Vesicoureteral reflux after kidney transplantation in children

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Abstract

Background. The prevalence and significance of vesicoureteral reflux (VUR) after kidney transplantation in adults varies between authors and there have been few reports in children.

Methods. We conducted a retrospective study in a single-centre paediatric cohort. Fifty-five of the 84 children who underwent kidney transplantation over a 5-year period were checked with routine cystography after a median of 8 months post-transplantation. Graft function and urinary-tract infections were assessed during the first 6 years after transplantation.

Results. VUR into the graft was present in 58% of the patients. Graft function and incidence of urinary-tract infections were similar in the two groups, independent of VUR. After having excluded infections attributed to the presence of a catheter, actuarial survival rates without pyelonephritis and without pyelonephritis following a first lower urinary-tract infection were worse in patients with VUR (P = 0.017 and P = 0.0039 respectively). None of the eight patients with VUR treated with antibiotic prophylaxis after a first acute pyelonephritis (APN) episode presented subsequent APN after 4.4 ± 3.3 years on therapy.

Conclusions. VUR to the graft occurred in more than half paediatric renal transplant recipients. This condition was associated with an increased risk of APN. Long-term antibiotic prophylaxis seems to be able to prevent APN in transplanted children with VUR.

Keywords: child; kidney transplantation; renal function; urinary-tract infection; vesicoureteral reflux

Introduction

Vesicoureteral reflux (VUR) is a risk factor for acute pyelonephritis (APN) [1], and has been claimed to be responsible for 2.7% of end-stage renal disease in childhood [2]. Its prevalence and significance after kidney transplantation (Tx) in adults varies between authors [3–7] and there have been only a few reports in children [8–10]. We therefore conducted a retrospective study in a single paediatric centre.

Subjects and methods

Excluded patients

Among 84 patients who received a kidney transplant between April 1987 and August 1992, 29 were excluded because of enterocystoplasty (n=3), follow-up in another centre (n=9), graft failure (n=10), death (n=2), absence of voiding films (n=4, without VUR), cystography refusal (n=1).

Recipients and donors

Fifty-five patients were finally enrolled in the study. The characteristics of recipients and donors are listed in Table 1. The urinary anastomoses consisted of 54 ureteroneocystostomies (49 using extravesical approach according to Depyle et al. [11] and five using intravesical Politano-Leadbetter technique [12]) and one ureteroureteral anastomosis. A urethral catheter was left for 5 days. Patients received three doses of prophylactic cefotiam (50 mg/kg), prior to surgery and 8 h afterwards, then at the time of catheter removal. A sequential protocol using rabbit antithymocyte globulin, azathioprine, prednisone, and delayed cyclosporin A was used [13].

Assessment of vesicoureteral reflux

VUR was assessed by direct contrast cystography (C) performed after a median of 8 months post-Tx (0.4–54). Recipients were routinely investigated 6–36 months after the operation, or earlier in case of urinary leak or APN. VUR was classified into two groups: those with and those without ureteral dilatation. The absence of urinary-tract infection (UTI) was checked prior to C by urinary dipstick (Multistix® 8SG) and patients received antibiotic prophylaxis from the day before to 5 days after C. The bladder was filled (1 m contrast medium column) using urethral catheterization with...
a flexible, 2-mm-wide tube without balloon. Contrast medium (Telebrix® 12 sodium) was previously warmed. Bladder filling was stopped as soon as the child had a voiding call. Voiding was obtained during the examination in 53 cases (including the patient with ureterooureteral anastomosis).

**Urinary-tract infection**

UTI was defined by the presence of $\geq 10^5$ colony-forming units per millilitre of bacteria (one single species) together with leukocyturia. Urine culture was obtained from either urine bag or midstream sample when (i) dipstick (leukocytes, nitriles) was positive, (ii) fever was present, (iii) anamnesis suggested UTI. Urinalysis using dipstick was routinely checked during follow-up, i.e. every day during initial hospitalization (mean duration 18 days), then three times weekly during the 1st month, twice weekly during the 2nd month, every week by the 6th month, twice monthly by the 9th month, every 3 weeks by 1 year, every month by 2 years, and every 2 months thereafter. APN was defined as the association of UTI and fever $\geq 38^\circ$C. UTI could be related to urethrovescical or ureteral catheterization when it occurred at the time of tube removal and during the 3 following days. Increased serum creatinine was relevant when it was 10% greater than initial concentration, and was considered secondary to infection when no other cause was demonstrated.

