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A Data Profile of Phenotypic Features in 72 Klinefelter Syndrome (KFS) Males

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ABSTRACT Klinefelter syndrome phenotype is associated with hypogonadism and infertility that results from 47,XXY or 46,XY/47,XXY karyotype. Men with mosaic status show milder phenotype than those of non-mosaics. The present study aimed to report, a data profile on the observed phenotypic features in 72 cytogenetically confirmed Klinefelter syndrome male gathered from duly filled proforma. The reported phenotype from the literature were categorized into 14 groups (highly arched palate, winged scapula, thin long fingers, flat feet, prognathism, liver cirrohsis, seizures, mental illness, penis, gonads, axillary hair growth, and pubic hair growth, presence of gynaecomastia and semen analysis). The calculated total number of the 14 features multiplied for the 72 samples was 1,008. Of the 1,008 features (14X72), KFS male manifested only 16.56% of abnormal features (167/1,008). Scanty axillary hair growth (25%, 18), scanty pubic hair growth (26.38%, 19), small sized penis (25%, 18), small sized gonads (55.56%, 40), presence of gynaecomastia (45.83%, 33) were of highest percentage. It was noticed that, for the entire sample of 72, the manifestation of the 14 categorised features was only 16.56%, irrespective of the karyotype; out of which, with 47,XXY, the manifestation of the phenotypic features was observed to be highest (18.52%, 153/826). The findings confirmed the reported observations that in Klinefelter syndrome, there seemed to be a wide variability in the phenotype.

INTRODUCTION

Henry Klinefelter initially in a series of nine men with gynaecomastia described Klinefelter syndrome (KFS) in 1942**,** although the chromosome abnormality was not recognized until 1959. (Simpson et al. 2003) The estimated incidence of KFS in male live births is 1/500 to 1/1000. Presence of a second normal X chromosome in a phenotypic male was diagnostic of KFS. Approximately 10% of boys with 47,XXY karyotype are identified prenatally either by CVS or amniocentesis for late maternal age, because, there is no characteristic prenatal ultrasound findings to prompt invasive diagnostic testing. 25% are identified in childhood, adolescence or adult hood. The few diagnosed in childhood come to attention because of language delay, learning difficulties or behavioral problems, because they are physically indistinguishable from their peers. Those who are identified as adolescents or young adults generally have gynecomastia, hypogonadism, or infertility. Between 2/3^{rds} and 3/4th of the expected number of males with 47,XXY, are never diagnosed, probably due to reticence on the part of affected men to seek advice and treatment, combined with the failure of health professionals to consider and/or recognize mild KFS (Lanfraco et al. 2004; Bojesen et al. 2003) The hallmark features of KFS are not present in newborns and children, so many geneticists reserve the term KFS for the untreated adult phenotype, preferring 47,XXY in other circumstances. Prospective studies of males with 47,XXY identified by newborn cytogenetic screening have dispelled many of the misconceptions previously created by methodological flaws and ascertainment bias (Visootsak et al. 2001). The variability of phenotype at different stages, lead to idea of develop a diagnostic criteria based on manifesting features in KFS male, hence the present study is carried out with the following aim.

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Aim

In the present, it is aimed to report the data profile on the observed phenotypic features in 72 male with the karyotype of KFS.

MATERIAL AND METHOD

The sample consisted of 72 KFS males confirmed with the karyotypes of KFS, 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, 14 features were obtained and categorized. The features of 72 KFS males were tabulated for the 14 features and the percentage analysis was calculated for the gathered information for each patient. Then, the categorized 14 features were correlated to the determined karyotype.

RESULTS

In Table 1, the features were categorized into 14 groups (Highly arched palate, winged scapula, thin long fingers, flat feet, prognathism, liver cirrohsis, seizures, mental illness, penis, gonads, axillary hair growth, pubic hair growth, presence of gynaecomastia and semen analysis). The calculated total number of the 14 features multiplied for the 72 sample was 1,008. Of the 1,008 features (14X72), KFS male manifested only 16.56% of abnormal features (167/1,008). From the table it is observed that, even though, there are number of phenotype features, the abnormal feature manifestations are comparatively less percentage (16.56% as in present case). The remaining may show the karyotype, but may show normal male phenotype.

