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ORIGINAL ARTICLE

Complications and long-term outcome of primary obstructive megaureter in childhood

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Abstract We assessed the clinical outcome of 49 children with 56 primary obstructive megaureters (POM) treated with the primarily conservative approach recommended by the 2001 German consensus guidelines. POM occurred more often in boys (71%) and on the left side (67%). Forty-three POM (77%) were treated conservatively. Four kidneys underwent immediate surgery and nine of 52 kidneys managed primarily conservatively worsened subsequently, requiring surgery. Urinary tract infections (UTI) were the most common complication (mean 1.3 per patient), with frequent hospital admission (45%). During the first year of life, the incidence of UTIs was 55% less during prophylactic antibiotic treatment (0.94 vs.0.42 UTIs per year, $p<0.05$). Spontaneous regression occurred in 80% of POMs with dilated non-obstructive renogram, but in <20% with intermediate or relevant obstruction. All megaureters with <8.5 mm sonographic diameter regressed, but none over 15 mm. Eight patients had a poor outcome (partial kidney function <40% ($n=6$), renal atrophy ($n=3$)), but in seven of the patients, these findings were already present postnatally. In summary, the long-term outcome of POM appears favorable with mainly conservative treatment. UTI as the most common complication was 55% lower with antibiotic prophylaxis in infants. Adverse outcome was more closely related to congenital kidney hypoplasia than to degree of obstruction.

Keywords Primary obstructive megaureter · Hydronephrosis · Uretero-vesical junction obstruction · Urinary tract infection · Antibiotic prophylaxis · Diuresis renography · Renal ultrasound

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Introduction

Ureteric obstruction is one of the most common presentations of infants in pediatric nephrology and urology. Congenital dilatation of the ureter (megaureter) in the absence of primary vesico-ureteric reflux or subvesical obstruction is termed primary obstructive megaureter (POM) [1] or vesico-ureteric junction obstruction (although relevant obstruction may not always be present). POM is the second most common form of ureteric obstruction in newborns [2] with an incidence of about 0.36 of 1,000 live births [3].

Historically, before routine prenatal ultrasound screening, most children presented as toddlers with urinary tract infection (UTI), abdominal pain, hematuria, or urolithiasis

in later life [2, 4, 5]. Surgical therapy was performed in most cases. With modern ultrasound techniques, about 40% of POMs are discovered prenatally [6] and the fraction of symptomatic children decreased to 22–50% [7, 8]. In the 1990s, several reports documented the high rate of spontaneous regression of prenatally diagnosed POM [7, 9–13]. Even though chronic renal failure has been described in rare cases of adults with bilateral POM [14], the lack of functional impairment of the great majority of kidneys with POM is an additional argument for taking a conservative approach [15].

In Germany, an important step towards harmonization of treatment was made by the 2001 consensus paper on the investigation and treatment of congenital urinary tract obstruction (Beetz et al. for the German Societies of pediatric nephrology (GPN), urology (DGU) and pediatric surgery (DGKIC) [15]). The consensus paper recommends a differentiated conservative approach, where operations are advised only after proven relevant obstruction on MAG3 isotope scan or in case of major complications. There are few studies examining the long-term outcome of patients with mainly conservative treatment [16–18] and no studies on the specific management approach of the consensus paper yet. In the largest POM outcome study published to date, which included 78 patients followed-up over an average period of 6.5 years, 85% of cases were still treated surgically [5].

The aim of this study is therefore to evaluate the long-term prognosis of children managed with the proposed primarily conservative approach, and to identify clinical and imaging study predictors of adverse outcome.

Patients and methods

Patients

We examined the records of all patients who were treated for obstructive uropathies between 1994 and 2006 in the pediatric nephrology clinic at the University Children's Hospital Heidelberg. Operations were performed at the Department of Urology at University Hospital Heidelberg. Of 151 patients with megaureters, we excluded those with secondary megaureters (e.g. urethral valves, Prune-Belly syndrome, megaureters with both obstruction and reflux and ureteroceles (n=29)) as well as congenital megaureters that were not obstructive (i.e. only type A on diuresis renogram, n=9). Patients with duplicated kidneys or duplicated ureters were also excluded (n=7) as the different underlying anatomy implies different rates of spontaneous regression. Since a number of patients were seen only once for a second opinion, only patients who were followed-up for at least 1 year and who had at least one ultrasound and one renal isotope scan were analyzed (this excluded another 47 patients). Ten patients had to be excluded due to missing records. Hence, data from 49 patients with 56 renal units affected by POM are presented here.

