



Klinefelter's Syndrome in an Adolescent

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Abstract

Klinefelter's syndrome is an important common sex chromosomal abnormality in humans and it remains an important genetic cause of male infertility. A 12-year-old student was referred to our hospital due to presence of small penis and testes since birth and progressive breast enlargement of five years duration. On examination, the height was 1.64 metres and weight was 75kg. Breasts and axillary hairs were well developed at Tanner stage IV and III respectively and hair distribution of external genitalia was at Tanner stage IV. The penis and testes were small but well developed. There was no hypospadias or epispadias.

Transperineal and transrectal ultrasound showed no ovaries or uterus. Hormonal profile was normal except low Follicle stimulating hormone. Karyotype was 47 XXY. Parent was concerned with the gynecomastia and subsequently was referred to general surgeon for mastectomy. We reported a first case of Klinefelter's syndrome in an adolescent presenting to our gynecology clinic. The various forms of differential diagnoses of gynecomastia were discussed.

Keywords

Klinefelter's syndrome, Hypogonadism, Gynecomastia, Mastectomy

Introduction

Klinefelter's syndrome is an important genetic cause of infertility in males [1]. We report the first case which presented in our gynecological clinic. The varied but relatively mild physical abnormalities may explain why many patients do not receive clinical attention until adulthood, when they seek medical advice on small testes or infertility. Diagnosis may also be hindered by the low awareness of the syndrome among health professionals [1]. Benefit of early diagnosis and treatment is paramount so as to improve the quality of life and avoid serious complications.

Case History

NA was a 12 -year old junior secondary school student who was referred to our hospital due to presence of small penis and testes since birth and progressive breast enlargement of five years duration. There was no history delay of descent of testis, trauma to the testis or mump orchitis. The patient had achieved early morning erection

but sexual activity had not been attained. The patient has two female siblings, both are alive and well. There was no family history of similar problem.

The increase in breast size was noticed at about seven years of age and has remained progressive since then. There was no associated breast trauma, pain or nipple discharge. The patient had been reared as male. The patient was not a known diabetic and had not been admitted in the hospital in the past. There was no history of ingestion of hormonal drug or concussion by the mother during pregnancy. The pregnancy, labor, delivery and neonatal period were uneventful. The patient received full immunization and achieved normal developmental milestones. The patient did well academically.

Examination revealed an adolescent in no obvious distress, afebrile, anicteric, not pale and acyanosed. The patient had no palpable lymph node. The height was 1.64metres and weight was 75kg. The axillary hairs were well developed at Tanner stage III. The breasts were bilaterally symmetrical and well developed at Tanner stage IV. The nipples were inverted. This is shown in Figure 1. There was no area of tenderness or palpable mass on the breast. The abdomen revealed normal findings.



Figure 1: The patient with Klinefelter's Syndrome.

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The external genitalia revealed female hair distribution at Tanner stage IV. The penis was well developed with stretched length of two centimeters. There was no hypospadias or epispadias. The patient was circumcised. The testis measured 1.0 cm X 0.5 cm.

A diagnosis of intersex disorder secondary to Klinefelter's syndrome was made. The packed cell volume was 36 percent. The urinalysis was normal. The abdominal ultrasound showed right and left testes with homogenous texture and measured 10mm by 0.8 mm and 11mm by 7.5mm respectively. Transperineal and transrectal ultrasound showed no ovaries or uterus. The hormone profile were within normal range except for follicle stimulating hormone that was less than 1.0mIU/ml (2 -10mIU/ml).

Buccal smear showed chromatin positive with numerous regular squamous cells with less than 10 percent showing nuclear barr bodies. The Karyotype was 47, XXY. The patient and parents were counseled on the diagnosis and they desired to continue to rear the child as male. The problem of sterility was discussed with parents and they consented to mastectomy. He was later referred to the general surgeon for mastectomy. The patient was lost to follow-up.

Discussion

As in the present case report, prepubertal gynecomastia is rare entity and a specific cause is hardly ever identified such that in 90% of patients, it is classified as idiopathic [2,3]. However, known causes of breast enlargement in children are diverse [4-6]. Therefore, further exploration of the etiology in children is often warranted, particularly to rule out any endocrine or malignant abnormalities. In prepubertal period, the following could be responsible: administration of estrogens or estrogenic compounds (androgens or other substrates for aromatase, clomiphene, phytoestrogens, xenoestrogens), administration of non estrogenic drugs (digoxine, hrGH), testicular or adrenal tumors, human chorionic gonadotrophins (HCG) secreting tumors, aromatase excess syndrome (familiar hyperestrogenism), central or peripheral precocious puberty, mammary tumors of different cell composition (usually unilateral), and idiopathic gynecomastia [7].

A variety of endocrinopathies, mostly as a result of an increased ratio of circulating estrogens to androgens, induce stimulation of breast tissue leading to gynecomastia. Calzada et al. showed that the presence of hormone receptors in gynecomastia may provide a setting favorable for mammary glands to develop gynecomastia [7].

In pubertal gynecomastia, the following are differential diagnosis. These include: physiologic gynecomastia of adolescence, feminizing tumors, drugs, familiar gynecomastia, primary hypergonadotropic gonadal dysfunction, Klinefelter's syndrome (47, XXY and variants), XX males, androgen insensitivity syndrome (with ambiguous external genitalia), defects in testosterone biosynthesis (with ambiguous external genitalia), true hermaphroditism (with ambiguous external genitalia). The other causes include hypergonadotropic hypogonadism (infections, chemotherapy, external radiation), secondary hypogonadotropic gonadal dysfunction, hyperthyroidism, hepatic damage and idiopathic causes [7].

