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Frequency of renal malformations in Turner syndrome: analysis of 82 Turkish children

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Abstract We evaluated the frequency of renal malformations in relation to nonmosaic 45,X (group A, 45 patients, 54.9%) and mosaic/structural abnormalities of X (group B, 37 patients, 45.1%) in 82 Turkish patients with Turner syndrome (TS). Ultrasonography of the kidneys and collecting system was performed in all patients. Of the 82 patients, 31 had different renal malformations (37.8%). Horse-shoe kidney was observed in 9 (29.0%) of the 31 patients, and 17 patients (54.8%) had various collecting system malformations, while 5 (16.2%) had malrotation and other positional abnormalities. The prevalence of renal malformations was significantly higher in group A (51.1%) than group B (21.6%) (2:7.94, $P<0.05$). Although 8 of the 9 patients with horse-shoe kidney had the 45,X karyotype, collecting system malformations were observed more frequently in group B. Recurrent urinary tract infections (UTIs) were detected during follow-up in 7 patients, and hypertension developed in 3 patients. In patients who had a normal baseline nephrological evaluation, no problem suggesting renal disease developed during follow-up. We conclude that all forms of TS should have routine nephrological screening on diagnosis, since structural malformations of the kidney occur more frequently in nonmosaic 45,X TS, while collecting system malformations are mostly seen in mosaic/structural X forms. Those included in the group for nephrological follow-up had an increased risk for hypertension and/or UTI.

Key words Turner syndrome · Renal malformation · Ultrasonography

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Introduction

Turner syndrome (TS) is a genetic disease first described by Rossle [1] in 1922 and later described in detail by Turner [2] in 1938. TS is characterized by short stature, gonadal dysgenesis, and various somatic features. At birth, the incidence of TS is about 1 in 4,000 to 1 in 10,000 [3, 4, 5]. A 45,X karyotype is observed in 55% of patients. Different forms of mosaicism involving X nullisomy, Xp or Xq deletions are also encountered [4, 6, 7, 8]. Developmental anomalies of kidneys and collecting system are associated malformations of TS that predispose patients to urinary tract infections (UTIs) and hypertension. Hypertension may also develop due to vascular abnormalities, such as coarctation of the aorta and/or intrarenal vascular changes [3, 4, 5]. The reported incidence of renal malformations varies between 33% and 66% in all groups of TS patients [4, 5, 9, 10, 11, 12]. In TS patients with nonmosaic 45,X karyotype, major anomalies of the cardiovascular and genitourinary systems are observed more frequently. However there are no data to date suggesting a direct correlation between the phenotype and cytogenetic findings in TS patients. Here we report the incidence of different types of renal malformations in relation to monosomy X and mosaic/structural X in 82 Turkish TS patients.

Patients and methods

Eighty-two girls with a diagnosis of TS were included in the study and were followed between January 1986 and December 1997. The mean age of the patients at admission was 11.7±4.6 years (range 1 day to 22.5 years). Patients displaying short stature, delayed puberty, and other somatic features suggestive of TS were

referred to the Division of Pediatric Medical Genetics of Istanbul Medical Faculty. The clinical diagnosis of TS was confirmed by cytogenetic study performed on peripheral blood lymphocytes in all patients. All patients were evaluated for cardiovascular malformations by echocardiography. Coarctation of the aorta was detected in 4 patients and other cardiac malformations [patent foramen ovale in 1, acyanotic tetralogy of Fallot in 1, ventricular septum defect (VSD) with parachute mitrale and bicuspid aorta in 2, VSD in 1, and mitral stenosis in 1] were observed in another 7 patients. In these 7 patients, malrotation of the kidneys was observed in 1, mild dilatation in another, and unilateral duplicated collecting system was observed in a further patient.

