AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Klinefelter Syndrome – A review

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ABSTRACT

Klinefelter syndrome is a chromosomal condition in which there is a presence of extra X chromosome in the males. It is characterized by small testicles, azospermia, gynecomastia, several general, craniofacial, oral manifestations and radiological manifestations. This review highlights the etiology, salient clinical features, features during the life span, other manifestations reported, oral and craniofacial radiological features, investigations, treatment, recent advancements in the management, risk factors of Klinefelter syndrome are discussed briefly.

Keywords: Klinefelter syndrome (KS), Taurodontism, Testosterone

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Received 11 August 2012, Accepted 22 August 2012

Please cite this article in press as: Sudarshan R *et al.*, Klinefelter Syndrome – A Review. American Journal of PharmTech Research 2012.

INTRODUCTION

The collection of symptoms known as Klinefelter syndrome was first put together in 1942 by a young doctor in Philadelphia called Harry Klinefelter. He described 9 men who had breast development, small testicles with no sperm in their semen, and a blood test revealed raised levels of the factors (gonadotrophins) which try to stimulate the testicles to produce more of the male hormone (testosterone) and greater numbers of sperm.[1]

Klinefelter syndrome is the most common numerical chromosomal aberration among men, with an estimated frequency of 1:500–1:1000 of live deliveries. Klinefelter syndrome is characterized by X chromosome polysomy with X disomy being the most common variant (47,XXY). Ninety percent of men with Klinefelter syndrome have nonmosaic X chromosome polysomy.[2]

Table 1: Clinical features:General features[4]

Feature	Percent
Craniofacial	
Ocular hypertelorism	30
Upslanting palpebral fissures	71
Epicanthic folds	85
Strabismus	57
Broad flat nose	96
Mandibular prognathism	47
Malformed ears	78
Central nervous system	
Mental retardation	100
Cardiac abnormalities	18
Genitalia	
Hypogonadism	91
Small penis	79
Abnormal scrotum	79
Cryptorchidism	24
Limb anomalies	
Limitation of elbow movement	89
Radioulnar synostosis	32
Clinodactyly, fifth finger	93
Coxa valga	84
Genua valga	13
Gap between hallux and second toe	55
Pes planus	54
Other skeletal findings	
Retarded bone age	89
Sclerotic cranial sutures	57
Capitate defect	83
Thoracic kyphosis	53
Scoliosis	35

After the initial description of the syndrome by Harry Klinefelter, Edward Reifenstein, and Fuller Albright, it was another 15 years before I A Jacobs and J A Strong confirmed the association between the extra X chromosome and Klinefelter's syndrome, establishing it as a genetic disease. Most cases occur through sporadic chromosomal non-disjunction during parental gametogenesis in either the sperm (53%) or the egg (44%). The remaining 3% of cases are caused by postzygotic mitotic errors. The extra X chromosome forms a dense chromatin mass, or Barr body, within the nuclei of somatic cells, but exactly how the presence of this extra chromosome leads to testicular failure is unknown. Testicular biopsy samples from infants with Klinefelter's syndrome sometimes show only a reduced number of germ cells. After puberty, fibrosis of the seminiferous tubules begins, eventually leading to small, firm testes and azoospermia.[3]

Table 2:Clinical features of Klinefelter syndrome throughout the life span[5]

Age	Features
Infancy	Usually none, occasionally hypospadias, small phallus, cryptorchidism
Toddler	Developmental speech delay
Childhood	Accelerated linear growth velocity
	Learning disabilities
Adolescence	Gynecomastia
	Eunuchoid body habitus; arm span> height
	Small testicular volume
	Sparse axillary, facial, pubic hair
Adult	Infertility
	Leg ulcers

Others:

Klinefelter's syndrome is also associated with mixed connective tissue disease, Rathke's cleft cyst, mediastinal polyembryoma, hematologic malignancies, seizures, and striatocapsular infarct. Klinefelter's syndrome is rarely associated with hypocalcemia. Sulimani described a case of Klinefelter's syndrome with PHP in a Saudi patient, while Poungvarin and Viriyavejakul described a case of myotonia congenita, Klinefelter's syndrome and primary hypoparathyroidism. The relationship between Klinefelter's syndrome and PHP remains unknown.[6]

