ORIGINAL ARTICLE

Comparison of Classical and Non-Classical Turner Syndrome at NICH Karachi

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Abstract

Objective: To analyse chromosomal abnormalities of the patients who were referred for the screening of short stature and delayed puberty and to verify the association between karyotype and phenotype in confirmed Turner Syndrome (TS) patients.

Study Design: Descriptive study.

Place and Duration of Study: Department of Pediatric Endocrinology and Diabetes Unit-II, National Institute of Child Health, Karachi, from January 2011 to June 2016.

Methodology: Patients referred for the evaluation of short stature or delayed puberty were for the assessment of karyotype and phenotype correlations; standard karyotyping was executed and analysed on the basis of routine G-banding technique. Echocardiography and pelvic ultrasonography was also performed.

Results: The study population consisted of 79 registered patients, with short stature and delayed puberty 48/79 (60.75%), short stature 68/79 (86.07%), and ambiguous genitalia 5/79 (6.32%). Conferring to the karyotype analysis, classical Turner Syndrome 45, X was found in 42/79 (53.16%), isochromosomes 13/79 (16.45%), and mosaicism was present in 11/79 (14.1%). Only 7/79 (8.86%) cases were diagnosed in infancy.

Conclusion: The results of the study showed the consistency of short stature and delayed puberty in most of patients. Monosomy of X chromosome was the commonest followed by isochromosomes, mosaicism and structural abnormalities of X chromosome. No remarkable difference was found among classical and non-classical TS patients' height.

Key Words: *Karyotype, Phenotype, Monosomy, Isochromosomes, Mosaicism.*

INTRODUCTION

Turner's Syndrome (TS) is the most common genetic disorder in females with prevalence of 1:2500, which is about 3% live births of females delivered, and approximately 15% of miscarriages.[1,2] Turner's syndrome is caused by the complete absence of X chromosome in XX, or rarely the absence of Y chromosome in XY, which results into 45-X. This condition can also be caused by partial deletion of X chromosome including deletions, duplications, inversions, translocations, iso-chromosomes or ring formation liable for disproportion of gene content of the X chromosome, crucial for normal physiology of women.[3] Monosomy of X chromosome is caused by non-disjunction of chromosome during meiosis, maternal origin of non-disjunction is reported in 75% of TS.[4] Mostly, chorionic villus sampling (CVS) and amniocentesis is recommended in advanced maternal age or with previous history of chromosomal abnormality. Counselling by physician and geneticist are often useful for the prenatal testing, which is obligatory for the decision making whether to terminate the pregnancy or not.[5] Regardless of statistics that TS patient can be equally qualified and serve quite normally.[6]

Girls with the Turner's syndrome are well-known for their short stature and ovarian dysfunction.[3,7] Obesity is also one of the common features of TS patients and it increases with the advancement of their age, which may be associated with hepatic dysfunction.[8] In TS patients' length progression is somewhat limited during intrauterine life but it is also slow during childhood and adolescence. The predicted average adult height is about 143 cm, which occasionally beats up to 150 cm.[9] However, growth hormone therapy can significantly increase the final height of Turner patients with variable rate.[10]

Other morphological features include: facial dysmorphism, short and webbed neck, lymphedema of hands and feets, hypoplastic or hyperconvex nails, low-set hair-line, shield chest and other skeletal abnormalities. Patients with TS undergo cardiovascular defects, renal malformations, osteoporosis, primary hypogonadism, and thyroid disease.[11,12] They could have audio visual disturbances, and typical cognitive and behavioral traits. However, the ultimate diagnosis can only be made through karyotyping.[13] The morbidity and mortality rate among TS is three times higher than normal population.[14]

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The current study was conducted to access the chromosomal and morphological abnormalities of the patients with classical *versus* non-classical TS who were registered in the tertiary care hospital for the assessment of short stature and delayed puberty.

METHODOLOGY

In this descriptive study of Pakistani children, cases of TS were included. The cases were registered in the Department of Endocrinology and Diabetes, National Institute of Child Health, Karachi Pakistan, from January 2011 to June 2016.

These patients had been referred for the evaluation of short stature, delayed puberty, and other congenital abnormalities common in TS. A detailed examination was performed by an experienced physician and approved by two of the authors, who were pediatric endocrinologist. Data was composed by assessing the medical records of all identified TS patients, including age at diagnosis, comprehensive clinical features, cytogenetic analysis, and presence of any complication. Informed consents were taken and high confidentially of data was maintained.

