Case Report

Multiple urinary tract malformations with likely recessive inheritance in a large Somali kindred

Andreas Pasch2, Julia Hoefele1, Herbert Grimminger4, Hans-Walter Hacker3 and Friedhelm Hildebrandt1

1University of Michigan, Department of Pediatrics, Ann Arbor, MI, USA, 2University Hospital Bruderholz, Department of Medicine, Bruderholz, Switzerland, 3University of Tuebingen, Department of Pediatric Surgery, Tuebingen, Germany and 4Private Practitioner, Reutlingen, Germany

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Introduction

Traditionally most non-cystic developmental disorders of the urinary tract have been regarded as sporadically occurring and morphologically distinct entities. However, familial occurrence of ureter-related abnormalities has pointed towards a genetic determination with a likely autosomal dominant mode of inheritance in a number of cases [1–5].

We report a Somali kindred with seven out of 15 children affected by urinary tract malformations in a variety not reported yet. Furthermore, in sight of consanguineous healthy parents, this is the first report on a likely autosomal recessive mode of inheritance of urinary tract malformations.

Case

The family presented is of Somali origin and immigrated to Germany some years ago. The parents are first-degree cousins. At age 15 months, the index patient (child 7; Figure 1, Table 1) suffered from a severe right-sided pyelonephritis. Upon hospitalization a palpable tumour in the right lower quadrant was noticed, which on ultrasonographic imaging was identified as the right kidney. This kidney was comprised of a massively dilated pyelon with a small parenchymal rim, findings that were also confirmed by an intravenous urogram (IVU). In neither examination could a left kidney be identified. After a normal pregnancy and a delivery without complications, at age 1 month the child had been hospitalized in Somalia because of a progressively distended abdomen. The mother reported that at that time the urine had to be artificially ‘drained from the boy’s flank’. Also in Somalia, at age 8 months, a surgical procedure had been performed. Unfortunately, clinical data and medical records on the initial presentation and treatment in Somalia are not available.

However, in the current hospitalization, an immediate percutaneous nephrostomy was performed. In a micturating cystourethrogram on hospital day 8, a vesico-ureterorenal reflux and a massively dilated pyelon was seen again. For definite treatment, a pyelocystostomy was performed. During intraoperative cystoscopy, a left-sided rudimental ureteral ostium (0.5 cm) was noticed. Furthermore, on the right side a stenotic ureteral opening, presumably the remnant of a right-sided uretero-cystostomy back in Somalia, was seen. From these findings we speculate that the initial presentation probably was a vesico-ureteral reflux on the right side.

At age 6 years, an older sister (child 6) was hospitalized for a febrile upper airway tract infection. On routine abdominal ultrasound, a right-sided hydronephrosis without a distended ureter and without signs of a pressure atrophy of the kidney was seen. The left kidney was missing. These findings could be confirmed by IVU and renal scan. The latter showed prolonged retention of contrast material in the right pyelon and no evidence of a restriction of renal function. These findings confirmed the suspected clinically asymptomatic right-sided ureteropelvic junction obstruction (UPJO), which was surgically corrected by an Anderson–Hynes pyeloplasty.

About 3 years later, when the mother was pregnant with child 10, an ultrasonographic diagnosis of bilateral hydronephrosis was made in utero. This diagnosis was confirmed shortly after birth of the
boy and bilateral UPJO was detected as the underlying anatomical cause. At age 1 month, bilateral percutaneous nephrostomy was performed and 4 months later the boy’s right-sided obstruction was corrected surgically by an Anderson–Hynes pyeloplasty. No surgery was performed on the left side.

With three out of 10 children at that time affected by urinary tract malformations, an ultrasonographic screening of all apparently healthy family members was performed and additional abnormalities were detected in another child, namely child 5.

In child 5, a 10-year-old boy, an ultrasonographic diagnosis of a decompensated left-sided UPJO and of a duplicate pyelon on the left side was made. The left-sided UPJO was corrected surgically, where an Anderson–Hynes pyeloplasty was performed. Furthermore, a right-sided UPJO was found that required no surgical treatment.

