

Klinefelter Syndrome: Clinical Spectrum Based on 44 Consecutive Cases from a South Indian Tertiary Care Center

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Abstract

Background: Klinefelter syndrome (KFS) is the commonest chromosomal abnormality, yet remains largely underdiagnosed due to its varied clinical presentation. This study was done to understand the clinical spectrum in our population. **Aim:** We intended to study the clinical characteristics of children and adults with KFS in our population. We also desired to identify any special features of Klinefelter variants. **Methods:** Forty-four patients with karyotype diagnosis of KFS during the time period 2007-2015 were included in this retrospective study. Clinical details and hormonal profile were obtained from hospital information system. **Results:** Our study population consisted of 17 (38.6%) participants in pediatric age group (age <18 years) and 27 (61.4%) adults. Clinical presentation prompting evaluation in the former group included cardiac anomalies (29.4%), dysmorphism (23.5%), hypogonadism (17.6%), developmental delay (11.8%), tall stature (11.8%), and cryptorchidism (5.9%). Among adults, 16 (59.2%) presented with hypogonadism and 9 (20.4%) had primary infertility. Six children (35.3%) had micropenis and four (three children, one adult) had unilateral undescended testis. Behavioral problems were detected in 19 (43.2%) subjects. Mean follicle stimulating hormone (FSH) and luteinizing hormone (LH) values were 38 IU/mL and 18 IU/mL, respectively. The classical 47 XXY karyotype was detected in 38 (86.4%) subjects and 6 (13.6%) had karyotype consistent with Klinefelter variants. **Conclusion:** KFS was diagnosed only after 18 years of age in two-thirds of patients. Developmental delay, cardiac anomalies, behavioral abnormalities, and intellectual disabilities were the common presentations in pediatric subjects. Adults predominantly presented with hypogonadism. Individuals with Klinefelter variant karyotype sought medical attention predominantly for non-gonadal concerns.

Keywords: Hypogonadism, karyotype, Klinefelter syndrome, Klinefelter variants

INTRODUCTION

Klinefelter syndrome (KFS) is the commonest aneuploidy syndrome which occurs in about 150 per 1,00,000 males.^[1] The diagnosis can be made in those individuals with a karyotype showing at least one extra X chromosome along with XY. Classical form is the 47 XXY karyotype which constitutes around 90% of cases.^[2] Mosaic forms with 47 XXY/46 XY karyotype constitute 10%-15% of cases.^[3] KFS variants are those with karyotypes showing more than one extra X chromosome. Classical description of this syndrome is a tall eunuchoid individual with small testes, variable levels of hypogonadism, and infertility. However, it is less commonly recognized as an etiology for developmental delay, language difficulties, attention deficit disorder, and impaired executive function. There seems to be an increased propensity for these

disabilities over and above the emotional problems brought about by the general physical characteristics and gonadal issues. Klinefelter variants are also associated with severe degrees of mental disability and dysmorphism. There is limited literature available from India^[4,5] and no major studies from South India. Hence, we sought to review the hospital data of patients diagnosed to have KFS with a view to ascertain the clinical characteristics and various forms of presentation across different age groups.

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MATERIAL AND METHODS

Subjects

This retrospective study analyzed all the karyotype reports with the diagnosis of KFS from 2007 to 2015 done at a tertiary care center in South India. There were 44 patients with karyotype diagnosis of KFS (presence of at least one extra X chromosome in addition to XY) during the study period.