**Graft function**

GFR was assessed by inulin clearance 6 and 12 months after Tx and every year thereafter, as described previously [13]. In order to assess the role of VUR on graft function, we selected 23 recipients from cadaver donors followed for more than 5 years. Among the 55 patients, 32 were excluded: 11 recipients from living related donor, 18 patients followed for less than 5 years (two deaths from sepsis without UTI, one de novo membranous nephropathy, 13 patients followed in another centre, two children transplanted less than 2 years ago) and three patients who missed more than one GFR assessment. In six patients who missed one GFR assessment, an estimation was provided by interpolation of previous and subsequent measurements.

**Statistics**

Results were expressed as mean ± standard deviation (median; range). The $\chi^2$ or Fisher’s exact tests were used to correlate the presence of VUR with various parameters. Actuarial survival curves were compared by the log-rank test.

**Results**

**Prevalence of vesicoureteral reflux**

A VUR into the graft was diagnosed on the first C with voiding film in 30/52 patients (58%) with uretero-neocystostomy; ureteral dilatation was associated in 17 of them. Among the 47 patients with extravesical surgery, a VUR was present in 28 (60%), together with ureteral dilatation in 16. A VUR was diagnosed by C without voiding films in two other patients with extravesical ureteroneocystostomy. The patient with uretero-ureteral anastomosis presented a VUR to the graft.

C was repeated 1.8–7.9 years later in six patients without VUR at the first examination: five of them remained free of VUR. Four patients with VUR underwent repeated C 6–23 months after the first one which showed persistent VUR in all. A VUR to the native kidneys was present in eight cases (including three patients with VUR to the graft).

**Risk factors for vesicoureteral reflux**

Among the 49 patients with extravesical anastomosis, no risk factor was significantly associated with the presence of VUR (Table 2).
Table 2. Risk factors of vesicoureteral reflux (VUR), among the 49 patients with extravasical ureteroneocystostomy

<table>
<thead>
<tr>
<th>Patients</th>
<th>With VUR</th>
<th>Without VUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>19/32 (59%) 13/32 (41%)</td>
<td>11/17 (65%) 6/17 (35%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.9 ± 4.6 10.0 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Primary disease</td>
<td>Urinary tract malformation 13/21 (62%) 8/21 (38%)</td>
<td>Glomerulonephritis and HUS 14/19 (74%) 5/19 (26%)</td>
</tr>
<tr>
<td>Other</td>
<td>3/9 6/9</td>
<td></td>
</tr>
<tr>
<td>Time on dialysis (years)</td>
<td>1.2 ± 1.6 0.6 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Diuresis prior to Tx (ml/kg/day)</td>
<td>23 ± 27 33 ± 34</td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>Cadaver 26/41 15/41</td>
<td>Living related 4/8 4/8</td>
</tr>
<tr>
<td>Ischaemia time</td>
<td>cold (hours) 17.8 ± 10.1 14.1 ± 10.6</td>
<td>warm (min) 26 ± 8 29 ± 5</td>
</tr>
<tr>
<td>Acute rejection episodes prior to cystography (mean per patient):</td>
<td>0.83 (n=29) 0.81 (n=16) 0.93 (n=15) 0.88 (n=8)</td>
<td></td>
</tr>
<tr>
<td>3 first months after Tx</td>
<td>0.83 (n=29) 0.81 (n=16)</td>
<td></td>
</tr>
<tr>
<td>6 first months after Tx</td>
<td>1.00 (n=15) 0.93 (n=15)</td>
<td></td>
</tr>
<tr>
<td>12 first months after Tx</td>
<td>1.00 (n=15) 0.88 (n=8)</td>
<td></td>
</tr>
<tr>
<td>Time to cystography (months)</td>
<td>17 ± 16 12 ± 13</td>
<td></td>
</tr>
</tbody>
</table>

P = non significant; HUS, haemolytic-uraemic syndrome; Tx, transplantation.

Vesicoureteral reflux and urinary-tract infection

Thirty-three of 55 patients (60%) suffered from UTI during a mean follow-up of 4.6 years, the first episode occurring mostly early after Tx (Figure 1). There was no difference between patients with and those without VUR, 15/33 and 7/22 respectively (n.s.) with comparable follow-up: 4.3 ± 2.6 (4.6; 0.2–9.1) and 5.3 ± 2.3 (5.3; 2.7–8.9) years respectively.