Forty-one children had imaging studies to exclude vesicoureteric reflux (voiding cystourography in boys and voiding urosonography in girls). No renal unit with POM also showed vesicoureteric reflux. Two children had reflux on the contralateral side and were excluded from the analysis of urinary tract infections to avoid bias.

Clinical and imaging data were taken from medical records. Glomerular filtration rate was estimated according to the Schwartz formula [19]; serum creatinine values during the first 3 days of life were excluded. Height standard deviation scores (SDS) were calculated using the normative values of Prader et al. [20].

Imaging studies

Interpretation of imaging studies was made from the original radiologists' reports. Where reporting of examinations was not detailed enough, the original images were evaluated. Per patient, a mean of 6.4±3.3 ultrasound examinations and 2.9±2.2 diuresis renograms were available.

Ultrasound

In accordance with the consensus paper, ultrasound examinations taken during the first 4 days of life were excluded due to physiological oliguria, which can mask obstruction of the ureters [15], and dilatation of the renal pelvis was graded according to Hofmann [21]. The width of the megaureter was measured at the level of the bladder while there was no peristaltic wave. As renal width is falsely elevated by hydronephrosis, renal length rather than volume was taken to assess kidney growth. To standardize for normal growth, kidney volume and length are also expressed as percent of expected (mean) based on the normal values by Dinkel et al. [22].

MAG 3 diuresis renography

Dynamic renography using 99mTc-MAG3 was performed only if intrarenal pelvis was dilated to >15 mm or to 12–15 mm with grade II dilatation of the renal pelvis/calyces [23]. Renographies were performed by the Department of Nuclear Medicine at the University Hospital Heidelberg, according to the guidelines of the European Association of Nuclear Medicine (EANM) usually at 6 weeks of age, and no earlier than 4 weeks [23]. Twenty minutes after application of the MAG3 i.v., furosemide was administered at 1 mg/kg body weight for infants and 0.5 mg/kg body weight for older children (max. 40 mg). A bladder

catheter was not routinely inserted. The grading of obstruction seen on renography was based on O'Reilly (see Fig. 1) [24]. Partial renal function was considered reduced when <45%.

Follow-up

Regression of a POM was defined by a normal diuresis renogram (type A) on follow-up or disappearance of hydronephrosis and megaureter on ultrasound in the cases without follow-up renogram. Adverse clinical outcome was defined as either reduced global renal function (estimated GFR<90 ml/min*1.73 m^2), renal atrophy on ultrasound (kidney length or volume <65% expected), reduced partial function on MAG3 renogram (<45%), loss of the kidney by nephrectomy, or renal hypertension.

Statistics

Data were analyzed with SAS 9.1 (SAS Institute, Cary NC, USA). Mean values are given as mean±standard deviation (SD). For correlations of continuous variables, Spearman's rank order correlation coefficient is given. Continuous variables were compared using Student's *t* test and categorical variables with the χ^2 test. Incidence rates (of urinary tract infections) were compared using the binomial test. Statistical significance was assumed when *p* was less than 0.05. Survival analysis was performed using the Kaplan Meier product limit method.

Results

The characteristics of the 47 children with 56 POMs analyzed subsequently are shown in Table 1. The mean duration of follow-up was 47±30 months (12 to 78 months). There were significantly more boys (n=35, 71%) than girls (p<0.01), and unilateral POMs occurred more often on the left side (n=35, 67%, p<0.05).