Nephrological evaluation

Ultrasonography (US) of the kidneys and collecting system was performed in all patients by Hitachi EUB 40 real-time sonography and Acuson 128-XP/10 Doppler sonography using 3.0-MHz and 5.0-MHz frequency probes. All patients who had abnormal renal US findings were followed by the Division of Pediatric Nephrology for increased risk of recurrent UTI and/or hypertension, and radiological evaluations such as intravenous pyelography (IVP), nuclear scintigraphy [Tc 99m dimercaptosuccinic acid (DMSA) and diethylene triamine penta-acetic acid (DTPA)], or voiding cystourethrography (VCUG) were performed for the definitive renal diagnosis. Hydronephrosis was graded according to the classification system of the Society for Fetal Urology [13]. Vesicoureteral reflux (VUR) was classified as grade 1–5 according to the classification of the International Reflux Committee [14]. UTI was defined as bacteriuria above 100,000 colonies/ml in mid-stream urine, and hypertension was defined as systolic and diastolic blood pressure above the 95th percentile for age on three consecutive measurements [15].

Cytogenetic study

Cytogenetic analysis was performed in all patients on peripheral blood lymphocytes. Ten metaphases were analyzed in all patients with high-resolution banding techniques to exclude structural abnormalities of the X chromosome; 20 other metaphases were also counted. Up to 50 metaphases were studied when a sex chromosome abnormality was detected in the first 30 metaphases. At least three G-banded metaphases having monosomy X and two metaphases for another X chromosome abnormality were accepted as mosaics. The study population was divided into two groups according to the cytogenetic results. The patients with nonmosaic 45,X karyotype were classified as group A and the patients with mosaic/structural X chromosome abnormalities as group B.

Statistical analysis

Chi-squared and Fisher exact tests were used to compare the frequency of renal malformations in group A and group B patients. $P<0.05$ was considered statistically significant.

Results

A total of 45 patients (54.9%) had nonmosaic 45,X karyotype (group A) and 37 patients (45.1%) had mosaic/structural X chromosome abnormalities (group B). The most-common mosaic/structural X chromosome abnormality was 45,X/46,X, i(Xq), occurring in 18 patients (48.6%) in group B (Table 1).

None of the patients displayed symptoms suggesting urinary tract disease at the time of referral. With the baseline US evaluation, 31 of 82 patients (37.8%) were found to have either renal or collecting system malformations. In 4 patients with coarctation of the aorta, no renal malformation was detected by conventional imaging techniques. Most of the malformations (54.9%) detected by US were of the collecting system and were not associated with additional kidney malformations, such as horse-shoe kidney, malrotation, or other positional abnormalities of the kidneys. Horse-shoe kidney was observed in 9 of 31 patients (29.0%), and 5 patients (16.1%) had malrotation and other positional abnormalities. The collecting system malformations observed in 17 (54.9%) patients were as follows: severe hydronephrosis (grade 3–4) in 3 patients, mild hydronephrosis (grade 1–2) in 6 patients, and uni-/bilateral duplicated collecting system malformations in 8 patients.

Table 1 Distribution of the study group according to the cytogenetic results

	Cytogenetic results	*n*	%
Group A	45,X	45	54.9
Group B	Mosaic/structural X abnormalities	37	45.1
	45,X/46,Xi(Xq)	18	48.7
	45,X/46,XX	6	16.2
	45,X/46X,r(X)	5	13.5
	45,X/47,XXX	5	13.5
	45,X/46,Xqdel	2	5.4
	45,X/46,Xpdel	1	2.7

The frequency of renal malformations was 51.1% in group A, while only 21.6% of group B patients had pathological US findings; the difference was statistically significant (2:7.94, $P<0.05$). The distribution of renal malformations according to cytogenetic results is shown in Table 2. Horse-shoe kidney, malrotation of the kidneys, and other rotational abnormalities were significantly correlated with 45,X karyotype ($P<0.01$). While 8 of 9 patients (88.9%) with horse-shoe kidney were in group A, 87.5% of the renal malformations detected in group B were localized in the collecting system ($P<0.05$).

In all 9 patients with horse-shoe kidney, Tc 99m DMSA, IVP, and VCUG were performed to confirm the US diagnosis and to rule out VUR and other associated malformations that were undetectable by US. One patient had unilateral duplicated system with grade 3 VUR into the lower system and renal scars, while no additional renal malformation was detected in the remaining 8 patients with horse-shoe kidney.