In 1998, Sher et al. analyzed the etiologies of 60 adolescent boys with gynecomastia greater than 4 cm in diameter, aged 10-20 years of age. Endocrine anomalies were detected in 7 subjects, Klinefelter's syndrome, XX male, primary testicular failure, and hepatocarcinoma. Different pathological processes were also diagnosed. In another 8 patients, and 45 subjects were labeled as idiopathic [8].

Although the presence of low FSH may appear that the gynecomastia seen in the present report may be pre-pubertal in type but we strongly believe that this is pubertal gynecomastia. This is because the increase in breast size was noticed at about seven years of age which is the time of onset of puberty and has remained progressive since then. Additionally, axillary hairs were well developed at Tanner stage III and hair distribution of external genitalia was at Tanner stage IV. Klinefelter's syndrome is a well-recognized, yet rare occurring clinical entity. It is the most common male chromosomal disorder

associated with hypogonadism [1,9,10]. Klinefelter's syndrome does not have any racial predilection [10]. Because the syndrome is caused by an additional X chromosome on an XY background, this condition affects only the males. It may go undiagnosed in most affected males. However, among males with known Klinefelter's syndrome, many do not receive the diagnosis until they are adults as was seen in our patient. Although some readers and gynecologists may view this differently, the case under consideration is a typical of Klinefelter's syndrome. This is because, it associates strongly with hypergonadotropic hypogonadism, small testes with azoospermia and intellectual deficit. Behavioral and school difficulties are frequent. Since gonadal dysfunction becomes evident at puberty, diagnosis is seldom made before adolescence.

Moreover, sometimes, signs are mild and diagnosis is not made, even in adults. Uni or bilateral cryptorchidism is frequent among boys with Klinefelter syndrome [7,8]. Puberty onset is usually at the right age, with pubic hair and genital development but testis remain small and of higher consistency. Hypogenitalism or micropenis might be present. Gynecomastia is frequent. Even though serum testosterone might reach normally low values, serum estradiol is relatively high, and it is assumed that an abnormal estradiol/testosterone ratio favors mammary development seen in the syndrome. Seminiferous tubules deterioration is progressive, ending in hyalinization and a further decrease in serum testosterone. In these conditions, replacement testosterone treatment improves hypogonadism, but not infertility. When gynecomastia disturbs patient's everyday life, surgical removal of the breasts is indicated.

Klinefelter's syndrome is characterized by gynecomastia, hypogonadism, infertility and psychological problems [9,11,12]. The other symptoms include fatigue, body weakness, erectile dysfunction, osteoporosis, language impairment, academic difficulty, poor self esteem, subnormal libido, and behavioural problems [9,12]. The latter symptoms were not observed in our patient. Children may be anxious, immature, excessively shy, aggressive, may engage in antisocial acts. Early diagnosis improves patients' quality of life and enables better medical treatment. To achieve this, it is crucial to increase both medical and general awareness of the disease, including through use of the mass media as well as the associations of the patients.

As was seen in the index case, the development of gynecomastia and eunuchoidism could be one of the most common signs leading boys and their parents to consult a doctor. This is caused by imbalance in the normal circulating levels of testosterone and a normal estrogen-testosterone ratio [5] eunuchoidism. Gynecomastia may also be caused by an imbalance between estrogen receptors and androgen receptors, leading to excessive estrogen action, deficient androgen action or a combination of these effects [12].

Most patients have normal height and weight as was seen in the present case. However, by five years, they may be taller than unaffected individuals [3]. Some individual with Klinefelter's variant 49, XXXXY have short stature [9]. Also, most males with 47, XXY karyotype have normal intelligence. Patients may lack secondary sexual characteristics because of a decrease in androgen production. This was not the case in our patient.

Gynecomastia, sparse facial hair, small testes and azoospermia are common and practically all individuals with a 47, XXY karyotype are infertile. Interestingly, patients with Klinefelter's syndrome mosaicism (46, XY/47, XXY) can be fertile [9,13].

The risk of developing breast carcinoma is at least 20 times higher than in healthy individuals [9,10]. Also, when the breasts are formidable psychological problem, surgical removal may be a satisfactory procedure. This may have influenced the patient's and parents' decision on mastectomy. The testes grow normally early in puberty, but by mid-puberty the testicular growth usually stops leading to low levels of testosterone.

Treatment involves education and speech, occupational, behavioural and physical therapies could be employed. Testosterone

replacement therapy is an option. Replacement therapy with long acting testosterone depends on the age of patient, and may be commenced at 11-12 years of age [10]. Testosterone therapy can help in the growth of body hair and may improve concentration, mood and self esteem. It may also increase energy and sex drive. Donor sperm may be offered for the treatment of infertility [9,10,12,14].

Conclusions

We reported a first purported case of a Klinefelter's syndrome occurring in an adolescent in our environment. Although reports regarding the rare entity of Klinefelter's syndrome have been published, reviews of literature and the clinical implications of this case are discussed including potential differential diagnosis for prepubertal and pubertal gynecomastia.

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The patient whose story appeared in this case report signed permission for its publication.

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