Two patients (4%) had pelvico-ureteric junction (PUJ) obstruction on the same side as POM. A total of 24% had urological pathology on the contralateral side, including seven patients with bilateral POM. Five patients had extrarenal anomalies, including ear tags (n=2), bilateral non-descended testes, rudimentary inguinal testis, dermal sinus, tracheomalacia and aortic aneurysm (n=1 each).

Twenty patients (41%) were diagnosed prenatally and 18 (37%) were discovered incidentally on ultrasound examinations for other reasons. Of the 11 patients that presented with symptoms, ten (20%) suffered a UTI and one had abdominal pain. Symptomatic patients presented mainly before their first birthday; the mean age of diagnosis in the cases that were not discovered prenatally was 10± 19 months (1 week–77 months).

At presentation, all children had normal height, weight, serum creatinine (mean 35±9 µmol/l (18–71)) and estimated creatinine clearance (mean 109±31 ml/min*1.73 m^2). Only one child had elevated blood pressure (125/75 mmHg, when 95th percentile for age and height was 110/74 mmHg), all others were normotensive however with

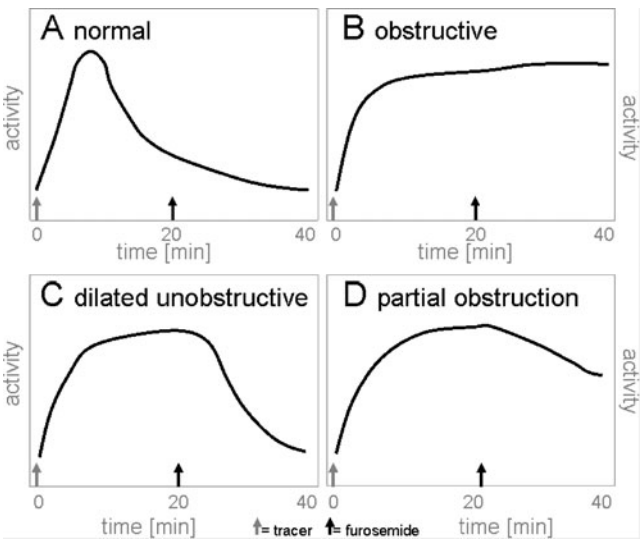

Fig. 1 Classification of renal obstruction on diuresis renography according to O'Reilly [24]: type A—normal, type B—obstructive, type C—dilated unobstructive, type D—intermediate/partial obstruction. ⇧=tracer ⇧=furosemide

Table 1 Patient characteristics

		Patients n=49	Ureters n=56
Male		35 (71%)*	41 (73%)*
Side	Left	28 (67%)**	35 (63%)
	Right	14 (33%)	21 (38%)
	Bilateral	7 (14%)	
Positive family history		15 (31%)	18 (32%)
Extrarenal anomalies		5 (10%)	6 (11%)
Other urological abnormalities			
Ipsilateral side			
	Renal hypo-/dysplasia	4 (6%)	4 (5%)
	PUJ obstruction	2 (2%)	2 (4%)
Contralateral side			
	POM	7 (14%)	14 (25%)
	PUJ obstruction	2 (4%)	2 (4%)
	VUR	2 (4%)	2 (4%)
	Renal agenesis	1 (2%)	1 (2%)

PUJ pelvi-ureteric junction, *POM* primary obstructive megaureter, *VUR* vesico-ureteric reflux; *p<0.01 (boys vs. girls), **p<0.05 (left vs. right in unilateral disease)

mean 90±18 mmHg systolic and 61±14 mmHg diastolic blood pressure.

The most common complication was urinary tract infections (UTI), which were observed 66 times in the whole group. In-patient care was required for 30 UTIs (45%), and 46 (70%) were febrile. The two children with contralateral VUR had one and two UTIs, respectively, and were excluded from further analysis to avoid bias. Only 14 children (30%) never suffered a UTI and 17 children (36%) had more than two episodes. Seventeen (36%) children required one or recurrent hospital admissions due to UTIs. All but two children with a UTI had investigations to exclude VUR on the contralateral side (a girl with first afebrile UTI at age 15 years with POM since birth, and a boy of 4 months with a single febrile UTI).