Diagnostic confirmation was done by karyotyping through routine cell culturing and G-banding of lymphocytes. Subjects of this study were selected from short statured girls whose chromosomal findings contained monosomy of X and/or mosacisim in X cell line or alternative X choromosomal abnormality. Children with normal XX or XY karyotype were excluded.

Data was analysed using Statistical Package for Social Sciences (SPSS) version-21. Mean, standard deviation and normality of variables were calculated for quantitative variables and frequencies with percentages for categorical variables. Independent t-test was applied and a p-value less than 0.05 was considered as statistically significant.

The study was conducted after the approval from Institutional Ethical Review Board. There was no conflict of interest or support by any funding agency.

RESULTS

The results of chromosomal investigations at NICH from 79 registered patients were categorised into two groups. Group A was classical TS 45-X with 42 patients, and Group B had non-classical TS in 37patients (Table I).

Most of the patients in this study were diagnosed in the age range of 12-15 years. The mean height in classical TS patients was shorter in the age group of 5-10 years, which is shown in Table II.

Each TS patient was carefully assessed by the pediatrician. Approximately all of TS girls presented with

Table I: Type of Turner's syndrome according to karyotype in 79 patients.

Category	Karyotype classification	N	%	Karyotype
Group A (Classical)	Standard Monosomy	42	53.16	45,X
Group B (Non-classical)	Isochromosome Xq / Xp	13	16.45	45 X,(11),XqIsocromosomes (21)
				45 XX, isoXq
				46 X,I (X) (q10) (09) 45 X (11)
				46 XX.i X(q)
				46 XX Isocromosomes X (P 15)
	X Mosaicism	11	13.92	45 X,46XX
				45 X/47 XXX
	Structural abnormality of X chromosome	6	7.59	46 X(Xqt)[15]
				46 XX t (X:16) (q28:qtr)
				46 XX t X:21 qtrqtr(20)
				46,X,t(X;3)(?q24;p25)[20]
	Structural abnormality of Y chromosome	6	7.59	45 X [15] 47 X,idic Y q 12(17) 46 X idicYq 12(12)
				45 X(197)46 X,idic Y, ? P11.32(39)
				46,X,del(y)(q11.22q12)[10]/45,X[10]
				45X [12] /46X idic (Y)(q12)(07)/46XY [01]
	Ring chromosome	1	1.26	45,XO/46,X,r(X)[17/13]

Table II: Distribution of age at diagnosis of TS with mean height, weight and standard deviation.

Age Group	Classical TS		Non-classical TS		p-value	Classical TS		Non-classical TS		p-value
	Height cm Mean ±SD	n	Height cm Mean ±SD	n		Weight kg Mean ±SD	n	Weight kg Mean ±SD	n	
0.1-1 year	48 ±4.6	4	55 ±11.5	3	0.310	4.07 ±1.42	4	4.33 ±2.02	3	0.849
1.1-5 years	90 ±7.6	2	85 ±9.1	3	0.856	16 ±6.3	2	13.33 ±5.6	3	0.789
5.1-10 years	104.3 ±8.7	14	126.5 ±7.5	7	<0.001*	17.5 ±2.17	14	20 ±4.8	7	0.358
10.1-16 years	126.9 ±6.91	20	125.4 ±6.7	17	0.512	26.7 ±4.62	21	28.8 ±7.25	17	0.292
>16 years	133.7 ±5.3	2	132.5 ±10.52	7	0.918	29 ±5.65	2	32 ±3.82	7	0.396

Total No. of patients = 79.

Table III: Frequency of dysmorphic features in classical and non-classical TS.

Dysmorphic Features	Classical TS n (%)	Non-Classical TS n (%)
Cubitus valgus	18 (22.78)	10 (12.65)
Webbing of neck	20 (25.31)	9 (11.39)
Short 4th metacarpal	15 (18.98)	5 (6.32)
Pigmented neavi	17 (21.51)	4 (5.06)
Widespread nipples	14 (17.72)	4 (5.06)
Low posterior hairline	9 (11.39)	7 (8.86)
Deformed / hyperconvex nails	11 (13.92)	4 (5.06)
Short and deformed structure of hands	6 (7.59)	2 (2.53)
Wrist ostepenia	5 (6.32)	2 (2.53)
Short 5th metacarpal	4 (5.06)	(0)
Sheild chest	4 (5.06)	(0)

short stature. Detailed description of patients' dysmorphic features are summarised in Table III.