Methods

The clinical details of the participants including anthropometry, phenotypic characteristics, clinical findings indicative of hypogonadism (micropenis, undescended testis, low testicular volume), and other anomalies when documented were retrieved from the hospital information system. Tall stature was defined as height above 97th percentile for age and sex or more than 2 SD above the mean in the Indian Academy of Pediatrics (IAP) growth chart. Mid-parental height (MPH) was not considered for defining tall stature in this series, although it is very useful in individual patients. Associated comorbidities like behavioral abnormalities, subnormal intelligence, and cardiac defects (type and number) were noted. Hormonal profile was also collected when available which included follicle stimulating hormone (FSH) (N: 2.5-10.2 IU/mL), luteinizing hormone (LH) (N: 1.9-12.5 IU/mL), and Total Testosterone (N: 2.8-10 ng/mL). FSH, LH, and Total Testosterone were done by Chemiluminescence Immunoassay (CLIA) using the ARCHITECT i2000 SR system, Abbott laboratories, throughout the study period. Data on the indications and detailed reports of karyotyping were also obtained. Karyotype analysis for constitutional, numerical, and structural chromosome rearrangements using GTG banding was done in our Institute by Department of Cytogenetics. In this method, 5 mL of venous blood is drawn from the patients in a vacutainer. The blood cultures are set up within 18 hours after collection. For each culture, 0.5 mL whole blood is mixed with 5 mL of Euro clone P culture medium and incubated for 72 hours in CO₂ cell-culture incubator. The culture tubes are then mixed 1-2 times per day for uniform cell growth. Colcemid is added 2 hours before harvesting. The culture tubes are centrifuged for 7 minutes and the supernatant is discarded. Then, 10 mL KCl (0.056 M, 37°C) is gently added, first 5 mL drop by drop (hypotonic treatment) and incubated at 37°C for 20 minutes. Centrifugation is done for 7 minutes at 1500 rpm following which the supernatant is removed and 1 mL is left to re-suspend the pellet. About 10 mL fixative (3:1 Methanol: Acetic acid) is then added drop by drop and centrifuged at 1500 rpm. The cell suspension is washed two more times in a fixative and a small cell pellet in 0.5 mL fixative is prepared. Also, 50-100 µL drop of cell suspension is placed on a pre-cleaned slide; the suspension is allowed to dry and is later examined under the microscope for good metaphase spreads.

Slides are dehydrated, treated with the enzyme trypsin, and then stained with giemsa stain. All karyotyping was carried out using a GTG banding technique and cells are analyzed using Zeiss microscope and Ikaros software. Metaphase chromosomes

are G-banded to facilitate the identification of structural and numerical abnormalities. In general, 20 to 25 cells are analyzed for constitutional analysis. Metaphase analysis involves a comparison of every set of homologues (including X and Y), band by band. The same method and techniques were used for karyotyping during the study period. This study was approved by the Institutional Review Board.

RESULTS

Characteristics

A total of 44 patients were diagnosed to have KFS during the study period. There were 17 (38.6%) pediatric (age under 18 years) and 27 (61.4%) adult patients in our study population. The mean age of the study population was 20.6 years. The youngest patient was 30 days old and the oldest was 50 years. Clinical characteristics of both age groups are shown in Table 1. Diagnosis of KFS before 18 years of age was made only in 17 out of 44 patients (38.6%). In children, karyotype was mainly requested for cardiac anomalies (5, 29.4%), dysmorphism (4, 23.5%), micropenis, lack of secondary sexual characters (3, 17.6%), developmental delay (2, 11.8%), tall stature (2, 11.8%), and cryptorchidism (1, 5.9%) in the order of frequency. While hypertelorism and low set ears were observed in all four dysmorphic children, frontal bossing and bilateral flared posteriorly placed pinna were noted in half of them. Microcephaly, micrognathia, hyperextensibility of knees and elbows, cubitus varus deformity, bilateral ptosis, down slanting corners of mouth, squared nasal tip, café au lait spots (>6 numbers), and skin tags in preauricular area and cheeks were also noted. But clinical features and biochemical parameters suggestive of hypogonadism were the main reasons for ordering karyotype in adults. While 16 (59.2%) patients presented with hypogonadism, 9 (20.4%) were diagnosed during evaluation of primary infertility. Fifty-two percent of adult or adolescent patients (16 out of 31) had documented gynecomastia while data are incomplete in 7 patients. Upper Segment: Lower Segment ratio and arm span data were available only for few subjects and hence is not being considered in this publication. Three out of 32 adult patients (9.3%) who were diagnosed with KFS elsewhere were on testosterone therapy. Incidental diagnosis was made in

