mechanism of kidney damage was not always clear.

Eight patients were identified. We collected demographic, clinical and laboratory data from the hospital electronic and clinical registries. Urine microbiology cultures were performed after transplantation, initially once a week, then monthly and finally every 3 to 6 months.

Graft survival was calculated from the date of kidney transplant until the date of irreversible kidney failure with return to long-term dialysis. Time was calculated from the date of second transplant in our only case of this kind.

Five patients were male and three were female with an age range between 13 and 39 years at the time of transplant (mean 23.5 years). All of them had dysfunctional bladders with VUR and recurrent UTI. The causes of the urinary tract disorders included myelomeningocele associated with neurogenic bladder (three cases), posterior urethral valves (one case), neurogenic bladder and anal imperforation (one case), congenital megaureter (two cases) and idiopathic neuropathic bladder and sphincter dyssynergia (one case). Seven patients presented other malformations, such as

hydrocephalus, anal atresia, cardiac defects and aortic coarctation (Table I).

One patient received her second transplant after failure of the first graft due to chronic rejection, whereas all the others were first transplants. All but one patient received a kidney from a deceased donor. Renal transplantation was executed using a standardized technique: the renal artery and vein were anastomosed to the iliac vessels and the ureter was anastomosed into the native, augmented bladder or ileal conduit using an antireflux ureteroneocystostomy after positioning of a double J catheter. This catheter was removed by cystoscopy after 4 weeks. In order to guarantee a complete drainage, a bladder catheter was introduced and kept for 5 to 7 days following transplantation.

After renal transplantation, patients were mostly managed with tacrolimus-based immunosuppressive protocols in combination with prednisolone and mycophenolate mofetil.

RESULTS

Before transplantation, all patients underwent surgical interventions to preserve renal function or to prepare for transplant. Open nephrectomy of the native kidneys was performed unilaterally in one patient and bilaterally in another patient as an attempt to control recurrent UTI. One patient underwent endoscopic fulguration of posterior urethral valves followed by a second valve ablation. Six patients were subject to bladder augmentation to increase compliance,

Table I

Gender, age at transplantation, aetiology, associated anomalies and previous surgeries

Patient No. – Sex; age at transplantation	Diagnosis	Other	Surgery
1 – M; 20	PUV	Epilepsy, levocardia	2 PUV resection; UBA
2 – F; 30	Megaureter	Aortic coarctation, microcephaly	UR; 2 NP
3 – M; 28	NB	Mild cognitive impairment	Ileal conduit
4 – M; 22	NB	Myelomeningocele	UBA
5 – M; 25	NB	Myelomeningocele	UBA
6 – F; 18	NB	Myelomeningocele	UBA
7 – M; 39	Megaureter and megabladder	–	NP; partial cystectomy; UBA; UR
8 – F; 13	NB	Anorectal malformation	UBA

Abbreviations: PUV, posterior urethral valves; NB, neurogenic bladder; UBA, urinary bladder augmentation; UR, ureteral re-implantation; NP, nephrectomy.

capacity and limit its contractility before transplantation. Five cases used ileum and one used colon as the source of tissue for augmentation.

Clean intermittent self-catheterization to assure effective emptying was performed after bladder augmentation in five cases. In one patient, continent diversion was assured using an appendicovesicostomy (Mitrofanoff principle) with intermittent catheterization through the Mitrofanoff canal. One patient had a non-continent urinary diversion with ileal conduit and an external collecting pouch. Only one patient was able to control voiding using the Valsalva maneuver and did not require a stoma or catheter.

Urinary tract infections was the most common complication after transplantation. Six of the eight patients (75%) experienced at least one acute graft pyelonephritis (AGPN) episode during follow-up, accounting for 20 hospital admissions, representing 31 episodes per 100 patient-years of AGPN requiring hospitalization. Frequent bacterial colonization and multiple UTI were documented, *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae* being the most frequent agents. Apart from sulfamethoxazole/trimethoprim during the first 6 months, longer chemoprophylaxis for UTI was not routinely performed.

One patient, whose graft ureter had been implanted into the ileal segment of the augmented bladder, developed a ureteric stenosis soon after double J catheter removal, requiring temporary nephrostomy. Later, this stenosis recurred and a surgical ureteral re-implantation was necessary.