The rate of UTIs was highest in the under-1-year-olds (48% of children observed during the first year) despite prophylaxis in a subgroup of these. However, among 1 to 2-year-olds, 33% also suffered a UTI, compared to only 13% of 2 to 3-year-olds and 19% of over-3-year-olds. The 27 UTIs in under-1-year-olds were often febrile (n=18, 67%) and required in-patient care (n=16, 60%). Children with a prenatal diagnosis did not suffer from more UTIs, but their UTIs occurred at a younger age than patients with postnatal diagnosis (0.9±1.4 vs. 8.4±15 months, p=0.01). The degree of obstruction on diuresis renogram did not predict the incidence of UTIs.

Out of 44 children studied during the first year of life, 30 received antibiotic prophylaxis. Seven UTIs occurred during 199 patient months with prophylaxis compared to 19 UTIs during 244 patient months without prophylaxis, corresponding to a reduction of UTI incidence by 55% attributable to prophylaxis (0.94 vs. 0.42 UTIs per year, $p<$ 0.05). Prophylaxis appeared particularly effective in the first 6 months of life, where an 83% reduction of UTI rate was found. About two-thirds of children with prophylaxis received a second-generation cephalosporin (cefaclor, 63%), while 32% received trimethoprim and 5% nitrofurantoin. Prophylactic antibiotics were stopped at a mean age of 1.4±1.3 years (0.5 months to 6 years). In the second and third year of life, only 38% and 21% of children received antibiotic prophylaxis, respectively. UTI incidence was still surprisingly high (0.46 UTIs/year) without prophylaxis in the second year of life, but decreased sharply after the second birthday to 0.14 UTIs/year.

Initial ultrasound findings showed mild abnormalities in most children. Mean pelvic width was 14.2±5 mm (7 to 26), calyceal width 5.7±1.6 mm (3 to 9) and diameter of megaureter 11.5±5 mm (4 to 24). Hydronephrosis was mainly grade II (n=39, 70%) and I (n=10, 18%), with only few grade III (n=5, 9%) and IV dilatations (n=1, 2%). One POM presented without hydronephrosis but was still dilated unobstructive on renogram. Sixteen renal units showed initial abnormalities of parenchymal differentiation on ultrasound. Mean kidney volume at first examination was elevated due to hydronephrosis (mean 130±48% of expected; range 64–265), but renal length was less affected (mean 107±13% of expected; range 88–135). The degree of hydronephrosis was not correlated to the width of the megaureter. Only two of the 11 renal units with a large megaureter (>10 mm) also had a high degree of hydronephrosis (grade III).

With follow-up of the degree of hydronephrosis, the width of the megaureter and the dilatation of the renal pelvis improved in the whole group and renal size increased steadily. In order to sensitively detect compensatory hypertrophy as a sign of renal impairment of the affected side, the renal length of the affected and the healthy contralateral kidneys was compared in 37 patients with normal appearance of the contralateral kidney. The longitudinal growth of the kidneys with POM was identical to that of the contralateral kidneys (Fig. 2).

Initial findings on diuresis renography were also mostly mild with mainly dilated unobstructive findings (O'Reilly type C, n=38, 68%). An obstructive pattern (type B) was seen in nine cases (16%) and partial obstruction in seven (type D, 12.5%). Two renal units (3.5%) were initially normal (type A) and controlled further because of an affected contralateral side. They did not progress beyond dilated unobstructive patterns.

Seven patients were found to have reduced partial renal function on initial renogram, including four of 37 patients with healthy contralateral side and three renal units with diseased contralateral side. However, only four of the seven renal units with reduced partial function had obstructive patterns on renogram and the other three showed dilated