Table 1: Prevalence of clinical signs in pediatric and adult population with Klinefelter Syndrome* (KFS)

	Pediatric KFS (n=17)	Adult KFS (n=27)
Small testes	NA	16 (59.3%)
Cryptorchidism	3 (17.6%)	1 (3.7%)
Gynecomastia	0 (0%)	8 (29.6%)
Micropenis	6 (35.3%)	3 (11.1%)
Dysmorphism	4 (23.5%)	0 (0%)
Cardiac anomalies	5 (29.4%)	0 (0%)
Subnormal intelligence	7 (58.3%)	5 (41.6%)
Behavioral problems	13 (76.5%)	6 (22.2%)

*From available data; NA=Not available

three patients when medical attention was sought for diabetes of which two patients also had cerebrovascular accident. One patient was diagnosed while evaluating for thrombocytopenia and chronic liver disease and was the oldest of the study cohort.

Genitalia development

Six of the pediatric population (35.3%) had micropenis at presentation and four (three children, one adult) had unilateral undescended testis.

Other aspects

Nineteen patients (43.2%) had some form of behavioral issues, out of which 13 (68.4%) belonged to the pediatric age group. Depression and ADHD were documented in four and three patients, respectively. Diabetes was observed in three and obesity in four adults. One patient with aplastic anemia and one with chronic liver disease were also noted. Thirteen patients (76.5%) in the pediatric age group were above the 50th percentile in height and four (23.5%) were less than 3rd percentile. Ten out of 44 (22.7%) patients had cardiac anomaly, and all of them were below 18 years of age at presentation. Single cardiac anomaly was detected in six of them (two Ventral Septal Defects [VSD]; two Atrial Septal Defects [ASD]; two Patent Ductus Arteriosus [PDA]), and more than one anomaly was seen in the remaining patients (VSD + PDA, VSD + TGA [Transposition of Great Arteries], DORV [Double Outlet Right Ventricle] + ASD + VSD, VACTERL [Vertebral defects, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Renal anomalies, Limb abnormalities] anomaly). Twelve (27.3%) of the total study cohort had subnormal intelligence, out of which seven (58.3%) were in the pediatric age group. Mental retardation and global developmental delay were observed in three patients each and all were under 18 years. Hypertension, pituitary microadenoma, testicular tumor, and proximal radio-ulnar synostosis were also observed. Pituitary microadenoma with asymmetric enlargement and poor enhancement to contrast was an incidental finding in magnetic resonance imaging (MRI) brain while evaluating for seizures. However, follow-up information of this particular patient is not available. The patient with testicular tumor underwent surgery in his late childhood with no available records.

Endocrine

In the adult population, FSH was elevated in all cases (values available in 22 patients) above the reference range and LH was elevated in all but two (values available in 21 patients). Mean FSH value was 38 IU/mL and mean LH value was 18 IU/mL in our study cohort. The median FSH, LH, and Total Testosterone were 24.6 IU/mL, 20.9 IU/mL, and 4.2 ng/mL, respectively. Among the pediatric population, FSH and LH were elevated only in three adolescents (data available).

Out of 44 patients, 38 patients (86.4%) had the classical 47 XXY karyotype and six (13.6%) were classified as Klinefelter variants. Comparison of clinical and biochemical characteristics of these two groups are shown in Table 2. The special phenotypic features of the less common Klinefelter variants are shown in Table 3.