Pelvic ultrasound findings were also noteworthy. Majority of the TS girls showed presence of uterus with no or dysgenetic gonads. Only nine (11.39%) of TS patients were found to have both ovaries and uterus. Moreover, five (6.32%) of them were found to have gonads in inguinal canal.

Echocardiography was also performed in all confirmed TS patients. Eight of TS patients (10.12%) were found to have abnormal echocardiogram, in which five patients presented with bicuspid aortic valve, which is the most common type of cardiac abnormality in TS. Two patients with coarctation of aorta and one patient with aortic stenosis plus mild pulmonary valve stenosis were also diagnosed.

DISCUSSION

TS is described as complete absence or abnormal presence of an X chromosome, as mixture of 45 X with 46 XX or 46 XY cell lines, or might be structural abnormality of X chromosome. Patients with TS showed characteristic features, which have a strong relationship with their chromosomal make-up.[15] In this cohort, most common karyotype is classical TS, which is 45 X comprising 53.16% of the total subjects and importantly this group is more associated with abnormal physical features in TS. Non-classical group of TS consisted of 46.83% of patients with isochromosomes, followed by mosaics and then structural abnormalities of X. These results are in agreement with a study by Stochholm. *et al*., in which classical TS appeared in 44.7%.[16]

Although the physical abnormalities are well understood but in present study, a wide range of phenotypic variability was found in TS patients which actually depends on the genetic constitution of the individual. Some of the included patients did not follow the typical pattern of physical features except short stature, at the same time others were found to have a range of dysmorphic features including webbing of neck, cubitus valgus, short 4th metacarpal and pigmented neavi. In term of height of the TS patients, short statures were found consistently, a significant difference was also observed in height of patients among the age group 5-10 years, Alwan *et al*., reported the similar findings.[17] Occurrence of obesity in TS children was reported previously.[9,18] In this study, no considerable difference of weight between classical TS and non-classical TS was found. Regardless of distinctive features, karyotyping should be the routine investigation in all short stature girls.

The age of diagnosis is very crucial. It is vital to identify accurately these children early in their life for future approaches in terms of hormone replacement for their growth and pubertal development. Majority of patients, who presented at the age of 12-15 years, had delayed puberty which is the hallmark of TS. In the present study 65.82% of the patients did not show gonads. Additionally, none of the patients showed normal pubertal development. All of them were supported by hormone replacement therapy to reach their puberty; this statement is sustained by Alwan *et al*.[17] Approximately in all classical TS patients, ovaries were absent or small. Moreover, infantile or anteverted uterus was scanned through pelvis ultrasonography. In case of 46 XX karyotype with mosaicism or isochromosome, minor abnormalities were found, though patients with 46 XY mosaicism or abnormalities in Y chromosome express with masculinisation in genitalia. These findings are supported by some previous studies done by Nazarabadi *et al*., and Miguel-Neto *et al*., who also reported that the incidence of classical TS is high than non-classical TS with typical features.[19,20]

Cases diagnosed in infancy generally have more clear clinical features. In the present subjects, the early diagnosed cases were 8.86% and most of them had genital ambiguity. The most severe condition associated with TS is congenital cardiac deformities, due to the complete absence of one X chromosome during the fetal development.[21] TS with cardiac abnormality cannot survive, and die during their infancy so the rate of cardiac abnormalities is low.[22] In this study, only eight patients were diagnosed with cardiac abnormalities. Six of them were diagnosed with 45 X. The same pattern was also seen with renal abnormalities. Two patients with congenital cardiac defect were diagnosed with coarctation of aorta. However, coarctation of aorta was reported as the cardiac defect in previous studies.[11] Phenotypic variability or absence of marked features can explain the reason of TS.

In a country like Pakistan, especially in rural areas, genetic diseases remain hidden until a significant abnormality produced. Therefore, TS patients with Y chromatin material were diagnosed earlier due to genital ambiguity.

CONCLUSION

In this study, the most frequently experienced karyotype among TS was 45 X followed by isochromosome of Xq / Xp, then the mosaic of 45 X / 46 XX karyotype, and also the karyotype having some or entire structure abnormality of Y chromosome. Phenotype-genotype correlation was more clearly found in classical TS and penetrance of disease was also high with standard monosomy. Patients with Y chromatin material found to have ambiguous genitalia, and for that reason, diagnosed early in their life. Though in every single TS individual, early diagnosis is vital for better management of disease.

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