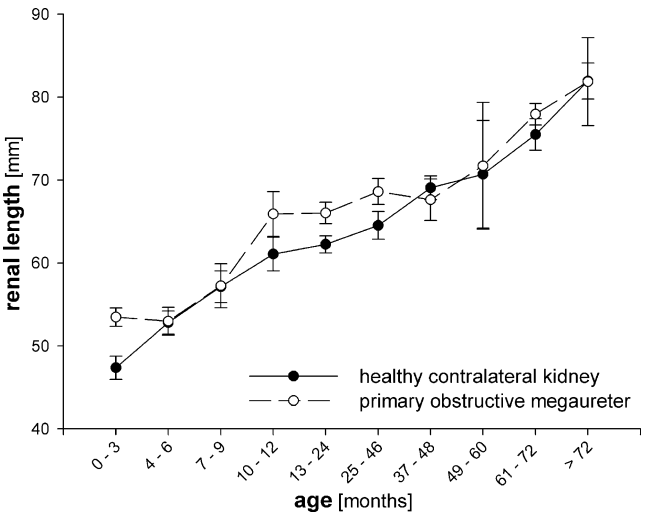

Fig. 2 Growth of renal length over time in 37 primary obstructive megaureters (both medical and surgical treatment) compared to the healthy contralateral kidney

unobstructive patterns. Estimated GFR was normal in all patients.

Follow-up renograms were performed in those patients who initially showed type D or B drainage patterns on renogram or type C without improvement on ultrasound. Later deterioration of unobstructive types was seen only in six of 38 renal units (16%) (Fig. 3a). Also, four of nine initially fully obstructive and two of seven initially partially obstructive megaureters (which were not operated on immediately) improved spontaneously to dilated unobstructive patterns (Fig. 3b).

During follow-up, a high rate of spontaneous regression was observed. At 7 years of follow-up, 70% of POM had regressed spontaneously (see Fig. 4a, operated patients were treated as censored observations at the date of surgery). Spontaneous regression could not be predicted with statistical significance by the grade of hydronephrosis, the size of megaureter, or the pattern on renogram. However, at 3.5 years follow-up, all patients with an initial megaureter of less than 8.5-mm diameter had regressed spontaneously, while none over 15 mm had regressed (Fig. 4b). Renal units with initial type C were much more likely to regress spontaneously than fully or partially obstructive types, however there was no difference between the latter two (Fig. 4c). There was no difference in the rate of spontaneous regression or incidence of surgical treatment between patients diagnosed pre- and postnatally, respectively.

In total, 13 renal units underwent surgical treatment. As shown in Fig. 5, only four renal units (7%) needed primary surgery, while nine were operated after a period of observation with repeated renogram. As an interim procedure, a percutaneous nephrostomy was placed twice, however this dislocated in one case and the kidney was removed as it had a partial function of only 19% and was causing treatment resistant renal hypertension. In the second case, partial renal function improved but drainage was still partially obstructed, so a uretercystoneostomy (UCN) was performed as corrective surgery. Twelve UCNs were performed in total, with eight using psoas hitch (two with ureteric tailoring), one with the Politano-Leadbetter technique and one using extravesical detrusor tunneling (one unknown). Only one child suffered a major postoperative complication with early stenosis of the anastomosis, which did not improve despite temporary external urine diversion and splinting. After re-operation, the obstruction could be permanently relieved, however. Mean hospital stay for surgical correction was 14.5 days per renal unit (including a regular second admission for removal of the double-J catheter).

The incidence of operations did not differ between initially partially obstructive and fully obstructive POM (type D four of seven (57%); type B (five of nine, 56%), only that initially fully obstructive ureters were operated on earlier. Among children with initially dilated unobstructed ureters (type C) four out of 38 renal units were operated on (11%).

Postoperatively, there was adequate renal growth with no significant difference of renal size in operated renal and healthy contralateral sides (data not shown).

No child developed reduced global renal function or significant long-term morbidity. In one child with treatment-resistant renal hypertension, blood pressure normalized after nephrectomy. Six children had reduced partial renal function (<40%) at last observation; all these children had already had impaired partial function on their first renogram. Three of these six children also had renal atrophy on final ultrasound (i.e. renal length <65% of expected); however two of these had renal hypo/dysplasia from birth, so they might have had additional reasons for poor kidney growth. The first was a boy with prenatally diagnosed bilateral POM with a positive family history and associated undescended testes. His left kidney was initially of normal size but had abnormal echogenicity and 15% partial function at 6-week renogram. Consequently, it shrank in size to <3rd percentile and partial function