Five patients with uni- and 3 with bilateral duplicated system, and 9 patients with varying grades of hydronephrosis, were also evaluated by IVP, Tc 99m DTPA with diuretic use, and VCUG. Two patients with severe hydronephrosis (grade 4) had ureteropelvic junction (UPJ) obstruction confirmed by IVP and diuretic renography; in 1 patient, severe obstructive hydronephrosis and a nonfunctioning kidney necessitated unilateral nephrectomy due to recurrent UTI; pyeloplasty was performed in the other. Nonrefluxing megaurether and megacalix were detected in the third patient with severe hydronephrosis. In none of the 6 patients with grade 1 and grade 2 hydronephrosis did nonobstructive dilatation of the pelvis renalis necessitate any urological procedure, and patients were followed by yearly US and urine cultures. Varying grades of VUR

Table 2 Nephrological evaluations of the patients with Turner syndrome according to the cytogenetic analysis (*UPJ* ureteropelvic junction, *VUR* vesicoureteral reflux)

	n	45,X	45,X/ 46,XX	45,X/ 46,Xi(Xq)	45,X/ 46,Xr(X)	45,X/ 47,XXX	45,X/ 46,Xqdel	45,X/ 46,Xpdel
Normal	51	22	4	14	3	5	2	1
Abnormal	31	23	2	4	2	0	0	0
Horse-shoe kidney	9	8	–	1	–	–	–	–
Associated malformation								
Yes	1	1[a]	–	–	–	–	–	–
No	8	7	–	1	–	–	–	–
Malrotation, positional abnormalities	5	5	–	–	–	–	–	–
Collecting system malformations	17	10	2	3	2	–	–	–
Unilateral duplication	5	3	1	1	–	–	–	–
With VUR	2	1	1	–	–	–	–	–
Bilateral duplication	3	2	–	–	1	–	–	–
With VUR	1	1	–		–	–	–	–
Severe hydronephrosis	3	2	–	1	–	–	–	–
UPJ	2	2	–	–	–	–	–	–
Megaurether-megacalices	1	–	–	1	–	–	–	–
Mild hydronephrosis	6	3	1	1	1	–	–	–

[a] One of the horse-shoe patients also had unilateral duplicated collecting system with VUR into the lower system

were detected in 3 of the 8 patients with duplicated collecting system (2 in unilateral, 1 in bilateral duplication).

All patients with TS were followed for increased risk of hypertension, and those with abnormal US findings for UTI . The mean duration of follow-up was 6.2±3.1 years (range 1–11.3 years) in the study group. During nephrological follow-up, recurrent UTI were detected in 7 patients who had collecting system malformations. Hypertension not associated with coarctation of the aorta was observed in 3 initially normotensive patients (2 with horse-shoe kidney and 1 with unilateral refluxing duplicated system). Four patients with coartation of the aorta (2 of which were treated surgically) developed hypertension during follow-up. One of the hypertensive patients had a scarred kidney due to recurrent UTI in a refluxing unilateral duplicated collecting system. In 2 other patients with horse-shoe kidney, the etiology of hypertension was investigated. While grade 3 VUR, recurrent UTI, and renal scars were detected in 1, no additional renal malformation leading to hypertension was detected in the other. Biochemical parameters, including cholesterol and triglyceride levels, were normal, and plasma renin activity was slightly above normal limits. Angiographic study was planned in this patient, but could not be performed due to lack of parental consent. Hypertension was controlled in all 3 patients with antihypertensive medication (vasodilatory agents in 2 patients with renal scars, captopril in the patients with horse-shoe kidney without scars).

A total of 5 urological procedures were performed during follow-up. These included; unilateral nephrectomy in 1 patient with a nonfunctioning kidney due to UPJ stenosis, Anderson-Hynes pyeloplasty in 1 patient with UPJ stenosis, Cohen transtrigonal ureteral reimplantation in 1 patient with horse-shoe kidney, hypertension, and duplicated system with grade 3 VUR, and embolization using subrothelial injection of teflon in 2 patients with duplicated system, for recurrent UTI and VUR.

Deterioration of renal function was not observed in any patients with TS, and in patients who had normal baseline nephrological evaluation, no problem suggestive of renal disease developed during follow-up.

Discussion

The prevalence of renal anomalies in TS has been as high as 60% in older series. In more-recent series, the prevalence varies from 33% to 60% [5, 9, 12, 16]. In the study of Lippe et al. [9], 141 patients with TS were evaluated by IVP, and 39% of patients had different renal anomalies. A study with a 65% incidence of mosaic/structural cytogenetic abnormality reported a renal malformation rate of 24% [17]. This is significantly the lowest prevalence reported. The renal malformation prevalence of 37.8% in our study population comprising 55% 45,X patients is in accordance with previous reports.