Five days after birth, child 11, a girl, presented with signs and symptoms of a urinary tract infection. Ultrasonographically and in an IVU, right-sided hydrenephrosis and a megaureter were seen and reflux was suspected. In a micturating cystourethrogram, these findings, including the suspected reflux, were confirmed. A follow-up ultrasound study 1 month later also revealed a beginning left-sided hydrenephrosis and ureteral dilatation, which showed slow progression in further follow-up studies. These malformations were treated surgically at age 3 months (right side) and 26 months (left side) by an anti-reflux operation each.

In child 13, a girl, 5 days after birth a UPJO and a massive hydrenephrosis on the right side were diagnosed. After immediate percutaneous drainage, this malformation was corrected surgically 1 month later with an Anderson–Hynes pyeloplasty. Furthermore, at 1 year of age, a UPJO on the left side was diagnosed by IVU. On follow-up, this anatomical defect resolved spontaneously and required no surgical intervention.

In child 15, a girl, ultrasonographically at day 1 after birth, a massive left-sided hydrenephrosis and a normal ureter was seen. Furthermore, in a micturating cystourethrogram and a magnetic resonance imaging urogram, a left-sided malrotation and a hydrenephrosis with UPJO were documented. At the right urinary tract, ureteropelvic reflux and a Hutch diverticulum were seen. A left-sided Anderson–Hynes pyeloplasty was performed at age 2 months; the

![Fig. 1. Pedigree and clinical findings. Affected children are represented by solid squares/circles; the parents are first-degree cousins. The images are representative of the urinary tract malformations, no image is available from child 5. Child 6: 99mTc-MAG3 renal scan showing agenesis of left kidney. Child 7: micturating cystourethrogram showing reflux into a massively dilated right pelvis; suprapubic catheter in place. Child 10: antegrade ureteropyelography of the right kidney showing a dilated pelvis due to a UPJO. Child 11: IVU showing a dilated right pyelon and pelvis. Child 13: IVU showing bilateral subpelvic stenosis. Child 15: micturating cystourethrogram showing reflux into the right pelvis and a Hutch diverticulum.]

<table>
<thead>
<tr>
<th>Child</th>
<th>Age at diagnosis</th>
<th>VUR</th>
<th>UPJO</th>
<th>Agenesis</th>
<th>Further findings</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>M 10 years</td>
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<td></td>
<td></td>
<td>Duplicate left pyelon</td>
<td>Left AHP</td>
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<tr>
<td>6</td>
<td>F 6 years</td>
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<td></td>
<td>Right AHP</td>
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<tr>
<td>7</td>
<td>M 1 month</td>
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<td></td>
<td>Remnant left ureteral ostium</td>
<td>Right UC</td>
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<tr>
<td>10</td>
<td>In utero</td>
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<td>Right AHP</td>
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<td>11</td>
<td>F 5 days</td>
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<td>Bilateral ARO</td>
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<td>13</td>
<td>F 5 days</td>
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<td>Right AHP</td>
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<tr>
<td>15</td>
<td>F 1 day</td>
<td></td>
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<td></td>
<td>Right Hutch diverticulum, malrotated left kidney</td>
<td>Left AHP</td>
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*Index patient.
*Presumed diagnosis before surgery in Somalia.
UC, uretero-cystostomy; ARO, anti-reflux operation; AHP, Anderson–Hynes pyeloplasty; M, male; F, female; VUR, vesico-ureteral reflux.
right-sided reflux did not require surgical treatment and ceased spontaneously.

In light of this broad spectrum of urinary tract malformations, it might be of interest that in at least 70 ultrasounds of the affected children no renal cysts were seen.

Unfortunately, no medical information is available about the parents, their siblings and their grandparents.

**Discussion**

Anatomical abnormalities, like obstructive uropathy, renal aplasia, hypoplasia or dysplasia, reflux nephropathy and cystic kidney disease, account for ~35% of cases of chronic renal failure in children [http://spitfire.emmes.com/study/ped/resources/annlrept.pdf]. These developmental defects of the upper urinary tract are, thus, among the leading causes of renal failure in childhood.