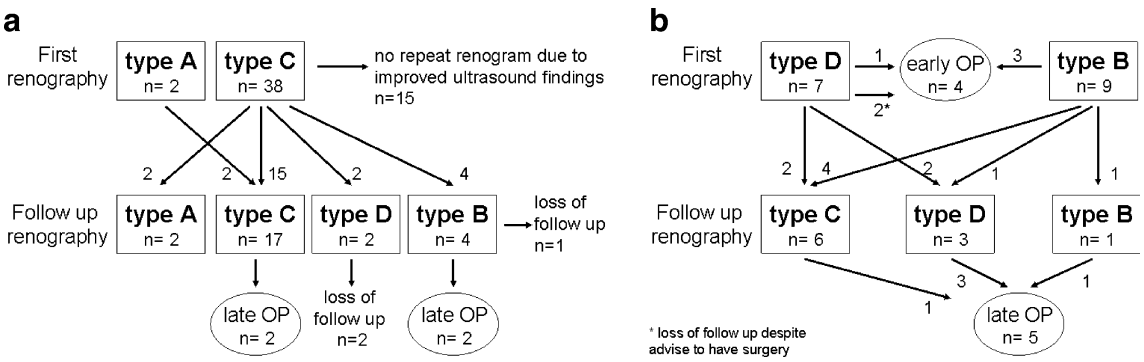

Fig. 3 Initial and follow-up findings on diuresis renogram in 56 primary obstructive megaureters with initially unobstructive (**a**) and initially partial or full obstructive findings (**b**). (type A: normal, type C: dilated unobstructed, type D: partially obstructed, type B: obstructed). OP: operation

