

Familial ureterocele: an evidence for genetic background?

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SUMMARY: Sözübir S, Ewalt D, Strand W, Baker LA. Familial ureterocele: an evidence for genetic background? Turk J Pediatr 2005; 47: 255-260.

In the pediatric population, ureteroceles may present with different clinical pictures, and the severity of the renal damage is greater than in adults. Ureterocele, an anomaly of ureteric budding, is likely a component of a spectrum of anomalies including vesicoureteral reflux and ureteral duplications. Both have been confirmed to have a genetic and familial basis. We document the largest series of familial cases of ureterocele, giving evidence for genetic background.

We retrospectively reviewed the charts of patients with familial ureterocele seen between 1992 and 2002. Coexisting ureteral anomalies and features of the cases were documented and compared to sporadic cases and all familial cases within the literature.

This is the largest series of familial ureterocele patients in the literature. The review of the literature revealed seven publications with seven ureterocele families (15 affected patients) between 1936 and 2002. Comparing sex, ureterocele location, and single versus duplex systems, familial series are similar to other sporadic cases. Three of the families have twin siblings with ureterocele.

Familial cases, despite their rarity, raise the issue of the genetic origin of ureterocele. Family members of ureterocele cases should be informed and followed carefully, especially twins. Increased reporting and genetic analysis of familial ureterocele may prove to link the genetic mouse models of abnormal ureteric budding to the human conditions.

Key words: ureterocele, genetics.

Abnormalities of the genitourinary tract are one of the most common groups of congenital anomalies in children. Ureterocele associated with duplicate system is not rare, with the reported incidences varying between 1 in 500 to 1 in 4,000 in autopsy series¹. That ureterocele is commonly associated with other malformations of the genitourinary tract and is more common in females and on the left side suggest that it is a congenital anomaly.

The familial occurrence of ureterocele was first described in 1936 by Riba² and reinforced with further studies³⁻⁸. Here, we report a review of the literature with the addition of three new familial ureterocele. This is the largest series of familial ureterocele patients in the literature. This report aims to represent additional evidence for the genetic background of ureterocele.

Material and Methods

We retrospectively reviewed the charts of familial ureterocele patients seen in our Department between 1992 and 2002. The detailed progress of each familial case was documented. Affected siblings, sex, age, presenting symptom, localization of ureterocele (left or right side), and single versus duplex systems were noted (Table I). The same parameters were also noted for the familial cases found in the literature (Table II). These results were compared to sporadic cases.

Family 1

Case 1

A 25-year-old pregnant woman was sent to the Pediatric Urology Clinic with the prenatal findings of unilateral left hydronephrosis. The baby girl was delivered and evaluated

Table I. Affected Siblings, Sex, Age, Presenting Symptom, Side and Location of Ureterocele, and Single vs. Duplex Systems Noted in our Familial Cases

	Cases	Sex	Age	Side	Orifice	System	Symptom	VUR
Family 1	Case 1	F	Prenatal	Left	Ectopic	Duplex	Prenatal	No
	Case 2	Sister	F	Prenatal	Right	Ectopic	Prenatal	R-grade II
Family 2	Case 3	F	3 months	Left	Ectopic	Duplex	UTI	R-grade I
	Case 4	Sister	F	2 months	Bilateral	Ectopic	Bilateral duplex	UTI
Family 3	Case 5	F	16 months	Left	Ectopic	Duplex	UTI	R-grade I
	Case 6	Sister	F	Prenatal	Right	Ectopic	Duplex	UTI

UTI: urinary tract infection, VUR: vesicoureteral reflux.