Eighteen of 55 patients (33%) experienced at least one APN episode, 13/33 (39%) with VUR and 5/22 (23%) without VUR (n.s.). Five patients (three with VUR) had recurrent APN.

Among the five patients without VUR who presented at least one APN episode, infection was related to the presence of a catheter in three children. All 13 patients with VUR and ≥1 APN presented at least one episode more than 3 days after removal of any catheter. After excluding episodes related to catheterization, the proportion of patients who presented at least one APN episode was higher in the group with VUR (P = 0.0155, Fisher’s exact test); the survival rate without APN and the survival rate without APN after a first lower-urinary-tract UTI were worse in the presence of VUR (Figures 2, 3).

Among the eight patients with VUR to native kidneys, three presented at least one APN (two of these three patients had no VUR to the graft).

Graft function

There was no influence of VUR on graft function among the 23 children studied (Figure 4). Mean glomerular filtration rate did not decrease during the 5 years of follow-up in the subgroup of seven patients with APN (independent of VUR).

Vesicoureteral reflux management

No patient was proposed to surgery. Three children underwent endoscopic treatment: VUR persisted but ureteral dilatation disappeared in two of them. Eight patients with VUR were given prophylactic nitroxoline or nitrofurane following APN: none of them experienced subsequent APN after 4.4 ± 3.3 (4; 0.4–11.9) years on therapy. None of the three patients with VUR and recurrent APN was under prophylactic treatment at the time of the second episode. Antibiotic prophylaxis was not started after the first episode in
Fig. 2. Actuarial survival rate free of APN in the absence of urinary catheter in the two groups, i.e. with and without VUR.

Fig. 3. Actuarial survival rate without APN (in the absence of urinary catheter) after a first UTI without fever in patients with and without VUR.

two cases and discontinued after 2.5 months in the third case.

Discussion

Occurrence of vesicoureteral reflux

The reference assessment of VUR is direct contrast cystography, which enables grading [1]. We limited the classification into two groups according to ureteral dilatation, because of ureteral hypotonia and ectopic position of the transplanted kidney, which might interfere with VUR grading.

When routinely checked, the frequency of VUR to the graft has been studied in only two paediatric centres: 24/67 (36%) [8,9] and 25/73 (34%) [10]. Such prevalence varies from 2 to 86% in adults [14,15]. The presence of VUR may depend on the timing of its assessment, whereas we had previously speculated that it was an intrinsic condition. The procedure of ureteral anastomosis may also influence the risk of VUR [3,8,14]. In a prospective randomized study [16], VUR was less frequently reported when Leadbetter–Politano’s technique was used. Nevertheless, the extravesical approach is preferred by most surgeons since (i) post-operative complications are less frequent, (ii) it enables the use of short
harvested ureter, and (iii) operative time is shorter. An immunological participation has been suggested but without any further confirmation [3,4,15]. In our population, we failed to show any risk factor significantly associated with VUR (Table 2).

The greater number of patients with VUR in our study could be explained by the young age of the recipients, as only one-third of adult recipients transplanted by the same surgical team using the same techniques presented a VUR [17].

Vesicoureteral reflux and urinary-tract infection

UTI is a common feature after kidney Tx, as an average 60% of patients experienced at least one episode [3,18]. The first UTI is usually observed soon after Tx and the incidence of a first episode further decreases with time after Tx [4,14,15]; this was confirmed by our results (Figure 1). Different risk factors for post-Tx UTI have been outlined: female gender [14], ESRD due to posterior urethral valves [19], diabetes [14,20], urinary catheterization [20]. This risk has been shown to be lowered by using antibiotic prophylaxis [20] but the presence of VUR does not increase the frequency of UTI after Tx [3–6,9,10,14,15,17,18].

Post-Tx APN is a rare event in adults and seems more frequent in children (Table 3); however, its definition varies among authors and all published series are retrospective. APN was particularly frequent in our population, since one-third of patients presented at least one episode. The young age of our patients could be one reason for such a high rate [21]: 18/55 of our patients were transplanted before the age of 7 years. A body temperature of 38.5°C has been proposed for diagnosing APN [9]; that might be controversial [8,18,21–24]. On the basis of a 38.5°C temperature threshold, we would have excluded only one APN episode in a patient who suffered from another episode with fever >38.5°C. Immunosuppression may actually underestimate inflammatory reaction in transplant patients with parenchymal invasion during UTI [25]. Hanevold et al. [8] excluded APN in the absence of acute renal dysfunction, which was present in 52–100% of the cases for others (Table 4).