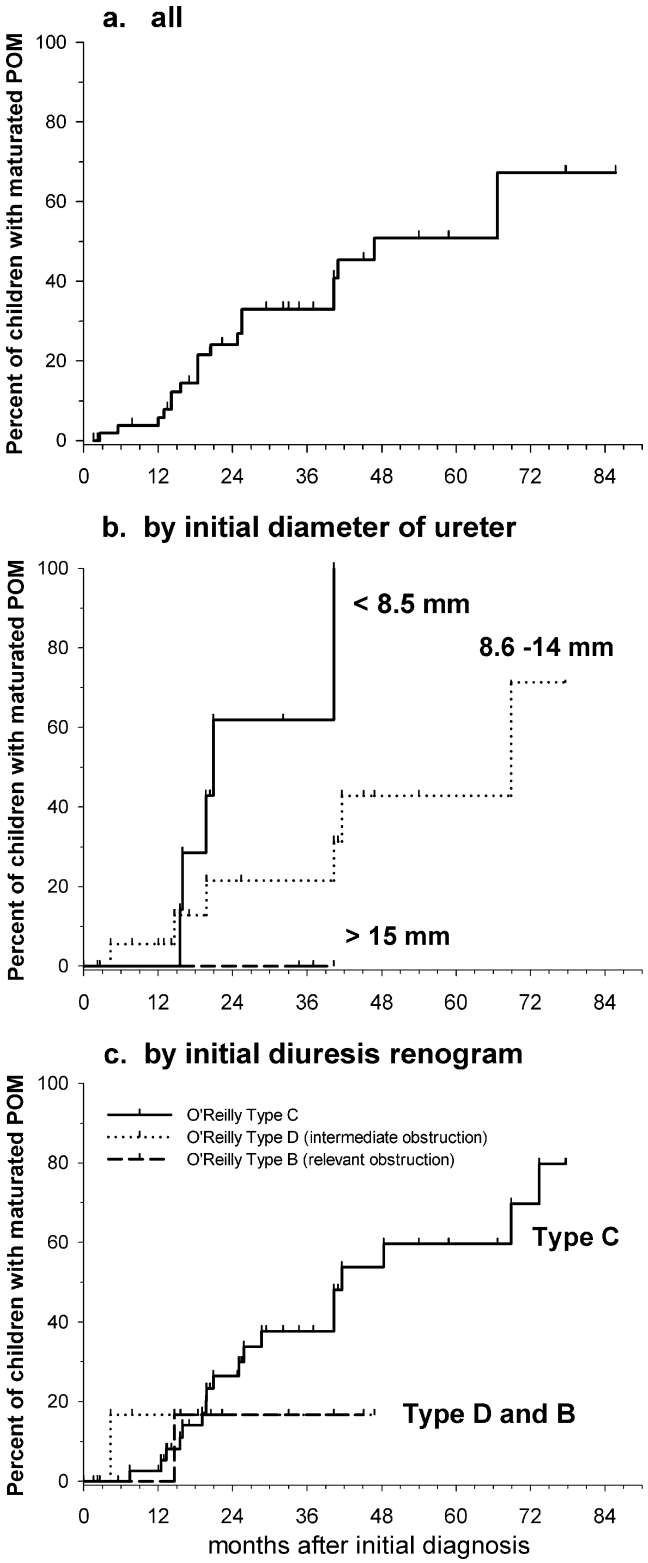

Fig. 4 Rate of spontaneous regression of 56 primary obstructive megaureters (renal units that underwent surgery were treated as censored observations at the time of operation)

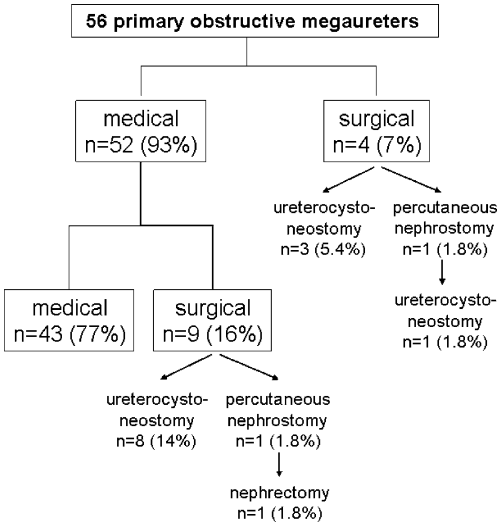

Fig. 5 Primary and secondary management of 56 primary obstructive megaureters

remained at 15%. The contralateral kidney was operated on and showed moderate compensatory hypertrophy (volume 97th percentile). The second boy had unilateral POM on the right without a positive family history and was diagnosed at an age of 7 months. Renoparenchymal echogenicity was abnormal at the time of diagnosis. Partial renal function declined from 29% at time of diagnosis to 20% 3 years later, by which time he had suffered from three febrile urinary tract infections. Renal dilatation by ultrasound increased over time with narrowed parenchyma and increased echogenicity.

On statistical analysis, we found no clinical prognostic factors for poor outcome. All children with poor outcome were boys (p=0.06 for sex difference).

Discussion

In this study we analyzed the characteristics and long-term outcome of 56 primary obstructive megaureters in childhood managed by a differentiated conservative approach.

The predominance of POM on the left side in our group and the male gender predominance is consistent with previous reports [5, 6, 9–12, 14–16, 18, 25, 26]. In a significant number of cases, POM was associated with other morphological anomalies such as renal hypo/dysplasia (CAKUT complex, four cases), ear tags (two children), tracheomalacia, and aortic aneurysm. These observations point to a potential genetic origin of POM. The combined finding of POM and hypo/dysplasia is consistent with the CAKUT hypothesis, which postulates that genetic abnormalities in individual renal developmental genes may cause a spectrum of associated kidney and urinary tract abnormalities [27].

Due to the primarily conservative stepwise approach, only 13 renal units (23%) were operated upon. This rate is within the range reported in recent publications (seven and 46%) [16–18, 25].

Of those children who were initially stratified to watchful-waiting according to the consensus guideline criteria (n=52, 93%), only nine (17%) deteriorated later and required operation, lending support to our differentiated conservative approach. Altered kidney growth on ultrasound in the absence of reduced renal function is considered a sensitive parameter of renal damage by some albeit not all authors [28, 29]. We observed entirely normal longitudinal growth of kidneys with POM when compared to healthy contralateral renal units; hence, long-term outcome as indicated by this parameter was excellent. Those patients who exhibited renal atrophy or reduced partial function at last observation usually had kidney abnormalities already from birth, leaving little scope for improvement by post-natal management.

