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ORIGINAL ARTICLE

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# Multicystic kidney dysplasia and Turner syndrome: two cases and a literature review

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**Abstract** Renal malformations occur in 33%–70% of cases of Turner syndrome (chromosome 45 and variants). We describe two cases of multicystic dysplastic kidney in Turner syndrome. A literature review of renal abnormalities in Turner syndrome shows the frequency of cystic disease to be 1.76%. In multicystic dysplastic kidney, diagnostic investigation of the contralateral kidney, including voiding cystourethrography, is necessary in view of the high incidence of associated diseases (15%–20% of cases, vesicoureteric reflux) and other anomalies.

**Key words** Multicystic dysplastic kidney · Turner syndrome · Literature review

## Introduction

Turner syndrome is a chromosomal disorder, characterized by short stature, hypogonadism, and specific somatic malformations, that affects 1 in 2,500 live newborns [1, 2]. Only 1 in 100 embryos with the 45X0 karyotype survive. More than half of the patients with Turner syndrome have a mosaic karyotype (46XX/45X0) [2].

Turner syndrome can manifest at birth with lymphedema of the hands and feet, webbed neck, low-set hair and auricles, and is confirmed by karyotyping from peripheral blood [2, 3]. Sometimes these characteristics can be detected by fetal ultrasonography and the diagnosis is then confirmed by amniocentesis or chorionic villus sampling [2]. The most-common clinical characteristics are listed in Table 1. Association of renal abnormalities and Turner syndrome varies from 33% to 70% [4, 5], with a greater prevalence in subjects with a mosaic karyotype than in 45X0 patients [6] (Table 2).

Two forms of cystic kidney disease have been described in Turner syndrome, multicystic dysplasia (MCDK) and simple renal cysts [7]. MCDK, the second most-frequent cause of neonatal abdominal masses, occurs in many chromosomal disorders, such as trisomy 13 and 18 [8]. The kidney is increased in volume and consists of a disorderly mass of clearly separated macroscopic cysts and of a lack of functioning renal parenchyma. The contralateral kidney may be normal, but often has malformations [9]. The bilateral form (4%–8% of cases) is incompatible with life. Simple renal cysts are single acquired lesions not associated with dysplasia [7].

A literature review shows that Turner syndrome is associated with renal abnormalities in 187 of 432 patients (43.28%) and with cystic renal disease in 1.76% of 397 cases: MCDK (4) and simple renal cysts (3). The diagnoses were obtained by urography up to 1988, and later by ultrasonography (Table 3).

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**Table 1** Clinical characteristics in Turner syndrome[a]

| |
|---|
| Short stature with growth rate below the 3rd percentile |
| Webbed neck |
| Low-set hair and auricles |
| Retrognathism |
| Epicanthus, hypertelorism |
| Cleft palate, dental malformations |
| Barrel chest |
| Small, hypopigmented areolae mammae |
| Pigmented moles |
| Short fourth metacarpus |
| Cubitus valgus |
| Cardiac malformations (nonstenotic bicuspid aorta, aortic coarctation, aortic stenosis) |
| Renal malformations (horseshoe kidney, renal agenesis, duplication of renal pelves and ureters, malrotations, hydronephrosis, cystic disease) |

[a] Modified from references 1–3, 12, and 13

**Table 2** Incidence of renal abnormalities in Turner syndrome compared with the general population[a]

| Renal abnormality | Monosomy/mosaicism Turner | General population |
|---|---|---|
| Duplication of pelves and ureters | 20%–30% | 0.75% |
| Malrotations and ectopic kidney | 14% | 0.5% |
| Horseshoe kidney | 7%–13% | 0.15%–0.5% |
| Monolateral renal agenesis | 2.8%–5% | 0.1% |
| Stenosis of the pyelo-ureteric and ureterovesical junctions | 2.5% | 0.5% |
| Multicystic kidney dysplasia | 0.9% | 0.02% |
| Simple renal cysts | 0.67% | 0.18% |