Table II. Features of Familial Cases Found in the Literature

Date	Author	Sex	Age	Side	Orifice	System	Affected sibling	VUR
1936	Riba et al. ²	F	39 yrs	Bilateral	Simple	Single	Twin	
1967	Deweerd et al. ³	F	5 yrs	Bilateral	Ectopic	Duplex	Mother	?
1977	Babcock et al. ⁴	F	11 weeks	Left	Ectopic	Duplex	Mother	?
1979	Ayalon et al. ⁵	M	4 weeks	Left	Ectopic	Duplex	Twin	No
1980	Abrams et al. ⁶	M	17 yrs	Right	Simple	Single	Brother	No
1997	Capasso et al. ⁷	M	7 yrs	Bilateral	Simple	Single	Twin	No
2000	Aubert et al. ⁸	F	4 yrs	Bilateral	Ectopic	Duplex	Father, Sister	Yes grade III

VUR: vesicoureteral reflux.

by sonography, which showed an enlarged renal pelvis of the upper half of the left kidney consistent with a duplicated system and a possible upper pole obstruction. A large ureterocele and lower pole reflux with upper pole hydronephrosis were revealed with VCUG (voiding cystourethrography) at one month of age. At three months, she underwent cystoscopy and an incision of a left, upper pole ectopic ureterocele. Sonography reflected good parenchyma on the left upper pole with hydronephrosis at six months. For this reason, DMSA renal scan was made, and it actually showed good function on left upper pole. Common sheath ureteral reimplantation of the left ureter was performed at nine months of her age. Her follow-up pyelogram showed little dilation of the left upper pole with good function (Fig. 1). There was no evidence of reflux on VCUG. She also had no urinary tract infection (UTI) without prophylaxis.



Fig. 1. Duplicated left upper tract in a ureterocele case.

Case 2

Thirty-one months after her initial admission for her first baby, the same mother was sent to the Pediatric Urology Clinic with prenatal MRI (magnetic resonance imaging) findings of the second baby of ureterocele and duplication of the right side. A female baby was delivered and was noted to have a prolapsing ureterocele (Fig. 2). When she was just over a week of age, she underwent cystoscopy and incision of prolapsing ureterocele. She did well after surgery and was prescribed antibiotic prophylaxis. VCUG revealed Grade II right-sided reflux at four months. Right common sheath ureteral reimplantation was carried out following cystoscopy. She is now without any urinary complaints under antibiotic prophylaxis.



Fig. 2: Prolapsed ureterocele in a newborn.

Family 2**Case 3**

A three-month old female infant was sent to the clinic with a recent history of febrile UTI. Sonography revealed a duplicated left collecting system and left ureterocele. Cystoscopy with incision of ureterocele was carried out at three months. The ectopic ureteral opening was

identified in a position distal to the level of bladder neck. Follow-up sonography revealed atrophic upper pole collecting system on the left associated with marked hydroureter. Pyelogram essentially showed no function of her left upper pole and grade I reflux with VCUG when she was one year old. Left upper pole heminephroureterectomy with excision of ureterocele, reconstruction of bladder base and bilateral ureteral reimplantation was carried out. Normal functions and no reflux bilaterally aside from a large bladder capacity without post-void residual volume were revealed on her radiological evaluation in the first year following the operation.

Case 4

The younger sister of the previous case had a severe UTI found at two months of age. Sonography revealed hydronephrosis and hydroureter on the right side, nonfunctioning obstructed upper pole with large ureterocele on the right and an unobstructed duplicating system on the left reflected by pyelogram and VCUG studies. One UTI was noted during her antibiotic prophylaxis. Right upper pole heminephrectomy with excision of ureterocele, right lower pole ureteral reimplantation, and excision of left ureterocele with common sheath ureteral reimplantation on the same side were carried out at one year of age. In addition to her initial pathologies, a left ureterocele was found. There was no evidence of hydronephrosis on either side postoperatively. She showed no evidence of reflux with VCUG. Her pyelogram appeared normal except for the partial duplication of the left collecting system. With these findings, antibiotic prophylaxis was terminated at 1.5 years of age.

Family 3**Case 5**

A 16-month-old female was admitted in the emergency room with a febrile UTI. She was found to have a left kidney duplication with obstruction of upper pole as well as a ureterocele in the left aspect of the bladder base with renal sonogram. The results of VCUG showed right-sided grade I vesicoureteral reflux (VUR) with a filling defect in the left bladder consistent with a ureterocele. Pyelogram demonstrated prompt function bilaterally with some preserved function

in the left upper segment. MAG-3 nuclear medicine renal scan showed poor function on left upper pole. She was operated for left upper pole nephroureterectomy, resection of ureterocele and bilateral ureteral re-implantation at 1.5 years of age. Some microcystic changes in upper pole of left kidney were also recognized during operation. Pathology from the upper pole renal segment demonstrated renal dysplasia with sclerotic glomeruli and dystrophic calcifications. When she was evaluated at two years of age, VCUG was also normal. She had a urinary tract examination at age five with sonogram showing normal findings including bilateral kidney growth.

