A CLINICAL AND CYTOGENETIC STUDY OF TURNER SYNDROME

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ABSTRACT

Forty five cases of Turner syndrome diagnosed in the Genetics Clinic, between January 1986 and December 1993, were analyzed. The most commonly observed karyotype was 45, X (44.4%), followed by 45, X/46, XX mosakhm (24.4%). Less frequently demonstrated karyotypes were 45, X/46, X, *i (Xq) mosaicism and 46, X, i (Xq) (13.3%). Mosaicism for chromosome was seen in 6.7% of patients.*

Patients with 45, X *karyotype had short stature (85%), dysmorphic fades (60%), delayed appearance of secondary sexual characters (100%) and primary amennorhea (100%). Those with 45, X/46, XX mosaicism were less often dysmorphic and presented with either primary or secondary amenorrhea. Patients with 45, X karyotype were younger at diagnosis and had a significantly shorter mean adult height than those with 45, X/46,* XX *mosaicism. The phenotype in patients with other karyotypic abnormalities was similar to the 45,* X *group.*

Short stature and primary or secondary amenorrhea occurring together in a female strongly suggests the possibility of Turner syndrome, which should be confirmed by chromosomal analysis.

Key words: *Turner syndrome, Cytogenetics.*

Turner syndrome (TS) is an X chromosomal disorder with variable karyotypic abnormalities and protean clinical manifestations. It was first described as a distinct entity in 1938, by Turner, in seven females with sexual infantilism, webbed neck and cubitus valgus(l). However, in 1930, Ullrich had reported on an 8-year-old girl with short stature, lymphedema, neck webbing, cubitus valgus and dysmorphic facies, which retrospectively was the first reported case of TS(2).

The chromosomal basis of Turner syndrome was first recognised by Ford *et al*.(3). It is now known that TS is characterized by the presence of a single normal functioning X chromosome. The other X chromosome may be missing or abnormal, or mosaicism may be present, so that the X-chromosome anomaly is present in at least one cell line(4).

To the best of our knowledge, no large series of TS has been reported from India. Our aim was to study the karyotypic and clinical profile of patients with TS and identify any karyotype-phenotype correlation.

Material and Methods

Forty five cases of TS, presenting to the Genetics Clinic of the All India Institute of Medical Sciences, between Janu-

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ary 1986 and December 1993 were studied. Thirty four cases were analyzed retrospectively and eleven cases evaluated prospectively.

Their presenting symptoms, clinical features and age at presentation were analyzed. Hormonal profile (serum FSH and LH levels) and pelvic ultrasound findings were also studied in patients 12 years of age and above. A detailed cardiovascular evaluation was done in cases where abnormality was suspected on clinical examination.

Peripheral blood lymphocyte culture was carried out by the standard technique of Moorhead *et al.(5).* Trypsin and quinacrine banding of metaphase chromosomes was performed in every case using standard methodologies(6,7). Twenty five metaphases were studied for karyotyping. If one metaphase showed a different chromosomal constitution, the difference was again looked for by evaluating an additional 25 metaphases. If the different cell line was noted again, a total of 75 metaphases were studied and the degree of mosaicism quantitated. Serum FSH and LH levels were assayed by ELISA, using commercially available kits (Boehringer Mannheim, GmbH).

The mean age at diagnosis and mean adult height (>18 years age) were compared between the 45, X group and the 45, X/46, XX mosaic group using the Wilcoxon rank sum test. These features were not compared with the third group of "other" karyotypes because the latter was a heterogenous mix of various chromosomal abnormalities associated with TS, which were not included in the first two groups.

Results

Cytogenetic abnormalities seen in 45 patients with TS are shown in *Table* I.