Skull radiology:

The radiographic changes of the skull in Klinefelter's syndrome are: temporal flattening, decreased width of the vault, narrowing of the mandible, decreased length of the skull, shortening of the anterior fossa cranii, decrease in the angle of the base, thinning of the vault bones at the major fontanelle, premature and excessive calcification of the coronal suture,

deepening of the posterior fossa and shortening of the mandibular rami.[7]

Oral manifestations:

The malocclusions that occur include primarily taurodontism, i.e. large teeth with small roots. One or more missing permanent teeth also seems to be a frequent occurrence, and in some studies an increased tendency towards other malocclusions, including open bite and class III malocclusion.[8]

A study in which smaller angles between the occlusal plane and the cranial base (NSL-OLs) and between the occlusal plane and the Frankfort horizontal plane (Fr-OLs) in Klinefelter males are attributed to the hereditary influence of an extra X chromosome on the smaller growth of the cranial base and the greater growth of the lower border of the mandible. Maxilla was also shifted forward in XXY males in relation to the cranial base it was not enough to compensate for the hereditary influence, due to the greater growth of the lower border of the mandible and the smaller cranial base in 47, XXY males, on the inclination of the occlusal plane to the Frankfort horizontal plane and the cranial base.[9]

Diagnosis:

Investigations[10]

- **T**wo morning samples of serum total testosterone, taken on different mornings
- Total serum testosterone, low or low normal from mid puberty (normal range 8–27 nmol/L)
- Serum LH, elevated from mid puberty (normal range 1-8 IU/L)
- Serum FSH, elevated from mid puberty (normal range 1-8 IU/L)
- Karyotype (47XXY) —10% mosaic 46XY/47XXY

Other investigations[10]

1. Bone density study, DEXA (osteoporosis)
2. Semen analysis if fertility is an issue (usually azoospermic)
3. TFT (hypothyroidism)
4. Fasting blood glucose (diabetes)
5. Histopathology[11]
    1. Testicular biopsies of a prepubertal Klinefelter syndrome boy may reveal preservation of seminiferous tubules with reduced numbers of germ cells; Sertoli and Leydig cells appear normal.
    2. The testes in the adult male with Klinefelter syndrome are characterized by extensive fibrosis and hyalinization of the seminiferous tubules and hyperplasia

of the interstitium; however, the tubules may show residual foci of spermatogenesis.

3. Histologic findings may include small, firm testes with seminiferous tubular hyalinization; sclerosis; and atrophy with focal hyperplasia of mostly degenerated Leydig cells. Germ cells are markedly deficient or absent. Spermatogenesis is rare.
4. In patients with mosaicism, progressive degeneration and hyalinization of seminiferous tubules take place after puberty despite the presence of normal-sized testes and spermatogenesis at puberty.
5. Histology of gynecomastic breasts reveals hyperplasia of interductal tissue.

Variations:

The 48, XXYY (male) syndrome occurs in 1 in 18,000–40,000 births and has traditionally been considered to be a variation of Klinefelter syndrome. XXYY tetrasomy is no longer generally considered a variation of KS. Additional variations include 48,XXXY, and 49,XXXXY. These variations are extremely rare. Each additional X chromosome is estimated to reduce IQ by approximately 15 points. Additional chromosomal material can contribute to cardiac, neurological, orthopedic and other anomalies.[12]

Males with Klinefelter syndrome may have a mosaic 47,XXY/46,XY constitutional karyotype and varying degrees of spermatogenic failure. Mosaicism 47,XXY/46,XX with clinical features suggestive of Klinefelter syndrome is very rare. Thus far, only about 10 cases have been described in literature.[12]

Treatment:

Treatment can help males overcome many of the physical, social, and learning problems associated with the syndrome. Males with Klinefelter syndrome should be seen by a team of health care providers. The team may include endocrinologists, general practitioners, pediatricians, speech therapists, genetic counselors, and psychologists. Surgery may be needed to reduce breast size. With treatment, men can lead very normal lives.[13]

There are, however, a number of treatments that are aimed at reducing the impact of the symptoms of the condition. In XXY syndrome, the testes do not function normally so that the production of the male hormone called testosterone is reduced. This means that the bodily changes that occur at puberty are impacted. Treatment is with the administration of male hormones (*androgens*) that promote the development of the secondary sexual characteristics (*virilisation*). This treatment starts when the boy is around 11-12 years but does not restore

function to the testes and infertility remains. The therapy continues until late adulthood.[14]

The use of testosterone therapy has secondary benefits in helping to improve self-image and self-esteem. This in turn will impact on a boy's performance at school and his ability to form friendships. Learning problems and language deficits can be helped with expert intervention following a thorough assessment.[14]

Due to testosterone deficiency, men with Klinefelter syndrome are at increased risk for osteoporosis. Optimal calcium and vitamin D intake should be encouraged. Men with Klinefelter syndrome seem to have an increased risk of breast cancer and may benefit from instruction in breast self exam and from counseling to bring any breast abnormalities to medical attention.[15]

Men with XXY are also at increased risk for autoimmune disorders and prone to varicose veins and leg ulcers due to venous stasis. Although no formal guidelines have been established, an annual physical examination should include an assessment of signs and symptoms of these disorders.[15]

Regardless of age at diagnosis, males with XXY should be evaluated for the presence of specific learning problems and for negative self-appraisal. Adults can be evaluated in hospital-based learning clinics or by psychologists and speech therapists in outpatient settings.[15]

Orofacial/odontological treatment:

- It may be difficult to perform root canal work on taurodontic teeth. This makes it especially important to maintain good dental status.[8]
- Neuropsychiatric diagnoses may also affect the potential for providing adequate dental treatment.[8]

Counseling:

Counseling for parents of males with Klinefelter syndrome -- as well as for the males themselves at different stages of development has been shown to be beneficial. Learning as much as possible about this disorder and possible problems is also important. Doctors, nurses, and other members of the healthcare team can answer questions that parents and their sons may have about treating Klinefelter syndrome or other activities.[14]

Patients and their families often find that they need help coping with the emotional and practical aspects of Klinefelter syndrome. Meeting with a social worker, counselor, or member of the clergy can be helpful for those who want to talk about their feelings or discuss their concerns.[14]

Klinefelter syndrome support groups can also help. In these groups, patients and their family members get together to share what they have learned about coping with the disease. Patients may want to talk with a member of their healthcare team about finding such a group. Support

groups may offer support in person, over the telephone, or on the Internet.[14]

New developments:

Until recently, the use of donated sperm or adoption were the only options available for those patients who were infertile; however reports of successful, karyotypically normal pregnancies after intracytoplasmic injection of sperm, obtained from testicular biopsy samples from patients with Klinefelter's syndrome have been published. Although some patients with Klinefelter's syndrome do not have any sperm, this technique could offer a chance at fertility for those who do.[3]

Several new technologies such as testis xenografting and spermatogonial stem cell transplantation are being investigated to work around the current lack of an in-vitro culture system that would support full spermatogenesis.[2]

Scrotal ultrasound and magnetic resonance spectroscopy to follow adolescents to determine the optimal timing for testicular biopsy.[2]

Risks:

The risk of having a child with Klinefelter's syndrome is slightly increased for older mothers. In addition, if one child has Klinefelter's syndrome, there is a slightly increased risk for future children (1 in 100).[16]

CONCLUSION:

Knowing the manifestations of few common syndromes is essential for a clinician so that a prompt diagnosis of such patients could be made and a multidisciplinary approach to such syndromes could be rendered. This would provide enhancement of the patient's overall quality of life and they could very well cope up in their social life as well.

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