[a] Modified from references 6, 7, 13, and 14

**Table 3** Review of the literature reporting renal abnormalities and renal cystic disease associated with Turner syndrome (*US* ultrasonography)

| Author | Year | Journal | No. of Turner syndrome patients studied | No. of renal abnormalities | No. with renal cystic disease | Diagnostic procedure |
|---|---|---|---|---|---|---|
| Jeune et al. [15] | 1963 | Ann Endocrinol (Paris) | 25 | 18 | 0 | Urography |
| Lemli and Smith [16] | 1963 | J Pediatr | 14 | 9 | 0 | Urography |
| Revens and Palubinskas [17] | 1966 | Radiology | 14 | 11 | 0 | Urography |
| Palma et al. [18] | 1967 | Radiol Clin | 30 | 16 | 0 | Urography |
| Hung and Lopresti [12] | 1968 | J Urol | 16 | 13 | 1[a] | Urography |
| Matthies et al. [4] | 1971 | Clin Pediatr (Phila) | 15 | 11 | 0 | Urography |
| Rosenberg and Tell [3] | 1972 | Pediatrie | 36 | 21 | 0 | Urography |
| Rahal et al. [5] | 1973 | Am J Dis Child | 1 | 1 | 1[b] | Urography |
| Litvak et al. [14] | 1978 | J Urol | 38 | 14 | 0 | Urography |
| Schulman and Giannakopoulos [13] | 1980 | Chir Pediatr | 23 | 14 | 0 | Urography |
| Barakat and Butler [6] | 1987 | Int J Pediatr Nephrol | 4 | 2 | ? | Urography/US |
| Lippe et al. [19] | 1988 | Pediatrics | 141 | 37 | 0 | Urography/US |
| Herman and Siegel [7] | 1994 | Pediatr Radiol | 12 | ? | 3[c] | US |
| Wax et al. [20] | 1994 | Am J Perinatol | 1 | 1 | 0 | US |
| Francois et al. [21] | 1996 | Eur J Pediatr | 1 | 1 | 0 | US |
| Flynn et al. [22] | 1996 | Pediatr Nephol | 43 | 10 | ? | US |
| Benjamin and al-Harbi [23] | 1997 | Ann Trop Paediatr | 1 | 1 | 0 | US |
| Personal series | 1999 | Unpublished data | 29 | 7 | 2[d] | US |
| Total | | | 444 | 187[e] | 7[f] | |

[a] Monolateral cyst
[b] Multicystic dysplasia
[c] Two simple renal cysts, one multicystic dysplasia
[d] Two multicystic dysplasia
[e] Excluding the series of Herman and Siegel [7]
[f] Excluding the series of Barakat and Butler [6] and Flynn et al. [22]

## Case reports

Patient 1

Patient 1 (45,X0) is a female born at 38 weeks' gestation of a second pregnancy. At 4 months, fetal ultrasonography showed right hydronephrosis (23 mm). Her birth weight was 2,760 g, length 47 cm, and Apgar score 9–10. Postnatal renal ultrasonography showed right MCDK (Fig. 1a) associated with left pyelectasis (anteroposterior diameter 10 mm) (Fig. 1b) and with congenital dysplasia of the hips; cardiological investigations yielded normal findings. Antibiotic therapy with cefaclor was initiated owing to evidence of a urinary tract infection (*Escherichia coli*).

On the 24th day of life, a voiding showed vesicoureteric reflux. The ultrasonography findings at the age of 3 months were unchanged on the right, while the left pyelectasis was reduced (7 mm). At the age of 9 months, renal ultrasonography revealed an involution of the dysplastic kidney and compensatory hypertrophy of the contralateral kidney (the pyelectasis described previously was no longer detectable). Growth measurements showed 3.5 cm growth in stature in 4 months. Ultrasonography and scintigraphy examinations were scheduled at 1 year.

Patient 2

Patient 2 (46,X,del (p21)[21]/45,X[16]) is a female born at 36 weeks' gestation. There was a prenatal ultrasonographic suspicion of right MCDK and left hydroureteronephrosis. Surgical delivery by cesarean section was needed due to acute fetal distress. The patient's birth weight was 2,270 g, length 45 cm, and Apgar score 8–9. At birth renal ultrasonography confirmed the renal abnormality (Fig. 2a, b). Cystourography showed a left refluxing megaureter with associated junction disease. The infant had surgical repair of thoracic aortic coarctation.

By day 23, ultrasonography revealed a slight reduction of the nephrosis, with a slight increase in renal parenchymal thickness and a normal resistance index by color Doppler sonography. Periodic urinary investigations revealed *Enterobacter* urinary tract infection (antibiotic therapy with netilmicin was given). Renal scintigraphy revealed a nonfunctional right kidney, with an enlarged left kidney with intraparenchymal stasis.