Renal malformations vary in TS, and the majority of these defects are anatomical curiosities with limited clinical significance. Although horse-shoe kidney is the most-commonly encountered, different rotational abnormalities, duplication of collecting system, and other collecting system malformations (such as hydronephrosis due to stenosis of different sites of the ureter) are also observed [3, 4, 5]. Although it is not easy to correlate clinical findings with cytogenetic results, malformations were more commonly observed in the 45,X patients [5, 7, 18].

The association between different renal anomalies and specific karyotypes has not been reported to date. In their review of data of all reported patients with X chromosome abnormalities during the years 1959–1993, Ogata and Matsuo [5] reported the frequency of renal abnormalities in 45,X patients as 20%, 13% in 46,Xi(Xq), 6% in 46,Xdel(X)(p11→pter), and 6% in 46,Xdel(X)(q22–25)

patients, while no patient had renal malformations in the group with other X chromosome abnormalities. In our series of 31 patients with renal malformations, the prevalence was significantly higher in 45,X TS patients (51.1%) than patients with mosaic/structural X chromosome abnormalities (21.6%).

In the patient group with mosaic/structural X abnormalities (group B), no patient with 45,X/47,XXX (*n*=5), 45,X/46,Xqdel (*n*=2), or 45,X/46,Xpdel (*n*=1) had any renal malformation, while 40% of 5 patients with 45,X/46,X,r(X), 22.2% of 18 patients with 45,X/46,Xi(Xq), and 33.3% of 6 patients with 45,X/46,XX had some renal malformations. Due to the limited number of patients in the different cytogenetic subgroups in this study, it is not possible to make a definite conclusion about the frequency of renal malformations in patients with different mosaic/structural X chromosome abnormalities. Horse-shoe kidney was observed more frequently in the 45,X form of TS, and patients with mosaic/structural X chromosome abnormalities tended to have various collecting system malformations which were of more-limited clinical significance. Phenotype-karyotype correlation is hard to investigate in TS, and many etiopathogenetic factors play a role. The widely approved hypothesis involves lymphatic stasis secondary to lymphatic hypoplasia and compression of organ systems due to enlarged lymphatic vessels. According to this hypothesis, the developmental renal malformation is the result of distended retroabdominal and iliac lymphatic vessels inhibiting rotation and migration of the kidneys [5, 7, 18]. This may also explain why group A patients have a higher incidence of renal malformations, since they exhibit lymphedema more frequently.

There have been early papers suggesting phenotypic differences in TS patients based on the parental origin of the chromosome in 45,X individuals [19]. In a series in which the origin of the single X was maternal in 80% of the live-born babies, there was no clinical difference between those with maternal and paternal origin [8]. We propose that 45,X TS subjects with renal malformations should be evaluated for parental origin in a much-larger or collaborative study to allow a definitive conclusion on phenotypic effects. Our series, with only 23 subjects with the 45,X karyotype and renal malformations, is too small to obtain statistically significant data.

It is recognized that hypertension may develop due to coarctation of the aorta and/or intrarenal vascular changes in TS patients [3, 5, 7]. However, renal malformations leading to scars are also risk factors for hypertension. In this study, hypertension developed during the follow-up period in 3 initially normotensive patients, in addition to 4 patients who presented with coarctation of the aorta without co-existing renal malformations. Hypertension could be attributed to reflux nephropathy in 2 patients, but in the third patient with horse-shoe kidney without associated renal malformations, the etiology of hypertension could not be clearly explained. We suggest that in this patient with slightly high renin levels, hypertension might be related to some intrarenal vascular changes, although an angiographic study could not be performed.

We conclude that routine nephrological screening should be performed in all forms of TS on diagnosis, bearing in mind that malformations of the kidneys, such as horse-shoe kidney, malrotation etc., occur more frequently in 45,X TS patients, while collecting system malformations occur more frequently in the other forms. Those who are included in the group for nephrological follow-up have an increased risk of hypertension and/or UTI, as observed in our study population.

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