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A Data Profile of Phenotypic Features in 181 Turner Syndrome (TS) Females

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KEYWORDS Turner Syndrome. Variability. Phenotype. Features. Percentage Frequency

ABSTRACT In the present study is reported the data on the observed phenotype in 181 cytogenetically confirmed Turner syndrome females. The features were categorized into 21 groups (skin, low hair line, webbed neck, cardiovascular system, bossing of forehead, highly arched palate, skeletal defects, micrognathia, build, chest, cubitus valgus, digital anomalies, external genitalia, axillary/ pubic hair growth, breast development, far apart position of nipple, ultrasound findings of uterus and ovary). The total number of the 21 features multiplied for the 181 was 3801. TS females manifested only 25% of the features (950/ 3801). Karyotype and its association to the features showed that probands with 45,X (85) manifested 47% (1785/3801) of the features and out of the 950, 45,X showed 50.4% (85) (479/950). The findings confirmed the reported observations that in Turner syndrome, there seemed to be a wide variability in the phenotype.

INTRODUCTION

Turner described TS also known as Ullrich – Turner or Bonnevie –Ullrich – Turner Syndrome (TS), in 1938 (Turner 1938); although the chromosome abnormality was not recognized until 1959 (Ford et al. 1959)**.** The estimated incidence of TS in female live births is 1 in 5000 to 10000; but; it is reported that 98% of the 45,X conceptions result in spontaneous pregnancy loss. (Turnpenny and Ellard 2012). The classical physical features of TS are the in- utero lymphedema sequence with congenital heart defects, short stature and gonadal dysgenesis. It is stated that, TS females demonstrate varied features because of the different karyotypes; such 45,X or X-mosaicism or X-structural abnormality. Individuals with 45,X more often demonstrate congenital lymphedema; spontaneous menarche is more likely in females with X mosaicism and women with 45,X/46,XX are, as a group, slightly taller than the others. A ring or marker X of variable size may be associated with a more severe phenotype and an increased chance of mental retardation. Deletion of short arm of second X, may result in full Turner phenotype though normal ovarian function is possible especially for distal deletions (Ogata et al. 2001; Sybert and Mac Cauley 2004)**.** Although deletions distal to Xq21 do not appear to affect stature, other terminal and interstitial deletions of long arm of X, are associated with short stature as well as primary and secondary ovarian failure. Presence of Y chromosome material, in whole or in part confers a risk of gonadoblastoma in 7 to 30% of cases (Gravholt et al. 2000; Canto et al. 2004) and may lead to masculinisation in some individuals. Thus, in TS females the phenotype is variable. (Jorde et al. 2010)

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Objective

In the present study, it is aimed to report the data profile on the observed phenotypic features in 181 females with the karyotype of TS.

MATERIAL AND METHOD

The sample consisted of 181 TS females confirmed with the karyotypes of TS, at Division of Human Genetics, Department of Anatomy, St. John's Medical College, Bangalore. The features were gathered from the proforma. It may be noted that due consent has been obtained from the probands and the family. From the literature, 21 features were obtained and categorized. The features of 181 TS females were tabulated for the 21 features and the percentage analysis was calculated for the gathered information for each patient. Then, the categorized 21 features were correlated to the determined karyotype.

RESULTS

In Table 1 is given the categorized features into 21 groups (skin , low hair line, webbing of neck, cardiovascular system, bossing of forehead, highly arched palate, skeletal defects with unkown abnormalities, micrognathia, build, chest, cubitus valgus, digital anomalies, external genitalia, axillary hair growth, pubic hair growth, breast development, far apart position of nipple, ultrasound findings of uterus and ovary). The calculated total number of the 21 features multiplied for the 181 sample was 3801 (21X181). TS females manifested only 25% of the features (950/3801).

Table 2 shows, the determined and classified karyotype and the association with the 21 features. Out of which, patients with 45,X karyotype (85) manifested 47% (1785/3801) of the features; X-mosaicism (47) 21.2% (987/3801); X-structural abnormality (45) 26.6% (945/38010) and Y- cell line (4) 1.2% (84/3801).

Out of the 950 phenotypic features, with 45,X the manifestation was 50.4% (479/950); X-