The mean follow-up duration was 104.4 ± 11.8 months. The 5- and 10-year graft survival was 100% and 62.5%, respectively. Three patients lost their grafts, 6, 9 and 10 years after transplantation. The reasons for graft loss were chronic pyelonephritis (one case) and interstitial fibrosis/tubular atrophy not considered related to recurrent AGPN (two cases). After graft failure, one native kidney open nephrectomy was performed to control recurrent UTI. The remaining five patients have functioning grafts 42 to 135 months after transplantation with mean serum creatinine of 1.17 ± 0.40 mg/dl (78.0 ± 30.0 ml/min/1.73m² of estimated glomerular filtration using the Modification of Diet in Renal Diseases equation).

No deaths occurred among the eight patients.

DISCUSSION

In general, the eight renal transplant patients with secondary VUR followed at our Centre after renal transplantation achieved excellent long-term graft and patient survival rates. According to the Spanish Renal Forum Database, relative to the period from 2000 to 2002, death-censored 5-year graft survival reported for patients under 40 years of age was 88%⁷. Our patients showed increased graft survival (100% and 62.5% at 5 and 10 years, respectively), which could be explained by the specific characteristics of our population, including a lower burden of cardiovascular disease and diabetes. As for the 5-year patient survival, it was 100% in our series, comparable to the 97.4% reported for patients under 40 years of age in the same Spanish series⁷.

The optimal treatment of patients with neurogenic bladder and ESRD is controversial. Good results have been reported for kidney transplantation done into abnormal bladders, as long as dysfunctions had been detected and corrected previously⁸. Bladder capacity, compliance, continence and emptying are important parameters to be considered. These patients should receive a complete evaluation of the urinary tract including ultrasonography, micturating cystourethrogram, uroflow and urodynamic studies⁹. Bladder cycling could also be useful to distinguish between high bladder pressure due to transient dysfunction in oligoanuric patients and pre-existing anomalies needing surgical correction¹⁰. In non-compliant bladders, augmentation cystoplasty (using the ureter or intestinal segments as the source of tissue for enlargement) should be considered as a safe and effective method to restore function⁸. Otherwise, as occurred for the native kidneys, the renal allograft might subsequently be threatened. Cystoplasty should be done at least 8 to 12 weeks before transplantation since immunosuppression impairs the healing of the augmented bladder¹¹.

In our series, only one patient had normal voiding. Five patients were instructed to perform CISC so as to prevent high-pressure reflux into the graft or residual urine after voiding which might favour UTI. The CISC is indicated for cooperative patients with normal urethras. It is usually atraumatic and requires basic antiseptic measure and application of lubricant⁹. When CISC is not possible, a Mitrofanoff stoma for suprapubic drainage can be used, as occurred in one

patient. Non-continent strategies, such as an ileal conduit are other alternatives with good results^{6,12}.

Patients with a conduit or augmentation cystoplasty are normally colonized with bacteria and show a higher risk of UTI after kidney transplantation¹³. In fact, in our series we report a rate of pyelonephritis about 6 times greater than described for a general renal transplant population where the incidence rate of AGPN was of 4.4 episodes per 100 patient-years^{14,15}. Graft loss due to chronic pyelonephritis (1 of the 3 graft losses – 33%) was also considerably higher than described for other transplant patients, where this cause represented 4.5% of all graft losses^{3,14}.

The use of prophylactic antibiotics on a long-term basis has been shown to minimize the risk for UTI, although most recommendations for prevention and therapy of UTI are based on small series^{16,17}. All our patients are on sulfamethoxazole/trimethoprim prophylaxis for at least 6 months. Asymptomatic bacteriuria was very common and treatment has not shown any clear benefit¹⁸.

Other complications described for patients with augmented bladders, such as bladder or upper urinary tract stones¹⁹, a higher risk of bowel adenocarcinoma²⁰ and electrolyte abnormalities due to intestinal secretions, were not identified in our series.

Transplantation into an otherwise normally functioning lower urinary tract, such as in primary VUR, may also carry an increased frequency of UTI. Comparison of transplant outcomes between patients with primary and secondary VUR would be an interesting future analysis.