Monosomy X (45X)

Of 20 patients with this karyotype, 12 presented before the age of 16 years, including 4 patients who were less than 2 years at diagnosis. The mean age at diagnosis was 11.2 + 6.8 years (median 13 years) and the mean adult height was 133.8 + 3.9 cm *(Table 11).*

The usual presenting complaint in the first two years of age was lymphedema. There were two neonates in this group, both of whom presented with low birth weight and edema over hands and feet. Patients between 2 and 16 years of age presented with short stature. In contrast, all the 8 patients who presented at or after 16 years of age

TABLE I– *Cytogenetic Abnormalities in 45 Patients with Turner Syndrome*

Karyotype	No.
45, X	20
45, X/46, XX	11
Others	14
45, X/46, X, i (Xq)	4
46, X, i (Xq)	2
45, X/46, XX, + marker	2
45, X/46, XX/47, XXX	1
45, X/46, XY	1
45, X/46, X, i (Yq)	1
45, X/45, X, 19q+	1
46, X, del X (p11.2-ter)	1
45, X/46, X, i (Xq)/47, X, i (Xq), Y	1

TABLE II— *Karyotype-Phenotype Correlations in Turner Syndrome (All Figures are percentages unless indicated otherwise)*

Features	45x (n=20)	45X/46XX (n=11)	Others (n=14)
Short stature	85	73	93
Dysmorphic facies	60	9	29
Pterygium colli	35	9	18
Short neck	15	18	14
Low posterior hairline	5	0	21
Cubitus valgus	45	18	57
Nail hypoplasia	15	9	0
Short 3rd to 5th metacarpals	10	0	21
Edema	20	0	0
Shield chest	30	0	43
#Delayed secondary sexual characters	100	80	67
*Primary amenorrhea	100	62.5	82
*Secondary amenorrhea	0	37.5	0
Congenital heart disease	5	0	7
^Renal anomalies	0	0	17
Mental retardation	5	0	14
Mean age at diagnosis (years)	11.2	19.5	18.2
~Mean adult height (cm)	133.8[$]	152.1[$]	142.7

#Calculated in patients >13 years of age (45, X group n=10; 45, X/46, XX group n=10; Others group n= 12).
*Calculated in patients 16 years of age or older (45, X group n=6; 45, X/46, XX group n=8; Others group n=11).
^Number of patients screened: 45, X group n=8; 45, X/46, XX group n=3; Others group n=6. -
~Calculated in patients 18 years of age or older (45, X group n=4; 45, X/46, XX group n=6; Others group n=7).
[$] p value for difference between mean adult height in the two groups <0.05.

had primary amenorrhoea as their presenting complaint.

Physical findings in our patients are shown in *Table II.* Dysmorphic facial features were noted in 60% of patients, which were epicanthic folds, low set or abnormal ears, micrognathia and high arched palate.

45XJ46XX Mosaicism

Of 11 patients in this group, 9 presented ≥16 years of age. The mean age at

diagnosis was 19.5 + 5.2 years (median 18 years) and the mean adult height was 152.1 +9.2 cm *(Table II).*

The presenting complaint was primary amenorrhea in 6, secondary amenorrhea in 3 and short stature in 2 patients. The most common physical findings were delayed secondary sexual characters and short stature. All the other Turner stigmata were infrequently seen *(Table II).*

Other X Chromosome Abnormalities Associated with Turner Syndrome

Apart from 45,X and 45,X/46, XX mosaicism, the other cytogenetic abnormalities seen in TS are shown in *Table I.* The most frequently seen karyotypes in this group of 14 patients were 45, X/46 X, i (Xq) in 4, and 46, X, i (Xq) and 45, X/46, XX, +marker in 2 patients, respectively.

Three patients were mosaic for the Y chromosome *(Table I).* Although by definition these patients would be classified as cases of mixed gonadal dysgenesis, we chose to include them in our study because they were unambiguously female (symmetric female external genitalia and female internal genitalia with presence of vagina, uterus and bilateral fallopian tubes) and had a chracteristic Turner phenotype.

Eleven patients in this group presented ≥16 years of age. The mean age at diagnosis was 18.2 + 4.7 years (median 17.5 years) and the mean adult height was 142.7 + 5.7 cm *(Table II).*

Nine patients presented with primary amennorrhea and 5 patients with short stature. Other clinical features of this group are shown in *Table II.* Short stature, cubitus valgus, shield chest and delayed secondary sexual characters were frequently seen, but other findings were seen less often.

