Klinefelter’s Syndrome – Unusual Associations

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Abstract
Klinefelter’s syndrome (KFS) is the most common male sex chromosomal disorder. KFS patients are usually tall and have complete male sexual differentiation. In this report, we present two interesting cases of KFS. Our first patient had genital ambiguity and second child had short stature due to growth hormone deficiency.

Keywords
Klinefelter’s syndrome; Growth hormone deficiency; Ambiguous genitalia

Introduction
Klinefelter’s syndrome is the most common chromosomal disorder associated with male hypogonadism and infertility. Klinefelter’s syndrome (KFS) is characterized by X chromosome polysomy with X disomy being the most common variant [1]. The syndrome is usually silent before the puberty except for tall stature and difficulties in learning and language. A single Y chromosome and the expression of the testis-determining gene (SRY) are sufficient to bring about testis organogenesis and male sex differentiation [2]. Hence, genital ambiguity is unusual in KFS patients. In this report, we present two interesting patients of KFS with genital ambiguity and short stature respectively.

Case 1
A 2 years old boy was referred for the evaluation of ambiguous genitalia. He was born at full term to non consanguineous parents by normal vaginal delivery. The mother noticed small penis and passage of urine from a perineal opening at birth. There was no history suggestive of salt losing crisis or seizures in the neonatal period. His statural growth, motor and mental milestones were normal. His height was 85 cm (50th percentile), upper / lower segment ratio 1.12, arm span – 86 cm, weight-10 kg (50th percentile) and head circumference 49 cm. Genital examination showed micropenis (stretched penile length 1.8 cm), severe chordee and bifid scrotum with both gonads palpable in the scrotal sac and perineal hypospadias (Figure 1). The rest of the systemic examination was normal. Hormonal assay revealed normal thyroid functions with FSH-1.04 IU/L (Normal 0.5 – 10), LH-0.07 IU/L (Normal 0.4 – 8.6) and testosterone-1mg/dL (Normal 0 – 10). HCG (Human Chorionic Gonadotropin) stimulation test done over 72 hours showed a subnormal stimulated response of testosterone (post HCG testosterone – 4 ng/dL). The stretched penile length increased by 1.4 cm after 3 doses of intramuscular testosterone (2 mg/kg/month). Ultrasonography revealed gonads in both scrotal sacs with absence of Mullerian structures. His karyotyping revealed 47 XXY giving a diagnosis of Klinefelter’s syndrome. The child underwent single stage urethroplasty, penoscrotal transposition and chordee correction. Parents were counselled about the future course of the disease and need of testosterone therapy at a later date.

Case 2
A male child was first seen in 2004 for evaluation of short stature at the age of 6 years 8 months. He was a product of non consanguineous marriage with a birth weight of 2.2 kg, delivered at full term. His motor, mental milestones and scholastic performance in the school were normal. There were no siblings and parents denied family history of short stature or delayed puberty. Anthropometry revealed: height – 104 cm (<5th percentile), weight 23 kg (50th percentile), upper/lower segment ratio 0.9, arm span – 105 cm, and no evidence of midline defects, goiter or systemic disease. His target height based on the parents stature was 174.5 cm. Estimated bone age was 5 yr by Greulich-Pyle method. Peak GH (Growth Hormone) following clonidine stimulation test was 0.26 ng/mL thereby, confirming the diagnosis of GH deficiency. GH deficiency was confirmed by repeat estimation of stimulated GH, but IGF-1 levels were not evaluated in the patient. His gonadal / thyroid hormones and MRI sella were normal. He was initiated on GH therapy at the age of 7 yrs and received GH therapy for past 6 years with good response and change in height SDS of +2.6. At 14 years of age, he was investigated for lack of spontaneous puberty with a possibility of partial hypopituitarism. His pubertal staging was P2G1 on Tanner staging and both testes were scrotal in location and firm in consistency with a volume of less than 4 ml. His LH – 12.4 IU/L, FSH – 30.5 IU/L and testosterone

Figure 1: Clinical image showing micropenis, bifid scrotum (A) and hypospadias (B)
-120 ng/dL were suggestive of hypergonadotropic hypogonadism and repeat evaluation confirmed the elevated FSH (41.5 IU/L). In view of hypergonadotropic hypogonadism, karyotyping was done which revealed 47, XXY. He was started on testosterone supplementation along with growth hormone therapy.

**Discussion**

In this report we present two interesting cases of Klinefelter’s syndrome with genital ambiguity and short stature respectively. Our patients reside in Hyderabad, a Metro city located in the state of Andhra Pradesh, India. Our first patient had features of undervirilized male suggesting a 46 XY sexual differentiation disorder. Genital anomalies associated with Klinefelter’s syndrome have been reported sporadically. The spectrum of genital abnormality ranges from female external genitalia (complete androgen insensitivity) to micropenis. Androgen insensitivity was proposed initially to explain the disordered genital development in KFS [3]. Recent evidence suggests that CAGn trinucleotide polymorphisms in Klinefelter’s patients are responsible for genital ambiguity. A longer CAGn was correlated with features of hypogonadism, such as gynecomastia, smaller testes and penile length [4]. The two patients in this report did not have evidence of any systemic or skeletal malformations.

Another possible explanation for genital ambiguity in KFS may relate to the dosage-sensitive sex reversal (DSS) or DAX-1 gene locus on the X chromosome [5]. The presence of two DAX-1 genes can suppress the SRY gene in utero resulting in poor differentiation of gonads located in the scrotal folds. In Klinefelter’s syndrome, the extra X chromosome (and DAX-1) is generally inactivated. However, incomplete X-inactivation is a possible mechanism of genital ambiguity [5]. Previous reports suggest that the genital ambiguity and statural abnormalities could be related to the number of extra X chromosomes in the patients [6,7]. The presence of extra X chromosomes leads to over expression of SHOX leading to tall stature.

Recent reports suggest that exposure to environmental chemicals like polychlorinated biphenyls and benzene lead to reproductive problems [8]. Exposure to these endocrine disruptors leads to increased rates of sex chromosome disomy resulting in syndromes like KFS [9]. Short stature associated with Klinefelter’s syndrome is reported very rarely. The etiology could be due to associated growth hormone deficiency as seen in our patient and reported previously [10,11]. Other causes could be due to hypothyroidism, autoimmune disorders, renal tubular acidosis and other systemic disorders [12]. The morbidity and mortality are increased in KFS patients due to a variety of non gonadal conditions [13]. This could be due to interaction between the genetic and environmental factors leading to enhanced susceptibility to tumorogenesis. The KFS patients have increased incidence of neoplastic conditions like gonadoblastoma, breast cancer and neuroblastoma [14].

The major limitation of our report is the failure to perform genetic analysis of the androgen receptor gene in both the patients due to lack of facility. The presence of genetic analysis could have thrown more light on the mechanisms behind the statural abnormality and ambiguous genitalia in our patients. To conclude, our report highlights the surprising associations of Klinefelter’s syndrome and the need to consider this diagnosis in atypical cases.

**References**


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**Genital Anomalies in Adolescents: Treatment Options that Improve Reproductive Outcomes** • Page 2 of 2 •