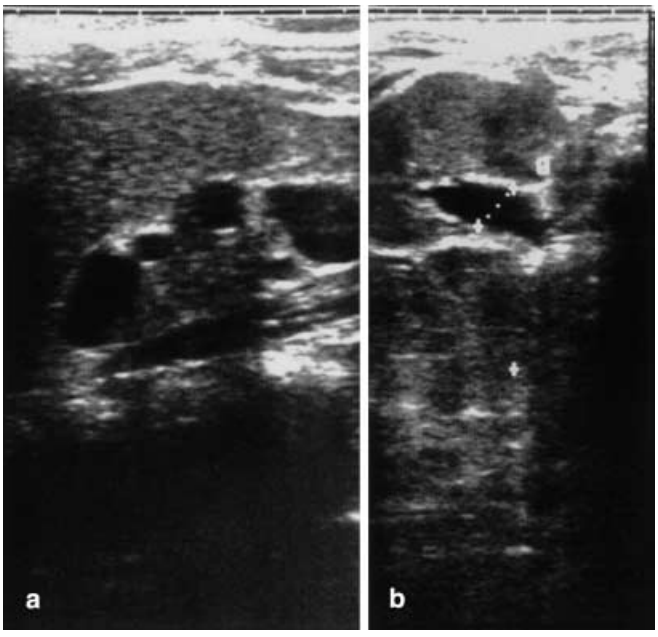


**Fig. 1** **a** Longitudinal sonogram. The right kidney is filled with cysts of various sizes. There is no recognizable renal pelvis (multicystic renal dysplasia). **b** Transverse sonogram. The left kidney shows mild dilatation of the pelvis (anteroposterior diameter 8 mm)

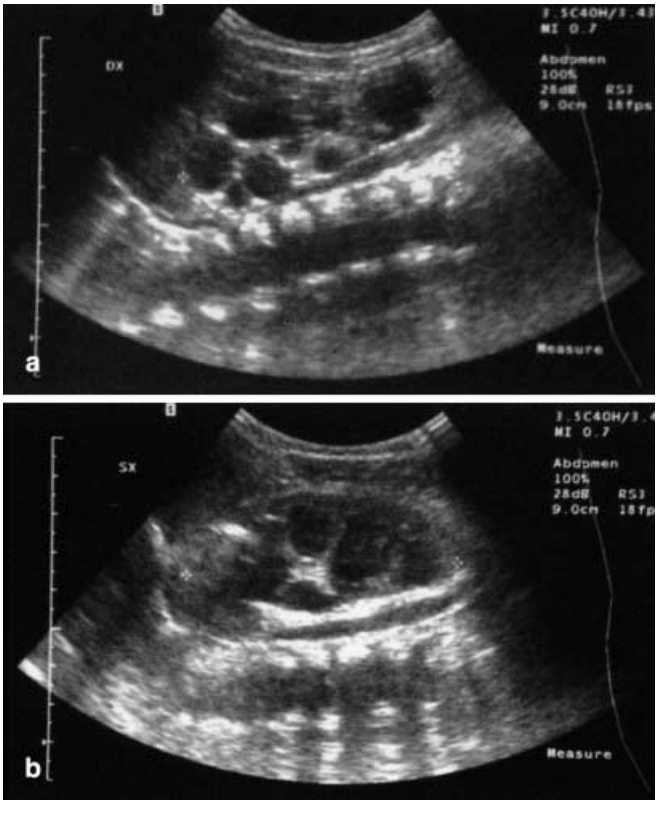


**Fig. 2** **a** Longitudinal scan of the right kidney demonstrates cysts of varying size. The kidney is mildly enlarged. **b** Longitudinal scan of the left kidney shows marked dilatation of the collecting system. The cortex is compressed and thinned

At 11 months, a right nephrectomy was performed, with submeatal injection of Macroplastique (left ureter), and urinary unidiversion, which entailed reimplantation of the distal ureteric stump on the left renal pelvis and temporary transurethral catheterized anastomosis of the left ureter. Serial ultrasonography revealed good growth of the left kidney, while voiding cystourethrography was normal.