Hormonal Profile

Serum FSH and LH levels could be estimated in only 18 of 37 patients, who were 12 years of age and above. These included 11 with monosomy X (45, X), 3 with 45, X/46, XX mosaicism and 4 patients with other karyotypes. The mean FSH and LH levels were 53.9 ± 43.4 (range 1.8-169.3) and 17.3 ± 13.8 (range 0.6-49.5) mlU/ml, respectively. FSH and LH levels were not compared between the various groups as the total number of patients in each group for whom the hormones were assayed were very small.

Thyroid function was assessed in 8 patients of whom 5 (62.5%) had elevated TSH levels and low thyroxine levels suggestive of early hypothyroidism. In 7 patients who were less than 12 years of age, the thyroid profile was done as part of the investigative workup for short stature, whereas in one 13.5-year-old patient thyroid function was assessed because of clinical features suggestive of hypothyroidism. these patients are being treated and followed up in the Pediatric and Adult Endocrinology Clinics.

Pelvic Ultrasound

Pelvic ultrasound findings were available for 20 of 37 patients who were 12 years of age and above. These comprised 9 with 45, X, 4 with 45, X/46, XX mosaicism and 7 with other karyotypes. In 10 patients (50%) neither ovary could be seen, 6 (30%) had bilateral streak ovaries, 2 (10%) had normal ovaries and

2 (10%) had other abnormalities. The 2 patients in the last group had only one ovary seen on ultrasound; in one patient it was a streak ovary while in the other it was large with a possibility of an ovarian tumor. The latter patient had 45,X/46, XX mosaicism and was lost to follow up. Except for the two patients with normal ovaries and uterus, all the others had hypoplastic uterus.

Of the 3 patients mosaic for the Y chromosome, 2 had bilateral streak ovaries whereas in the third patient neither ovary could be seen. As already mentioned all the 3 patients had unambiguous female internal genitalia with small hypoplastic uterus and both fallopian tubes seen on ultrasound. Laparotomy followed by removal of streak gonads, where present, is planned for all three patients.

Discussion

The approximate incidence of Turner syndrome is estimated to be 1 in 2500 live female births(8). The pathophysiology of Turner syndrome is not fully understood. It is suggested that a gene dosage inequality due to absence of part or all of the X chromosome is responsible for the phenotype(4). Prior to 12 weeks of *in utero* development the ovaries in a 45, X female appear normal histologically, but thereafter, there is a decrease in the number of follicle cells per oocyte. In the absence of a functional second X chromosome the oocytes degenerate more rapidly than normal, so that at the time of birth there are few, if any, left and the ovarian tissue resembles fibrotic streaks(9). Most of the other phenotypic features may be due to the presence of lymphedema at critical points in development, leading to failure of normal development(4). Failure to open the embryonic lymphatic channels may be responsible for the lymphedema(4). The cytogenetic profile of our patients is similar to those reported in earlier studies *(Table III)*. Many studies have attempted to correlate the karyotypic and phenotypic abnormalities in TS(10,12,13). The streak gonads appear identical regardless of the karyotype(13).

Short stature and primary amenorrhea were the commonest presenting features in our patients, regardless of karyotype. Final adult height (>18 years of age) was significantly less in patients with 45, X karyotype as compared to patients with 45, X/46, XX mosaicism ($p < 0.05$). Other common clinical features in the 45, X group were dysmorphic facies, pterygium coli, cubitus valgus and shield chest *(Table II)*. All these features were infrequently seen in the 45, X/46, XX mosaic group and less frequently seen in the group with other karyotypes. Our figures for these features in the 45, X group are similar to those reported by other authors *(Table IV)(9,1*0,12,13).