In our family, the affected siblings are descendants of healthy consanguineous parents who are first-degree cousins. In the absence of syndromal features or known teratogenic influences, it is very likely that a single genetic alteration is responsible for the developmental changes encountered. In light of healthy consanguineous parents, the mode of inheritance is well compatible with an autosomal recessive trait and the high rate of affected children (seven out of 15) most likely is due to a random genetic effect. These assumptions are supported by an obviously strong penetrance and expressivity of the genetic defect.

In conclusion, we consider an autosomal dominant transmission unlikely, although based on the data presented it cannot be ruled out with absolute certainty. Interestingly, the broad spectrum of morphological changes and the range of time of onset resemble that encountered in autosomal dominant traits [3–5].

Malformations of the upper urinary tract are currently classified using the Potter classification [6], which assigns patients to four separate classes, depending on phenotypic patterns. In recent years, however, two major groups of non-classifiable conditions have emerged, challenging this traditional system.

First, there are syndromal urinary tract-related entities, exhibiting a broad spectrum of morphological changes. Among these syndromes, the genetic defects in Kallmann’s syndrome (mutation of KAL, a cell-signalling gene [7]), in branchio-oto-renal syndrome (mutation in EYA1, an apoptosis-limiting factor [8]) and in renal-coloboma syndrome (mutation in PAX2, a transcription factor [9]) have been identified.

Second, autosomal dominantly inherited upper urinary tract malformations with a wide variety of clinical findings have been reported [3,5].

The difficulties to classify syndromal and most familial cases show the need for a new aetiology-based classification system. Such a system has been proposed by Pohl et al. [10]. To classify an individual case in their system, the underlying genetic defect and the function of the affected gene has to be known. This is a prerequisite that, unfortunately, is not met in the large number of so-called ‘sporadic’ cases. However, many of these cases are truly ‘sporadic’ or are, in contrast, due to rare recessive mutations is not known.

Different genetic backgrounds may play a role in the disturbance of the ordered interplay of developmental genes during the short period of organogenesis. As examples of the importance of the genetic background, patients with identical PAX2 mutations [11] and different EGF-deficient mouse strains [12] show a broad variability of phenotypes. Also, recently, the importance of modifying genes has been shown in Bardet–Biedl syndrome [13]. Whether a distinct genetic background in our case contributed to the high number of clinically affected family members remains speculative.

The clinical spectrum of changes in our family points towards a gene playing a role in early nephrogenesis, specifically in the process of ureteric bud induction or in the process of ureteric bud branching morphogenesis. The induction of the ureteric bud, which sprouts from the mesonephric (Wolffian) duct into the metanephric blastema, is a prerequisite for the formation of kidneys. Genes involved in this process include WT1 [14], Eya-1 [15] and GDNF [16], among others. Mutations in these genes lead to renal agenesis, a feature that was seen in only two children of our family. Therefore, we consider it unlikely that a gene involved in ureteric bud induction is causally related to the findings in this family.

In contrast, defects in the process of ureteric bud branching morphogenesis have a broader spectrum of clinical manifestations and can lead to hypoplastic/dysplastic kidneys, to ureterovesical junction obstruction, to duplex kidneys and to renal agenesis [10]. This spectrum of changes resembles the clinical spectrum encountered in our family. As an example, in a mouse knockout model of bone morphogenetic protein 4 (bmp4), it was shown that bmp4 has two functions in the early morphogenesis of the kidney and urinary tract [17]. One is to inhibit ectopic budding from the Wolffian duct or the ureter stalk by antagonizing inductive signals from the metanephric mesenchyme to the illegitimate sites on the Wolffian duct. The other is to promote the elongation of the branching ureter within the metanephros, thereby promoting kidney morphogenesis [17]. These features would make bmp4 a strong candidate gene. Therefore, bmp4 along with a number of other strong candidate genes involved in the process of ureteric bud branching morphogenesis (EMX2 [18], BF-2 [19], RARx, RARβ2 [20], Gata3 [21]) are currently under investigation to further refine their possible role as disease-causing factors in this family.

Taken together, to our knowledge, this is the first report on familial clustering of urinary tract malformations inherited in a likely autosomal recessive
trait. Against this background it is tempting to speculate about recessive inheritance as the true cause of a number of ‘sporadic’ cases of urinary tract malformations.

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Conflict of interest statement. None declared.

References


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