## Discussion

The diagnosis of Turner syndrome warrants investigations for associated malformations, particularly cardiac and renal malformations. In particular, the association of renal malformations is significantly greater in monosomy than in mosaicism. Although renal disease is frequent, cystic kidney disease is rare: 1.76% of 444 cases. However it must be emphasized that imaging prior to 1988 (when ultrasonography was introduced) would likely grossly underestimate the percentage of patients that have simple cysts and/or have MCDK. In fact urography in children is notorious for missing simple cysts that are now clearly demonstrated by ultrasonography in patients with Turner syndrome.

The incidence of single renal cysts calculated in our series (0.75%) is far lower than that previously reported in the literature (16%) [7]. In all seven patients, including our two patients, the cystic disease was unilateral. However investigations must be extended to the contralateral kidney, which also may be abnormal. In the two patients described, the contralateral kidney presented left pyelectasis in one patient (which then resolved spontaneously over time) and, more importantly, a left refluxing megaureter in the other patient.

The prognosis of multicystic dysplasia depends on the functional capability of the contralateral kidney. Abnormalities of the contralateral kidney and urinary tract are found in 50% of patients with MCDK. Vesicoureteric reflux is the most-common associated abnormality (15%–20%) [10, 11], and for this reason thorough diagnostic investigation of the contralateral kidney by voiding cystourethrography and, as necessary, scintigraphy, is always necessary [9].

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## LITERATURE ABSTRACTS

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### ATP depletion increases tyrosine phosphorylation of beta-catenin and plakoglobin in renal tubular cells

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This study examines the hypothesis that the loss of integrity of the junctional complex induced by ATP depletion is related to alterations in tyrosine phosphorylation of the adherens junction proteins beta-catenin and plakoglobin. ATP depletion of cultured mouse proximal tubular (MPT) cells induces a marked increase in tyrosine phosphorylation of both beta-catenin and plakoglobin. The tyrosine phosphatase inhibitor vanadate has the same effect in ATP-replete (control) monolayers, whereas genistein, a tyrosine kinase inhibitor, reduces phosphorylation of both proteins in ATP-replete monolayers and prevents the hyperphosphorylation of these proteins with ATP depletion. This study also demonstrates that the fall in the transepithelial resistance of MPT monolayers induced by ATP depletion can be reproduced by treatment of ATP-replete monolayers with vanadate, whereas genistein substantially ameliorates the fall in transepithelial resistance induced by ATP depletion. Also, using immunofluorescence microscopy it was demonstrated that ATP depletion results in a marked diminution of E-cadherin staining in the basolateral membrane of MPT cells. Vanadate mimics this effect of ATP depletion, whereas genistein ameliorates the reduction in the intensity of E-cadherin staining induced by ATP depletion. Because it is has been well established that hyperphosphorylation of the catenins leads to dissociation of the adherens junction and to dysfunction of the junctional complex, it is proposed that the increase in tyrosine phosphorylation of catenins observed in MPT cells during ATP depletion contributes to the loss of function of the junctional complex associated with sublethal injury.

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### Urothelial lesions in Chinese-herb nephropathy

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Rapidly progressive renal fibrosis after a slimming regimen including Chinese herbs containing aristolochic acid (AA) has been identified as Chinese-herb nephropathy (CHN). We reported urothelial atypia in three patients with CHN, with the subsequent development in one patient of overt transitional cell carcinoma (TCC). Therefore, it was decided to remove the native kidneys, as well as the ureters, in all patients with CHN. Nineteen kidneys and ureters removed during and/or after renal transplantation from 10 patients were studied to assess critically urothelial lesions and to characterize the cellular expression of p53, a tumor-suppressor gene overexpressed in several types of malignancies. Multifocal high-grade flat TCC in situ (carcinoma in situ; CiS) was observed, mainly in the upper urinary tract, in four patients, a prevalence of 40%. In one of those patients, a superficially invasive flat TCC of the right upper ureter, as well as two additional foci of noninvasive papillary TCC, were found in the right pelvis and left lower ureter, respectively. This patient also presented recurrent noninvasive papillary TCC of the bladder. Furthermore, in all cases, multifocal, overall moderate atypia was found in the medullary collecting ducts, pelvis, and ureter. All CiS and papillary TCC, as well as urothelial atypia, overexpressed p53. These results show that the intake of Chinese herbs containing AA has a dramatic carcinogenic effect. Carcinogenesis is associated with the overexpression of p53, which suggests a role for a p53 gene mutation. The relationship of this mutation with the reported presence of AA DNA adducts in the kidney remains to be explored.