Almost a third of our patients with 45,X/46, XX mosaicism presented with secondary amenorrhea *(Table II)*. These patients had lower levels of mosaicism, *i.e.,* a larger number of metaphases studied were normal 46, XX and fewer were 45, X. Between 10-20% of patients with Turner syndrome have spontaneous onset of menstruation(4). This is seen less often in the 45, X group. Many of these patients have irregular periods or premature menopause.

TABLE III—*Comparitive Analysis of Cytogenetic Findings in Turner Syndrome from Different Studies (All figures are percentages except Reference Number and Number of Patients)*

Authors	Ref.	n	45, X	45, X/46, XX	Other
Ferguson-Smith (1965)	10	236	49.6	16.1	34.3
Hook & Warburton (1983)	8	902	53.1	14.7	32.2
Kleczkowska *et al.* (1990)	11	478	52.1	10.9	37
Lippe (1990)	9	141	56.7	8.5	34.8
Present study		45	44.4	24.4	31.2

Ref. : Reference number; n : Number of cases.

Pregnancy was only reported in one of our patients with TS. This patient had a 47, XXX/46, XX/45, X karyotype and had a history of recurrent spontaneous abortions. Pregnancy is extremely rare in patients with Turner syndrome, regardless of karyotype (monosomy or mosaic 45,X)(14). Approximately half the patients with TS who become pregnant are likely to have a miscarriage, while a large number have fetal malformations and chromosomal abnormajities(14,15). Recently, *in-vitro* fertilization using donor oocytes has been used to overcome the above problems(14).

Lymphedema was observed in all our 45, X patients who presented at or before two years of age. None of our older patients had lymphedema, regardless of karyotype. Lymphedema is known to decrease or disappear during childhood(12,16).

Mental retardation was rarely seen in our patients *(Table* 77). A much higher incidence of mental retardation has been reported in patients with a small ring X chromosome(17), but we did not have any patient with this karyotype.

None of our patients presented with hearing impairment. This finding has been reported in 50-70% of patients with 45, X karyotype and 100% of patients with 46, X, i (Xq)(4). None of our patients had an audiometric assessment and this may be the reason for the complete absence of this finding in our series.

Only 2 patients in our series had a congenital cardiovascular anomaly. These included a 21-day-old baby who had coarctation of aorta and a 45, X karyotype, and a 12.5-year-old child with aortic stenosis and 45, X/46, XX, +marker chromosomal constitution. The diagnosis of aortic coarctation was made clinically. Echocardiogram was not confirmatory in the neonate with coarctation of aorta and MRI was done to demonstrate the anatomical abnormality. A recent study has compared these two modalities for the diagnosis of

TABLE IV—*Comparative Analysis of 45, X Phenotype from Different Studies (All Figures are Percentages Except Number of Cases)*

Features	Lemli & Smith(12) (1963)	Ferguson-Smith(10) (1965)	Simpson(13) (1975)	Lippe(9) (1990)	Present study
No. of cases	25	117	#	141	45
Short stature	100	100	95	100	85
Dysmorphic facies	64	-	25-36	60	60
Pterygium coli	52	54	46	25	35
Short neck	68	-	74	40	15
Low posterior hairline	88	-	71	42	5
Excessive nevi	64	52	63	26	-
Cubitus valgus	72	-	54	47	45
Nail hypoplasia	80	77	66	13	15
Short 4th metacarpal	-	58	48	37	10
Edema	92	39	38	22	20
Shield chest	92	80	53	-	30
Delayed secondary sexual characters	15^	-	95	-	100
Primary amenorrhea	-	92	97	96	100
Congenital heart disease	52	21	10-16	55	5
Renal anomalies	64	-	38	39	0
Mental retardation	4*	8	11-17	-	5

#Compiled from several reports--hence variable number of cases (*e.g.*, short stature was looked for in 228 cases, whereas nail hypoplasia was looked for in only 47 cases).
- Figures not available; ^2 of 13 patients assessed; *1 of 24 patients assessed.

congenital heart disease in patients with Turner syndrome, and found that MRI is superior to echocardiogram for this purpose(18). The incidence of congenital heart disease in Turner syndrome is reported to be highest in the 45, X group (10-55%) and lowest in the other karyotype group (0-8%) comprising isochromosomes and long or short arm deletions of the X chromosome(4,9,12,13).