Table 2: Comparison of clinical characteristics between the classical KFS and Klinefelter variants

Clinical features	Classical KT (n=38)	Variant KT (n=6)
Age at presentation	>20 years	<7 years
Major concern at presentation	Hypogonadism and infertility	Non-gonadal issues
Behavioral issues	14 (36.8%)	5 (83.3%)
Cardiac anomalies	6 (15.7%)	4 (66.6%)

KT=Karyotype

DISCUSSION

KFS is the commonest chromosomal abnormality in humans but still remains largely underdiagnosed.^[6] It has been shown that only 25% of estimated cases are diagnosed and very few cases are identified early in life.^[7] In our study, diagnosis was not suspected in majority of patients in the prepubertal age group as evidenced by only 38.6% diagnosed before 18 years. Delay in diagnosis is not uncommon, and previous studies have shown that only 21.2% were diagnosed before 20 years of age and 6.1% before 10 years.^[8] Developmental delay, cardiac defects, dysmorphism, and behavioral problems were the main reasons for karyotype analysis and subsequent diagnosis of KFS in our pediatric population. It is quite easy to miss the diagnosis in childhood as there are myriad ways of presentation. Moreover, lack of classic features of hypogonadism in this age group may contribute to the delay in diagnosis. This is likely due to the fact that the Leydig cell function is preserved till mid-puberty and may even remain normal till later.^[9] On the contrary, more than half of the adults presented with sexual infantilism and one-fifth sought for infertility evaluation proving that majority of patients had late presentation.

Although tall stature and eunuchoid proportions in post pubertal males is considered to be mainly due to hypogonadism, the extra copy of the SHOX gene mapping to X and Y chromosome also contributes to linear growth in these children.^[10] The most common behavioral problem was depression followed by attention deficit hyperactivity disorder (ADHD). Studies have shown that socialization inadequacies, learning difficulties, and neurocognitive disorders were common in children^[11] but has not been studied much in adults.

Cardiac anomalies were observed in one-fifth of the study participants and all of them were under 18 years. Congenital cardiac anomalies are common in KFS than in general population.^[12] ASD, VSD, and PDA were the common single defects detected in our patients like previous observations.^[13] FSH and LH were elevated in all adults and three adolescents clearly showing that the biochemical evidence of hypogonadism occurs later. The most common karyotype observed in the study population was 47 XXY. Klinefelter variant karyotype was observed exclusively in children, and their presentation was predominantly non-gonadal issues like behavioral abnormalities, intellectual problems, and cardiac anomalies similar to previous observations.^[14] Klinefelter

Table 3: Special features of Klinefelter variants

Karyotype	Age at diagnosis (months)	Behavioral issues	Intelligence	Comorbidities
49 XXXXY	12	Yes	Subnormal	ASD with PAH
48 XXYY	12	Yes	MR	VACTERL anomaly
48 XXYY	24	NA	Subnormal	Global developmental delay Dysmorphism
49 XXXXY	18	Yes	Low	VSD Dysmorphism
47 XXY/48 XXXY/49 XXXXY	15	Yes	Subnormal	Hypothyroidism Dysmorphism
49 XXXXY/48 XXXY/46 XX	84	Yes	MR	ASD Dysmorphism Proximal Radio-Ulnar Synostosis

MR=Mental Retardation; NA=Not Available; VACTERL=Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, Limb abnormalities; VSD=Ventricular Septal Defect; ASD=Atrial Septal Defect

variant karyotype 48 XXYY found in two of our cohorts is infrequently observed and is associated with more pronounced phenotype abnormalities and greater cognitive impairment.^[15] The rarest variant, 49 XXXXY, observed in two patients occurs in 1:85,000 to 1:1,00,000 and is described to be the most severe variant. Apart from the prominent mental retardation and severe phenotype abnormalities, these variants are not tall rather have short stature. This has been attributed to the nonlinear effect of the number of sex chromosomes on height.^[16] Thus, in KFS variants with more number of extra X chromosomes, overall IQ and height decrease.^[17,18]

CONCLUSION

Diagnosis of KFS was made after 18 years of age in about two-thirds of our study population. Developmental delay, cardiac anomalies, behavioral abnormalities, and intellectual disabilities were the common clinical presentations in children. Adults most commonly presented with hypogonadism. The most common karyotype observed in our series was 47 XXY. Six Klinefelter variant karyotypes were detected in this study, and medical attention was sought predominantly for non-gonadal concerns.

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Conflicts of interest

There are no conflicts of interest.

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