CONCLUSION

Renal transplantation is the treatment of choice for selected patients with ESRD. Our results have shown that renal transplantation in patients with CALUT is feasible after careful urologic evaluation, surgical correction of poorly compliant and high-pressure bladders when indicated. This strategy has revealed good results despite a much higher frequency of urinary tract infectious complications.

Disclosure of Potential Conflicts of Interest: None declared.

References

1. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol* 2012;27(3):363–373.
2. Toka HR, Toka O, Hariri A, Nguyen HT. Congenital anomalies of kidney and urinary tract. *Semin Nephrol* 2010;30(4):374–386.
3. El-Zoghby ZM, Stegall MD, Lager DJ, *et al.* Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009;9(3):527–535.
4. Sullivan ME, Reynard JM, Cranston DW. Renal transplantation into the abnormal lower urinary tract. *BJU Int* 2003;92(5):510–515.
5. Serrano DP, Flechner SM, Modlin CS, Wyner LM, Novick AC. Transplantation into the long-term defunctionalized bladder. *J Urol* 1996;156(3):885–888.
6. Surange RS, Johnson RW, Tavakoli A, *et al.* Kidney transplantation into an ileal conduit: a single center experience of 59 cases. *J Urol* 2003;170(5):1727–1730.
7. Morales JM, Marcén R, del Castillo D, *et al.* Risk factors for graft loss and mortality after renal transplantation according to recipient age: a prospective multicentre study. *Nephrol Dial Transplant* 2012;27 (Suppl 4):iv39–46.
8. Nahas WC, Mazzucchi E, Arap MA, *et al.* Augmentation cystoplasty in renal transplantation: a good and safe option-experience with 25 cases. *Urology* 2002;60(5):770–774.
9. Mishra SK, Muthu V, Rajapurkar MM, Desai, MR. Kidney transplantation in abnormal bladder. *Indian J Urol* 2007;23(3):299–304.
10. Errando C, Batista JE, Caparros J, Araújo P, Villavicencio H. Is bladder cycling useful in the urodynamic evaluation previous to renal transplantation? *Urol Int* 2005;74(4):341–345.
11. Taghizadeh A, Mahdavi R, Mirsadraee S, Ghorbani HR, Patel HR. Ureterocystoplasty is safe and effective in patients awaiting renal transplantation. *Urology* 2007;70(5):861–863.
12. Warholm C, Berglund J, Andersson J, Tydén G. Renal transplantation in patients with urinary diversion: a case-control study. *Nephrol Dial Transplant* 1999;14(12):2937–2940.
13. Pereira DA, Barroso U Jr, Machado P, *et al.* Effects of urinary tract infection in patients with bladder augmentation and kidney transplantation. *J Urol* 2008;180(6):2607–2610; discussion 2610.
14. Fiorante S, Fernández-Ruiz M, López-Medrano F, *et al.* Acute graft pyelonephritis in renal transplant recipients: incidence, risk factors and long-term outcome. *Nephrol Dial Transplant* 2011;26(3):1065–1073.
15. Giral M, Pascuariello G, Karam G, *et al.* Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney Int* 2002;61(5):1880–1886.
16. Maki DG, Fox BC, Kuntz J, Sollinger HW, Belzer FO. A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation. Side effects of trimethoprim-sulfamethoxazole, interaction with cyclosporine. *J Lab Clin Med* 1992;119(1):11–24.
17. Giessing M. Urinary tract infection in renal transplantation. *Arab J Urol* 2012;10(2):162–168.
18. Coussement J, Abramowicz D. Should we treat asymptomatic bacteriuria after renal transplantation? *Nephrol Dial Transplant* 2014;29(2):260–262.
19. Kronner KM, Casale AJ, Cain MP, Zerlin MJ, Keating MA, Rink RC. Bladder calculi in the pediatric augmented bladder. *J Urol* 1998;160(3 Pt 2):1096–1098; discussion 1103.
20. Soergel TM, Cain MP, Misseri R, Gardner TA, Koch MO, Rink RC. Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. *J Urol* 2004;172(4 Pt 2):1649–1651; discussion 1651–2.

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