While VUR is considered as a risk factor for APN in the general population, its role in the pathogenesis of APN in transplanted patients is still debated. It has been associated with an increased risk of APN in one pediatric study [9] and one adult cohort [26]. However, Thomalla et al. [23] found no VUR in 18 adult transplant patients with APN, which was confirmed by another study [6]. In our series, VUR into the graft was associated with APN after exclusion of episodes related to catheterization.

Vesicoureteral reflux, acute pyelonephritis, and graft function

VUR was associated with a worse graft survival in two series [3,5], which was not confirmed by other authors on the basis of serum creatinine, creatinine clearance, and graft survival [4,6,7,10]. A persistent increase in serum creatinine has been observed after 10–33% of APN episodes. In our series this proportion was 8% (2/25) (Table 4), but we failed to demonstrate any decline in the mean GFR during the first 5 years post-Tx in the group of patients with APN.

Vesicoureteral reflux management after transplantation

Long-term continuous prophylaxis was sufficient in most cases [9,10]. Only few patients have been successfully managed with open surgery [3,9,10,21] and

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Fig. 4. Glomerular filtration rate determined by inulin clearance (mean, SD) in the two groups: —— with (n=15); — – without (n=8) vesicoureteral reflux to the graft.
endoscopic treatment has been efficient in only 29% of transplant patients [27]. None of our patients have been treated surgically because of (i) the apparent efficacy of antibiotic prophylaxis and (ii) the risk of surgical treatment. Indeed Neuhaus et al. [21] reported transient functional obstruction and persistent increased serum creatinine in 3/5 children who underwent surgery.

In summary, VUR into the graft was diagnosed in 58% of transplanted children at our centre. This condition was associated with frequent episodes of APN (39% of patients), while the incidence of both lower UTI and graft dysfunction was not increased. Cystography is no longer routinely performed after transplantation, but it should be done after a first UTI. Due to the increased risk of APN after a first lower UTI in case of VUR, long-term antibiotic prophylaxis should be proposed in patients with VUR after a first UTI.

Acknowledgements: The authors thank Mrs Patricia Darnand for her assistance in statistics, and Mrs Gabrielle Gervézie for reviewing the English wording.

References

8. Hanevold CD, Kaiser BA, Palmer JA, Polinsky MS, Baluartetion was associated with frequent episodes of APN (39% of patients), while the incidence of both lower UTI and graft dysfunction was not increased. Cystography is no longer routinely performed after transplantation, but it should be done after a first UTI. Due to the increased risk of APN after a first lower UTI in case of VUR, long-term antibiotic prophylaxis should be proposed in patients with VUR after a first UTI.

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References


Table 3. Acute pyelonephritis after kidney transplantation: review of the literature

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th>Transplantations (n)</th>
<th>Mean follow-up (months)</th>
<th>Acute pyelonephritis Patients (%)</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prat 1985 [18]</td>
<td>299</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Pearson 1980 [22]</td>
<td>1100</td>
<td>NA</td>
<td>15 (1.4)</td>
<td>20</td>
</tr>
<tr>
<td>Thomalla 1988 [23]</td>
<td>800</td>
<td>NA</td>
<td>18 (2.2)</td>
<td>21</td>
</tr>
<tr>
<td>Zaontz 1988 [24]*</td>
<td>166</td>
<td>NA</td>
<td>7 (4.2)</td>
<td>10</td>
</tr>
<tr>
<td>Hanevold 1987 [8]*</td>
<td>56</td>
<td>30</td>
<td>5 (8.9)</td>
<td>≥11</td>
</tr>
<tr>
<td>Dunn 1987 [9]*</td>
<td>67</td>
<td>NA</td>
<td>11 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Neuhaus 1997 [21]*</td>
<td>41</td>
<td>NA</td>
<td>6 (14.6)</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 4. Changes in serum creatinine (Scr) associated with acute pyelonephritis (APN)

<table>
<thead>
<tr>
<th>Author, year (Reference)</th>
<th>APN episodes</th>
<th>Increased Scr episodes patients (%)</th>
<th>Persistent increase in Scr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson 1980 [22]</td>
<td>20</td>
<td>11 (55)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Thomalla 1988 [23]</td>
<td>21</td>
<td>15 (71)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Neuhaus 1997 [21]</td>
<td>9</td>
<td>9 (100)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Present study</td>
<td>25</td>
<td>13 (52)</td>
<td>2 (8)</td>
</tr>
</tbody>
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