Case 6

A 16-day-old female was admitted to the emergency room with a high fever with the history of prenatally diagnosed right renal cyst. This female is the sister of the previous case treated at two years of age. She was treated with intravenous antibiotics after UTI was detected. Sonography indicated right upper-pole hydronephrosis with a large right ureterocele. Grade II VUR was also detected on right lower pole of the kidney with VCUG. Transurethral incision of ureterocele and cystoscopy were performed at the 21st day of age. At two months, she presented at the emergency room again with febrile UTI. DMSA nuclear renal scan was performed and showed very poor function at the right upper pole. Right upper pole heminephroureterectomy, resection of ureterocele and bilateral ureteral reimplantation were carried out at three months. She did well postoperatively but was not maintained on any antibiotic prophylaxis contrary to recommendations. She developed febrile episodes consistent with UTI twice. She was found to have some right hydronephrosis on renal sonography and no VUR or post-void residual urine volume on VCUG at one year of age. MAG-3 nuclear medicine renal scan indicated asymmetry of renal function but no evidence for obstruction. Her antibiotic prophylaxis was continued for two more months following the last UTI.

Results

This is the largest series of familial ureterocele patients in the literature. The review of the literature revealed seven publications with seven ureterocele families (15 affected patients) between 1936 and 2002.

Ureterocele is four times more common in girls. In familial cases, 67% of the cases were girls and 33% boys. In children, ureterocele is located ectopically in 80% of the cases; we found an ectopia rate of 79% in familial cases. Duplication of upper urinary tract is more common in children compared to the diagnosis in adults, with the association of 60-95%. We found a duplicated system rate of 74% associated with ureteroceles in familial cases. Comparing sex, ureterocele location, and single versus duplex systems, familial series are similar to other sporadic cases.

Vesicoureteral reflux is the most frequent anomaly found in ureterocele cases. In the literature, VUR in ureterocele cases has been reported at a rate of 54%. We also found VUR in 50% of the familial cases.

Three of the families had twin siblings with ureteroceles. In other families, three affected siblings were parents and five were sister and brothers.

Discussion

A ureterocele is defined as cystic dilatation of the submucosal or intravesical ureter. Ureteroceles may present in a variety of locations, orifice sizes, degrees of musculature and associated anomalies. Therefore, several classifications have been described for ureterocele, but the simplest is to separate the ureteroceles of the upper part with a duplicate system, which is the most common form in children, from the ureteroceles associated with a single system. In both types the ureteral orifice can be either in the bladder (intravesical form) or in the urethra or at the bladder neck (ectopic form). In children, between 60% and 75% are ectopic¹.

The severity of hydronephrosis and associated complications with ureteroceles generally appears to be more significant in children than in adults. As this pathology can lead to important complications, early diagnosis is strongly recommended⁷. Presently, ureteroceles are frequently recognized during the antenatal period. Sonography is the modality of choice for prenatal screening of fetal anomalies. It provides cost-effective, real-time imaging, has a high-resolution capacity and is safe to the fetus and mother. However, in some circumstances like maternal obesity, oligohydramnios or unfavorable position of the fetus, sonography

is limited⁹. Nevertheless, many fetal urinary tract malformations are associated with oligohydramnios, which impairs sonographic visualization. Thus, MRI may be a useful adjuvant when sonography is indeterminate, especially with the new ultrafast MRI technique available with scan times of <1 s which also decreases the amount of motion artifacts^{9,10}. However, there are few reports of prenatal MR imaging of genitourinary anomalies in the literature¹⁰⁻¹². Our Case 2 is the only case in the literature showing prenatal diagnosis of prolapsed ureterocele with prenatal MRI¹³.