Table 2 shows, the determined and classified karyotype and the association with the 14 features, which were multiplied for 72 sample, that is, 1,008. Out of which, it was observed that patients with 47,XXY karyotype (59) manifested 81.94% (826/1,008) of features. Of 826, the abnormal manifestation includes 18.52% (153/826). Similarly, the abnormal phenotypic manifestations in KFS male with X-mosaicism were 8.33% (14/168) and no abnormal phenotypic manifestations were observed in the KFS variant. In the entire sample of 72 KFS, the manifestation of 14 catagorized features was only 16.56% irrespective of the karyotype. Out of which, 47,XXY KFS male, manifested 91.61% (59) (153/167) of abnormal features, whereas, with X-mosaicism, it was only 8.38% (12) (14/167). From the above observation, it is opined that, KFS male with 47,XXY manifested more percentage of phenotypic features.

DISCUSSION

It was observed from the literature that a wide range of phenotypic features were ascertained to KFS, but published literature pertaining to the ascertainment of specific phenotypic features to specific karyotype were limited, however, there were single case studies to report the phenotypic features. The reported features were mainly associated with 47,XXY karyotype.

Polani (1961) reported that KFS male with either 47,XXY or KFS variant karyotype primarily expressed small testes, azoospermia, severe intellectual subnormality, ambiguous genitalia, bifid scrotum, very small penis and tiny testes.

Table 1: KFS: Phenotypic features

S. No.	*Features*	*n*	*%*	*S. No.*	*Features*	*n*	*%*
1	Highly arched palate	01	1.39	11	Axillary hair growth		
2	Winged scapula	01	1.39	-	Scanty	18	25
3	Thin long fingers	01	1.39	-	Absent	04	5.56
4	Flat feet	01	1.39	12	Pubic hair growth		
5	Prognathism	01	1.39	-	Scanty	19	26.38
6	Liver cirrohsis	01	1.39	-	Absent	03	4.16
7	Seizures	02	2.78	13	Presence of gynaecomastia	33	45.83
8	Mental illness	01	1.39	14	Semen analysis		
9	Penis			-	Azoospermia	17	23.61
	Small sized penis	18	25	-	Not known	54	75
	Small sized penis due to other reasons	01	1.39	-	Features: Total	1,008	-
10	Gonads			-	Normal	841	83.43
	Small sized gonads	40	55.56	-	Abnormal	167	16.56
	Atrophic gonads	03	4.16	-	-	-	-
	Hypogonadism	02	2.78	-	-	-	-

Table 2: KFS: Phenotypic features vs karyoytpe

S. No.	*Feature*	*47,XXY*	*46,XY/47,XXY*	*KFS variant*
1	Highly arched palate (01)	01	-	-
2	Winged scapula (01)	01	-	-
3	Thin long fingers (01)	01	-	-
4	Prognathism (01)	01	-	-
5	Flat feet (01)	01	-	-
6	Liver cirrhosis (01)	01	-	-
7	Seizures (02)	02	-	-
8	Mental illness (01)	-	01	-
9.	*Penis*			
	Normal (53)	41	11	01
	Small (18)	17	01	-
	Small due to other reasons (01)	01	-	-
10.	*Gonads*			
	Normal (27)	16	10	01
	Small sized gonads (40)	38	02	-
	Atrophic gonads (03)	03	-	-
	Hypogonadism (02)	02	-	-
11	*Axillary Hair Growth*			
	Normal (50)	39	10	01
	Scanty (18)	17	01	-
	Absent (04)	03	01	-
12	*Pubic Hair Growth*			
	Normal (50)	39	10	01
	Scanty (19)	17	02	-
	Absent (03)	03	-	-
13	*Gynaecomastia*			
	Present (33)	30	03	-
	Absent (39)	29	09	01
14	*Semen Analysis*			
	Normal (1)	-	01	-
	Azoospermia (17)	14	03	-
	Not informed (54)	45	08	01
	Total (1,008)	826	168	14
	Normal (841)	673 81.47%	154 91.67%	14 100%
	Abnormal (167)	153 18.52%	14 8.33%	-

Jenkins (1968) in a single KFS case with 47,XXY karyotype reported, doubtful gynaecomastia, small penis and testicles, sparse secondary sexual hair distribution, pes cavus and clawed toes and degenerated seminiferous tubules with few Sertoli cells and clumps of interstitial cells.

Odell and Swerdloff (1976) reported in two cases with 47,XXY and KFS X-mosaicism, with moderately diminished axillary and pubic hair growth, pronounced tubular atrophy and pronounced bilateral gynaecomastia.

Boisen (1979) reported in a study of 12 men with 47,XXY karyotype, a significant reduction in testicular size and opined that significant reduction in testicular size may be one of the important clinical feature associated with KFS.

Bender et al. (1983) reported by evaluation, that, the severity of the language dysfunctions, problems in coding, information on memory was less in KFS males with 47,XXY karyotype.

