A Prospective Study on Klinefelter Syndrome: A Basket of Multiple Systemic Disorders in a Tertiary Care Hospital

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ABSTRACT
Background: When one or more extra X chromosome is added to a normal male karyotype (46-XY), then a new aneuploidy appears called Klinefelter Syndrome (KS). Every day approximately more than 50 new such cases are added in the male population of India. Traditionally they are lean, tall, azoospermic, hypogonadic, infertile males with low social and educational profile. As the age advances level of testosterone decreases and many new symptoms of multiple systemic disorders appear in these cases. Methods: A well designed questionnaire of infertile males attending the above-mentioned OPD’s was filled with history, clinical examination and semen analysis (twice as per the WHO criteria). Results: In our series of 500 azoospermic males, we encountered 56 classical KS cases (11.2 %) of 47-XXY karyotype, who were hypergonadotropic hypogonadic and diagnosed with multiple diseases when evaluated in detail. Conclusions: Hence, every KS must receive androgen replacement therapy, which should begin at puberty and continue for lifelong that helps in preventing the development of high comorbidity rate and premature deaths because these are very high in such condition as compared to normal male population.

Key words: Klinefelter Syndrome, Infertility, Chromosomal disorder.

INTRODUCTION
Klinefelter Syndrome (KS) - A most common aneuploidy of sex chromosomes which is found only in males. It was discovered by Harry Klinefelter in 1942 at General Hospital, Boston (USA). He reported a group of 9 males with enlarged breasts, lean, thin and tall with sparse facial and body hair, small testes and inability to produce sperms.⁵ Subsequently, in 1950’s Jacobs et al recognized that KS is a chromosomal disorder in developing male foetus with a combination of XXY (47,) also known as trisomal karyotype,⁶ which is caused by an extra X chromosome because of an error in meiotic non-disjunction during gametogenesis or mitotic non-disjunction in the developing zygote, seen more in advanced maternal age. In some cases, there is increase in number of X chromosomes and XXXY (48) karyotype is seen, likewise 32 hyperplody can exist. More the number of X chromosomes, severe will be the manifestations of the disorder.⁷ It is not an inherited condition. Usually this disorder is of 2 types- (A) Classical KS - where all body somatic cells consist of XXY (47) or more X chromosomes. (B) Mosaic KS - where a mixture of XY (46) and XXY (47) chromosomes present in different somatic cells of the same person,⁸ then fewer will be the symptoms. The prevalence rate is 1 in 700-1000 born male child worldwide.⁹ In India, approximately 70,000 deliveries take place per day, hence average 50 new KS will be added in Indian population thus making huge health, social & economic burden on the country. Clinical features of this syndrome vary widely, few are noticeable, and many go undiagnosed until adulthood. In India usually they are diagnosed when an infertile couple approaches for treatment and during that semen analysis shows azoospermia with under androgenization in male
In early childhood, there is delay in learning and speaking, teenagers have either absent, delayed or incomplete puberty. Few show enlarged breast tissue; they are of quiet, shy and docile personality. Features of angry young man are absent. The adult males have arm span app. 5-10 centimeters more than vertical height with small firm pea-nut size testicles, sexual maturity rating (SMR) very poor. Gynaecomastia and increased belly fat are seen. These patients develop many disorders like endocrinal, autoimmune, cardiovascular, malignancies and leg ulcers, in addition to infertility and sexual dysfunction. Hence, from our series of azoospermic cases 56 proved Klinefelters were observed from last more than 1 and half decades for developing new signs and symptoms of systemic disorders. Literature shows that many undiagnosed hypogonadic patients in their middle and old age, suffer from various diseases and does not respond well during the specific treatment of that disease and in last, they retrogradely diagnosed by karyotyping as a KS and then with supplementation of testosterone replacement therapy (TRT) and disease specific treatment, patients improves dramatically. Hence this study was carried out to raise the awareness among clinicians treating infertile azoospermic males with hypogonadism, peanut size small testes, to advice karyotyping in future to rule out any association of KS with developing systemic disorders.

Objective
1. Diagnosis and assessment of prevalence of KS among azoospermic, hypogonadic, infertile males of Southern Rajasthan
2. To find out association between emerging multiple systemic disorders in established KS at the time of diagnosis and during follow up treatment.
3. To raise the awareness among clinicians regarding the use of TRT among hypogonadic males.