The rate of spontaneous regression in our study was about 50% at 4-year follow-up, which is somewhat higher than reported previously [17]. The timing of regression (50% of regressions had occurred by the second birthday) is in keeping with previous literature. Spontaneous regression was not confirmed by diuresis renogram if sonographic improvement was evident. However, since sonographic dilatation of the ureter often persists for some time after relief of obstruction, our study is unlikely to overestimate the rate of spontaneous regression.

In contrast to McLellan et al. [26], but in keeping with Calisti et al. [18], we observed the initial diameter of the ureter, rather than the initial degree of hydronephrosis, to predict the rate of spontaneous regression. While this may be due to the more homogenous cohort of only prenatally diagnosed POMs in the previous study or to the different sonographic classification system used, it is also plausible that the degree of obstruction at the distal ureter is more closely mirrored by the direct measurement of retrovesical ureteric distension than by the assessment of pelvic dilatation. The strongest predictor of an adverse outcome was the presence of renal hypo/dysplasia on initial ultrasound. Hence, careful screening for pre-existing parenchymal abnormalities is essential.

Although diuresis renogram is widely regarded as the most useful tool for assessing the degree of obstruction, there is little exact data [6, 15, 25] and the prognosis of intermediate obstruction (O'Reilly type D) is unclear. We found a very similar risk of later deterioration and surgery, as well as of spontaneous regression, in patients with initially intermediate obstruction and those with relevant obstruction. Therefore the assumption of a better prognosis for patients with type D, as assumed in the German consensus paper, may need to be reconsidered.

In accordance with previous studies, we did not find any clinical predictors of spontaneous regression or adverse long-term outcome [26, 30].

The overall good long-term outcome in this group should not be taken to mean that screening or follow-up is unnecessary, as is well illustrated in a study from India [14]. In a series of 55 adolescents and adults with POM who had presumably not been screened during pregnancy or childhood, 20 patients presented with renal stones, five (with bilateral POM) with renal insufficiency, and one with jaundice due to compression of the choledochal duct. However, late renal functional deterioration has been reported only after residual dilatation of the urinary tract and not after spontaneous regression.

Even though the majority of children presented here were diagnosed asymptomatically either prenatally (41%) or at routine screening examinations during the first year of life (33%)—reflecting the change in this patient population since the introduction of prenatal ultrasound screening—there was a surprisingly high rate of UTIs, which altogether affected more than two-thirds of the patients. UTIs caused significant short-term morbidity with 17 children (35%), requiring at least one hospital admission. Although the rate of UTI in infants with POM has not yet been formally studied, many authors (including the German consensus paper) recommend antibiotic prophylaxis in infancy until an obstructive megaureter has been excluded [7, 10, 15]. We found the incidence of UTIs in untreated infants with POM to be 0.94/year. In the group receiving antibiotic prophylaxis, the UTI rate was 83% lower in the first 6 months of life and 55% lower in the first 12 months of life, supporting the current recommendations. However, a residual risk of UTI remains even with prophylactic treatment. During the second year of life, there was still a surprisingly high incidence with 0.46 UTIs/year in the untreated group, which can be taken to support previous recommendations for prophylactic treatment even in the second year of life [5, 31]. A limitation of this study was that confirmation of UTIs by suprapubic puncture was not sought in all cases, leaving the possibility of inclusion of some false-positive cases.

Taken together, we found a good long-term outcome in this group of POM managed according to the German consensus guidelines. The recommendation for antibiotic prophylaxis is underlined in the first year of life and may have to be extended to the second year of life. While clinical prediction of long-term outcome is difficult, this study establishes the superior predictive value of renography and sonographic retrovesical ureteric dilatation over pelvic dilatation measures. Patients with intermediate obstruction patterns should be managed carefully as it is questionable whether they have a better prognosis than fully obstructive POM.

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