Table 1: TS: Phenotypic features

S. No.	*Features*	*n*	*%*	*S. No.*	*Features*	*n*	*%*
1	Skin	19	10.5	15	External genitalia – clitoris	27	14.9
-	Course skin texture	08	4.4	-	Small	09	4.9
-	Skin pigmentation	11	6.1	-	Infantile	13	7.1
2	Low hair line	49	27.1	-	Enlarged	04	2.2
3	Webbing of neck	56	31	-	Absent	01	0.5
4	Cardiovascular system	06	3.3	16	External genitalia – vagina	19	10.4
-	Coarctation of aorta with bicuspid valve	02	1.1	-	Absent	01	0.5
-	Systolic murmur	02	1.1	-	Blind	03	1.6
-	Ventricular septal defect	01	0.5	-	Infantile	15	8.2
-	Heart defects	01	0.5	17	Axillary hair growth	123	67.9
5	Bossing of forehead	01	0.5	-	Absent	62	34.2
6	Highly arched palate	07	3.8		Scanty	61	33.7
7	Skeletal defects	06	3.3	18	Pubic hair growth	119	65.7
8	Micrognathia	07	3.8		Absent	54	29.8
9	Build	60	33.1		Scanty	65	35.9
-	Thin build	24	13.3	19	Breast development	103	56.9
-	Short build	23	12.7		Not developed	58	32
-	Obese	13	7.2		Hypoplastic	45	24.8
10	Chest	31	17.1	20	Far apart nipple position	49	27
-	Barrel shaped chest	02	1.1	21	Ultrasound findings – internal reproductive organs	80	44.2
-	Broad shaped chest	20	11	-	Hypoplastic uterus	20	11
-	Funnel shaped chest	02	1.1	-	Hypoplastic uterus with no ovaries	17	9.4
-	Shield shaped chest	07	3.8	-	Infantile uterus	14	7.7
11	Cubitus valgus	99	54.7	-	Uterus and ovaries not seen	09	4.9
12	Digital anomalies	21	11.6	-	Mullerian agenesis	04	2.2
-	Aerodactyly	01	0.5	-	Hypoplastic uterus and ovaries	03	1.6
-	Clinodactyly	02	1.1	-	Gonadal dysgenesis	03	1.6
-	Syndactyly	16	8.8	-	Ovaries not seen	02	1.1
-	Short toes	02	1.1	-	Absence of uterus, fallopian tubes and ovaries	02	1.1
13	External genitalia – labia majora	33	18.2	-	Hypoplastic ovaries	02	1.1
-	Not prominent	21	11.6	-	Ovaries are present, uterus is not seen	01	0.5
-	Mildly padded	01	0.5	-	Streak uterus without gonads	01	0.5
-	Infantile	11	6.1	-	Anteverted uterus with thin endometrium	01	0.5
14	External genitalia – labia minora	35	19.3	-	Uterus and right ovary are found to be absent	01	0.5
-	Not apparent	24	13.2	-	Total	3801	-
-	Infantile	11	6.1	-	Normal	2851	75
-	-	-	-	-	Abnormal	950	25

Table 2: TS: Phenotype vs classified karyotype

S. No.	*Feature*	*N*	*45,Xn 85*	*X-mosaicism n 47*	*X-structural abnormality n 45*	*Y – cell line n 4*
1	Skin	19	09	04	05	01
-	Course Skin Texture	08	03	01	03	01
-	Skin Pigmentation	11	06	03	02	-
2	Low hair line	49	28	10	10	01
3	Webbing of neck	56	27	16	13	-
4	Cardiovascular system	06	04	01	-	-
-	Coarctation of aorta with bicuspid aortic valve	02	02	-	-	-
-	Systolic murmur	02	01	01	-	-
-	Ventricular septal defect with systolic murmur	01	01	-	-	-
-	Heart defects	01	01	-	-	-
5	Bossing of forehead	01	01	-	-	-
6	Highly arched palate	07	06	-	01	-
7	Skeletal defects	06	03	02	01	-
8	Micrognathia	07	05	01	01	-
9	Build	60	29	13	16	02
-	Thin build	24	14	06	03	01
-	Short build	23	10	03	09	01
-	Obese	13	05	04	04	-
10	Chest	31	17	06	09	-
-	Barrel shaped chest	02	02	-	-	-
-	Broad shaped chest	20	11	03	06	-
-	Funnel shaped chest	02	01	-	01	-
-	Shield shaped chest	07	03	03	02	-
11	Cubitus valgus	99	56	21	21	01
12	Digital anomalies	21	08	03	09	01
-	Aerodactyly	01	-	01	-	-
-	Clinodactyly	02	01	01	-	-
-	Syndactyly	16	06	01	08	01
-	Short toes	02	01	-	01	-
13	External genitalia – labia majora	33	14	04	12	01
-	Not prominent	21	07	03	08	01
-	Mildly padded	01	-	-	01	-
-	Infantile	11	07	01	03	-
14	External genitalia – labia minora	35	15	06	12	01
-	Not apparent	24	08	05	09	01
-	Infantile	11	07	01	03	-
15	External genitalia – clitoris	27	10	07	10	
	Small	09	01	01	07	-
	Infantile	13	07	03	03	-
	Enlarged	04	01	03	-	-
	Absent	01	01	-	-	-
16	External genitalia – vagina	19	08	06	05	-
	Absent	01	01	-	-	-
	Blind	03	-	02	01	-
	Infantile	15	07	04	04	-
17	Axillary hair growth	123	62	27	33	01
	Absent	62	33	11	17	01
	Scanty	61	29	16	16	-
18	Pubic hair growth	119	59	27	32	01
	Absent	54	29	11	13	01
	Scanty	65	30	16	19	-
19	Breast development	103	54	19	29	01
	Not developed	58	32	12	13	01
	Hypoplastic	45	22	07	16	-
20	Far apart nipple position	49	24	13	12	-
21	Ultrasound findings – Uterus & ovaries	80	39	21	20	
-	Hypoplastic uterus	20	07	09	04	-
-	Hypoplastic uterus with no ovaries	17	09	04	04	-
-	Infantile uterus	14	08	01	05	-
-	Uterus and ovaries not seen	09	05	02	02	-

Table 2: Contd.....