Between 2 and 5% of TS patients in most series are mosaic for the Y chromosome^). Three patients (6.7%) in our series were mosaic for the Y chromosome *(Table* I). One of these cases had a 45, X/46, XY karyotype. Traditionally, these patients are said to have mixed gonadal dysgenesis. However, our patient had short stature, symmetric female external genitalia and hypo-

plastic uterus, fallopian tubes and streak ovaries. She also had short neck with low posterior hairline, cubitus valgus and short 4th metacarpals. Eighty seven metaphases were counted during karyotyping of this patient of which seventy seven showed 45, X pattern and only ten showed 46, XY pattern. A Turner phenotype with a 45, X/46, XY karyotype is well known(9,16), and may be related to the degree of mosaicism. Our patient may have had a TS phenotype because a larger number of her cells had 45, X constitution and only very few cells had 46, XY constitution.

Patients with TS who are mosaic for the Y chromosome are at high risk for developing gonadoblastoma in their streak gonads(19). Every effort must be made to rule out the presence of the Y chromosome in patients with TS. Recently, molecular methods have been used to demonstrate the SRY gene in patients with TS, as a marker for the Y chromosome(20). Laparotomy with bilateral gonadectomy is planned for all our cases with a Y chromosome cell line. We also had 2 patients with a 45, X/46, XX, +marker karyotype *(Table I)*. A large majority of chromosome markers seen in cell lines of patients with TS are derived from the Y chromosome, thus putting these patients also at risk of developing gonadoblastomas(21). Both our patients with a marker cell line are being recalled for molecular studies, using polymerase chain reaction, to look for the presence of the SRY gene in their genome.

Serum gonadotrophin levels were high in most of our patients as expected, with FSH levels being consistently higher than concomitant LH levels. Although the release of both the hormones is stimulated by gonadotropin-releasing hormone, the difference in the metabolic clearance of the two hormones is responsible for the levels of FSH exceeding those of LH(9). However, we did have some patients with normal serum FSH and LH levels. It is possible that these patients would have had elevated levels if the tests were repeated or would have had exaggerated responses if a gonadotropin-releasing hormone test was undertaken(22).

Biochemical findings of early hypothyroidism were documented in 5 of 8 (62.5%) patients who had thyroid function tests performed. A high incidence of autoimmune hypothyroidism has been reported in patients with TS, thus highlighting the importance of detailed thyroid function evaluation in these patients(23).

Pelvic ultrasound findings in our patients are somewhat different from those reported by Adams *et al.(14)*. In their study of over 70 cases with TS with a wide range of karyotypes, they found streak ovaries in 50% of their patients, bilaterally absent ovaries in 20% and an "intermediate" pattern in the rest of the patients. The "intermediate" pattern consisted of ovaries which were slightly larger than streaks and contained 2-3 mm cysts. Only 3 patients had normal ovaries. They also demonstrated a range of ovarian morphology in all karyotypes, with as many as 20% of patients with 45, X karyotype having an "intermediate" pattern. The majority of our patients had bilaterally absent ovaries. None of our patients snowed the "intermediate" pattern and as many as 10% had normal ovarian morphology.

None of our younger patients with TS received recombinant growth hormone (rGH) therapy. Recent recommendations are in favor of using rGH in TS(25). Growth hormone increases growth velocity and leads to an average gain of 5 cm in terms of final height(26). However, cost is the major prohibitive factor for this form of treatment(27).

TS is a chromosomal disorder that is frequently misdiagnosed or missed completely. It should be thought of in any female with short stature and primary or secondary amenorrhea, even if other phenotypic features of TS are absent. Diagnosis should be confirmed by chromosomal analysis. The buccal smear test to look for Barr bodies is not a reliable screening test for patients with suspected TS(28).

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