METHODS
Sample
A sample of 56 KS cases was selected out of suspected hypergonadotrophic hypogonadic persons, from a series of 500 azoospermic infertile males, attending Human Fertility Research Center at R.N.T. Medical College and Pacific Medical College & Hospital, Udaipur, Rajasthan since January 2005 to December 2016 and who were showing karyotyping 47-XXY [Fig 1]

RESULTS
All 56 KS cases were infertile males of age group 22 to 34 years, azoospermics, showing a wide range of intelligent quotient (IQ), educational background of all patients were very poor, specially their performance in language and job. Their secondary sexual characters were poorly developed and all were under androgenized with small pea-nut size testicles. Genetically all were classical KS cases and their karyotyping were 47 XXY. They were non-aggressive with poor libido, very high level of FSH and low level of testosterone [Table no. 1]. SMR grade 1 to 2, with scanty semen volume (< 0.5 ml) and low fructose. 31 cases had gynaecomastia. Various patients showed features deviated from traditional observations. Only few KS cases were the sons of elderly gravida mothers. Systemically in different patients individually or in combination developed disorders like: 28- anaemia, 16- impaired GTT, 13- hypertension, 11-hypothyroidism. 3 cases were overweight, and their BMI were more than 30, hence considered as Syndromic obesity. 1 case was having chronic leg ulcer (varicose), who prematurely expired by pulmonary thromboembolism secondary to leg ulcer. All the cases included in our study were not taking TRT.

DISCUSSION
Out of 500 cases of azoospermia series, only 56 (11.2%) turned out to be classical 47 XXY, which is very much consistent with others studies observed. In our observation gynaecomastia was seen in 31 (55.3 %) while Smyth et al. reported as 56 % to 88%. Traditionally Klinefelters are sons of elderly gravida mothers. We found only such 14 cases (25%), while others were younger or in middle order among their siblings. Now a day a changing trend is seen in phenotypic appearance of these hypogonadic males, like in our study 3 cases (5.3 %) were overweight with very high BMI (>30), labeled as syndromic obesity. Out of them 1 case of KS develop varicose vein, leg ulcer, thromboembolism and sudden death at 29 years of age. This abnormal phenotypic presentation is rarely reported and it can be explained as in presence of low level of testosterone unfavorable body composition and accumulation of body fat is seen. We reviewed the data on body composition, insulin resistance and testosterone in hypogonadal males (other than KS) and found that those who supplemented with androgen, improved their body composition in clinical and experimental studies. The development of leg ulcer in KS may be because of obesity, chronic venous insufficiency, arterial dysplasia in leg. Very low levels of testosterone is associated with elevated levels of plasminogen activator inhibitor-1 (PAI-1). This increased activity of PAI-1 promotes ulceration, syndromic obesity and thromboembolism.
Table 1: Hypogonadotropic Hypogonadic Profile of 56 Males in Our Study

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REFERENCE RANGE-  1. FSH -1.4-18.1 mIU/ml  2. Testosterone - 24T-827 ng/mldl

Usually KS couples present to gynecologists, surgeons, physicians, endocrinologists and IVF centers and being azoospermic they are advised gamete (sperm) donation without proper work up of aetiology of male factor. Hence KS remains undiagnosed and untreated lifelong. As the age advances from childhood to adulthood, from fertility period to old age where because of apoptosis their low level of testosterone goes on further decline in titer with appearance of newer complications of systemic diseases. Then clinician diagnose it retrospectively because patient does not improve with conventional treatment of that systemic disorder, therefore the total work up and follow up is recommended at one center.

Fig 2: Syndromic Obesity

Testosterone replacement is the primary treatment of hypogonadism, if it is used timely and in appropriate doses, ideally around 12 years of age, sufficient to maintain age appropriate serum concentration of Testosterone, Estradiol, FSH and LH. Most hypogonadic cases either do not receive it or do not receive it timely. This study was conducted to assess the myths for TRT among hypogonadic patients (KS) and the impact of open air discussion on its acceptance in the patient, relatives and society.

CONCLUSION

KS is a commonest sex chromosomal aneuploidy, where diagnosis will be confirmed by karyotyping. In our study of KS cases, we came across large number of reproductive and systemic disorders that can be prevented if TRT is started on time. Androgen replacement promotes normalization of body proportions and development of normal secondary sexual characteristics general improvement in behavior and work performance but does not treat infertility, gynecomastia, and small testes [14]. It has also long term beneficial effects that might reduce the risk of osteoporosis, autoimmune diseases, cancers [15], dermatological changes and premature andropause. Hence this human basket will be full of diseases without timely supplementation of TRT, which leads to very much bad sufferings in old age.

Wider implications of the findings

Our aim is to raise the awareness among clinicians and community regarding timely supplementation of testosterone in KS cases so that along with improvement in hypogonadism, prevention of systemic abnormalities can also be achieved. Therefore, we recommend all male partners with azoospermia showing hypogonadism with small testes must be screened for KS. This study reveals the myths regarding TRT and suggests that community based education programs helps to increase in the acceptance of TRT

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