Schwatz et al. (1991) reported the clinical indications in KFS and KFS variants. The authors opined that KFS male with 47,XXY, at birth showed the clinical signs of microphallus and hypospadias; in childhood learning disabilities, behavioral disorders, tall stature, eunuchoid habitus and small testes; at puberty, delayed puberty, gynaecomastia, increased gonadotrphins and infertility and in adulthood with variant KFS shows stasis dermatitis. KFS male, with X-mosaicism, in childhood expressed learning difficulties, tall stature and small testis and at puberty delayed puberty, gynaecomastia, increased gonadotrophins and infertility. KFS variant male expressed at birth, microphallus, hypospadiasis and cryptorchidism; at puberty, mental retardation, learning disabilities, behavioral disorders, tall stature, eunuchoid habitus, short stature and small testes; at puberty, expressed delayed puberty, gynaecomastia, increased gonadotropins, infertility and during adulthood stasis dermatitis.

Advani et al. (1991) in an Indian study, reported in 2 KFS male with 47,XXY karyotype, not developed pubic or axillary or facial hair and soft testes.

Isobe et al. (1992) reported in a 41 year old KFS male with 47,XXY karyotype, obesity, decreased skin tension, anemic conjunctiva, distended and soft abdomen, small sized penis, small testes and sparse pubic hair and facial hair.

Smyth and Bremner (1998) reported in review, that the clinical manifestations of KFS includes infertility, small testes, gynaecomastia, decreased pubic and facial hair, testosterone and gonadotropin levels and penis size, breast cancer, autoimmune disorders, intellectual and motor disturbances.

Patwardhan et al. (2000) reported that KFS males showed decreased left temporal grey matters, which is consistent with the verbal and language deficits associated with KFS.

Pinyerd and Zipf (2002) reported in a review, that 95% of KFS males irrespective of karyotype expressed elevated gonadotropin levels, infertility, small testes; 75% decreased testosterone level; 70% expressed facial hair; 62% gynaecomastia; 45% pubic hair and 18% small penis.

Kamischke et al. (2003) reported significant tall statue, sparse body hair distribution, significant low volumes of testes in KFS male with 47,XXY karyotype.

Visootsak and Graham (2003) in a review on KFS opined that, males with small testes, infertility, gynaecomastia, long legs and arms, speech and language deficits, learning disabilities, psychosocial difficulties and behavioral issues, need cytogenetic evaluation.

Lanfraco et al. (2004) in a review on KFS, opined, that the clinical picture of patients seeking medical attention varies according to the age. Before puberty, only discrete physical anomalies may be noticed such as slightly lower than normal testicular volume or long leggedness. In adolescence and after puberty, KFS is characterized by varying symptoms of androgen deficiency.

Zinn et al. (2005) opined that CAG repeat on AR gene, significantly influences the KFS phenotype especially on penile length, a biological indicator of androgen action. However, the authors opined, that KFS with mosaicism will not account for the phenotypic variability.

In the present study, the features gathered from the pateients proforma were analyzed with the 14 features from the literature (highly arched palate, winged scapula, thin long fingers, prognathism, flat feet, liver cirrhosis, seizures, mental illness, penis, gonads, axillary hair growth, pubic hair growth, gynaecomastia, semen analysis). For the entire sample of 72 KFS, the expected manifestation was 1008 (72x14). But, the manifestation of the 14 features was only 16.56% (167/1,008), irrespective of the karyotype; whether the karyotype was 47,XXY or X-mosaicism or KFS variant. Out of which, with 47,XXY (59) the manifestation of the phenotypic features of KFS was 91.61% (154/167).; X- mosaicism (12) 8.38%.

The observations of present study indicated that, any male with the listed 14 features, the chances of having 47,XXY is 18.52% (153/826) and X-mosaicism is 8.33% (14/168).

Thus, any male with definite suspected features of KFS as well as scoring 50% and above of the listed features might be associated to 47,XXY karyotype. The reported percentage of 47,XXY in the present study and its association to the KFS phenotype is more or less as per the information provided in literature.

The observation of the 16.56%, (167/1,008) of the manifestation of the KFS features in the present study could be interpreted that in Indian KFS men the severity of the KFS features might be less.

CONCLUSION

From the findings, it is seen, thus, a KFS diagnostic criteria can be emerged for the individuals with KFS in India. The findings confirmed the reported observations in KFS, that is, in KFS there seemed to be a wide variability in phenotype. The observed features seemed to correlate with the karyotype, that is, genotype 47,XXY of KFS individuals.

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