Hereditary origin of urinary tract malformations has always been a point of interest over the years. Ureteral duplication occurs in a number of families at an incidence many times that of the normal population, suggesting an inherited basis of this condition. Pedigrees of such families are consistent with an autosomal dominant mode of inheritance⁴. The most consistent finding with complete duplication is VUR to the lower segment or obstruction of the upper segment secondary to either ureteral ectopia or ureterocele¹⁴. VUR is well known as the most common inherited disease of the genitourinary tract in the literature^{15,16}. The results of those studies showed clearly the autosomal dominant transmission of this condition. Interestingly, in this multiple gestation birth group the second most common genitourinary anomaly following VUR was ureteral duplication, which confirms the results of previous studies.

Even though the number of families is not quite enough, it does give the clue that ureteroceles may also be familial. The literature shows that three of seven families have ureterocele in twins (1 is non-identical female twins) and this genetic inheritance is not only shown with duplex systems but also with single system simple ureteroceles. However, our families do not include any twin family or single system. All of these familial cases, despite their rarity, raise the issue of the genetic origin of ureteroceles, such as duplications and VUR.

Confirmation of the specific mechanisms of transmission for genitourinary anomalies awaits identification of the molecular determinants responsible for their occurrence. Several genes have been identified in experimental studies to control ureter maturation, including AGTR2

(angiotensin type-2 receptor), Foxc1 and Foxc2 (murine forkhead/winged helix genes, also known as Mf1 and Mfh1), BMP4 (bone morphogenetic protein 4) and ret gene¹⁷⁻²⁰.

Studies of AGTR gene in two independent cohorts found that a significant association exists between congenital urinary tract anomalies and nucleotide transition within the lariat branchpoint motif of intron1, which perturbs AGTR2 m-RNA splicing efficiency. AGTR2, therefore, has a significant ontogenic role for the kidney and urinary tract system¹⁷. Most infants with Foxc1 gene mutations are born with abnormalities of urinary tract, also including duplex kidneys and double ureters, one of which is hydroureter¹⁸. BMP4 likely plays a number of important roles during urinary tract morphogenesis. In the lower urinary tract, it controls ureter maturation by regulating the budding site and elongation¹⁹.

Maternal vitamin A deficiency in rodents and most probably in humans results in malformations in most organs and tissues, including the urinary tract²⁰. Mammals obtain vitamin A from the diet in an inactive form called retinol, which can be stored in the liver or released and transported through the blood to tissues when needed. Inside cells retinol is converted to its active form, retinoic acid (RA), which transmits the vitamin A signal by binding to and activating retinoic acid nuclear receptors (Rars and Rxrs), which act as transcriptional transducers of the retinoid signal during development²¹. It has been shown that Rara and Rarb2 are required for generating stromal cell signals that maintain c-ret expression in the embryonic kidney²². Mouse mutants lacking two Rar family members, Rara and Rarb2, display urinary tract malformations including ectopically terminating ureters^{20,22}. As far as the growth and branching of the ureteric bud are concerned, ret gene is another mediator of epithelial mesenchymal interactions. The ret gene encodes a receptor, tyrosine kinase, required for formation of the ureteric bud and for its subsequent growth and branching within the kidney²⁰. Ret signals via co-receptor Gfra1 and a number of ligands, including Gdnf (glial cell line-derived neurotrophic factor). Ret and Gfra1 are expressed in ureteric bud epithelia; Gdnf is secreted by mesenchyme. Inactivation of these three components results in renal agenesis²¹. It has been recently

published that ret is an important downstream target of vitamin A signaling, and that vitamin A regulates branching morphogenesis by controlling ret expression²³.

In conclusion, we recommend that family members of ureterocele cases should be informed and followed carefully. It might be premature to recommend screening or to perform complete urologic evaluation in all family members because ureteroceles are encountered, but in twins a more compelling case can be made. Sonography is an ideal screening method when the family needs reassurance. If the diagnosis is made prenatally and there is a suspicion, MRI is the choice of modality for evaluating the fetal genitourinary tract even with oligohydramnios. It is obvious that molecular genetic studies will give important details of urinary tract morphogenesis in the near future.

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