S. No.	*Feature*	*N*	*45,Xn 85*	*X-mosaicism n 47*	*X-structural abnormality n 45*	*Y – cell line n 4*
-	Mullerian agenesis	04	01	02	01	-
-	Hypoplastic uterus and ovaries	03	01	-	02	-
-	Gonadal dysgenesis	03	03	-	-	-
-	Ovaries not seen	02	01	01	-	-
-	Absence of uterus, fallopian tubes and ovaries	02	02	-	-	-
-	Hypoplastic ovaries	02	-	02	-	-
-	Ovaries are present, uterus is not seen	01	01	-	-	-
-	Streak uterus without gonads	01	-	-	01	-
-	Anteverted uterus with thin endometrium	01	-	-	01	-
-	Uterus and right ovary absent	01	01	-	-	-
Features: Total		3801	1785	987	945	84
-	Normal	2851	1306	778	694	73
			73.1%	78.8%	73.4	98.8
-	Abnormal	950	479	209	251	11
			26.8%	21.2%	26.5%	1.2%

mosaicism 22% (209/950); X- structural abnormality 26.4% (251/950) and Y-cell line 1.2% (11/950).

The occurrence of the typical features of the syndrome were: webbed neck (30.9%,56), low hair line (27.1%,49), abnormal build (30.1%, 60), cubitus valgus (54.7%,99), absent/scanty axillary (68%,123)/ pubic hair growth (66.4%, 119); not developed and hypoplastic breast development (57%,103) and far apart nipple position (27.1%,49). From the above observations, it is opined that, for the entire sample of 181 TS, the manifestation of the 21 categorised features was only 25%, irrespective of the karyotype; whether the karyotype was 45,X or X-mosaicism or X-structural abnormality or with Y-cell line. With respect to karyotype, the phenotypic manifestions was more with 45,X karyotype (50.4%).

DISCUSSION

It was observed from the literature that a wide range of phenotypic features were ascertained to TS, but published literature pertaining to the ascertainment of specific phenotypic features to specific karyotype are limited, especially in India.

Temtamy et al. (1992) opined that the highest somatic features in TS was found in patients with pure 45,X karyotype, followed by 45,X/ 46,XX mosaics and X structural abnormalities. Linden et al. (1996) listed selected features of common sex chromosome abnormalities and reported that TS with 45,X may have more TS cardinal features and TS mosaics often may appear normal with slight short stature.

Dennis et al. (2000) reported a more severity or quantitatively different physical phenotype and psychological and behavioral problems in ring X patients rather than 45,X patients, in TS. Sybert et al. (2004) reported that infants with 45,X karyotype were most likely to have congenital lymphedema. Patients with karyotype of 45,X/46,XX or 45,X/47,XXX were most likely to have spontaneous menarche and fertility. Women with mosaicism for 45,X/46,XX were marginally taller than other women with TS. The presence of isochromosome Xq suggested an increased risk for hypothyroidism and inflammatory bowel disease. The presence of ring or marker chromosome conferred an increased risk of mental retardation and atypical phenotypic features. The authors also opined that phenotypic predictions for a given patient based on karyotype might be unreliable in patients with TS. The phenotype in TS may vary as per the age at referral (Jorde et al. 2010).

In the present study**,** the features recorded from the patients' proforma were analyzed. For the entire sample of 181 TS, the expected manifestation of the features was 3801 (21x181). But, the manifestation of the 21 features was only 25% (950/3801), irrespective of the karyotype; whether the karyotype was 45,X or X-mosaicism or X-structural abnormality or with Y-cell line. Out of which, with 45,X the manifestation of the phenotypic features was 50.4% (479/950); X- mosaicism 22% (201/950); X- structural abnormality 26.4% (251/950); and Y-cell line

1.2% (11/950). In the present study too, most of the noted cardinal features in TS were associated with 45,X karyotype and X-structural abnormality. The observations of the present study**,** indicated that, any female with the listed 21 features, the chances of having 45,X is 26.8% (479/1785), X-mosaicism 21.2% (209/987), X-structural abnormality 26.6% (251/694) and Y cell line 1.2% (11/84). The observed features seemed to correlate with the karyotype i.e. the phenotype with the genotype of TS. The findings confirmed the observation that in TS there seemed to be a wide variability in phenotype. The observed differences may be because of the sample size and the ascertainment bias.

CONCLUSION

The observation of the 25% (950/3801), of the manifestation of the TS features, in the present study could be interpreted that in Indian TS women the severity of the TS features might be average. From the findings, it is seen, thus, a TS diagnostic criteria has emerged for the individuals with TS in India.

RECOMMENDATIONS

Any female with suspected features of TS should be referred for the determination of the karyotype and for further appropriate management.

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