Gnoscience Group

Case Reports and Reviews: Open Access

Case Report | Vol 1 Iss 1

Klinefelter Syndrome in an Identical Twin: A Case Report and Review of Literature

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Received: April 13, 2020; **Accepted:** April 23, 2020; **Published:** April 30, 2020

Abstract

Klinefelter Syndrome (KS) is reported to be the most common sex chromosome disorder in the males. It has an incidence of 150/100,000 males. The basic pathology is the presence of an extra X-chromosome in a male. The supernumerary X-chromosome could be from either the father or mother of the male patient. The genetic material in the supernumerary chromosome often is inactivated and no phenotypic changes are seen in the male. In some patients, failure of inactivation of the genes in the extra X-chromosome results in development of Klinefelter Syndrome. The phenotypic hallmark of KS is the presence in a male of a female body habitus, gynaecomastia, tall stature, small and hypoplastic testes, hypergonadotrophic hypogonadism and cognitive impairment. Most cases go unnoticed till the patient present with primary infertility. Prenatal diagnosis is possible or even a Pre-Implantation Genetic Diagnosis (PGD) of embryos obtained from invitro-fertilisation. KS is associated with high morbidity related to hypogonadism. These include Metabolic syndrome, type 2 diabetes, infertility and associated psychiatric disorders. Cognitive impairment is mainly a speech difficulty that may require speech therapy. Medical treatment in form of hormone replacement therapy(testosterone), assisted reproductive therapy and management of associated morbidities are the mainstay of treatment. The increased morbidity associated with KS is said to reduce life span by 2-years in affected patients, the risk may be higher in African countries with delayed diagnosis and poorly equipped health care system. Literature review did not yield a report of KS in one of identical twins with a phenotypically and genetically normal sibling. We report our experience of managing one.

Keywords: ***Klinefelter, Identical twin, Africa.***

1. Introduction

The American rheumatologist and endocrinologist, Harry Fitch Klinefelter and his colleagues first described the phenotypic appearance of a male with the features of KS in 1942 [1] and the clinical syndrome is named after him.

It was more than a decade later that the chromosomal abnormality of supernumerary X-chromosome was identified. The males were discovered to have a chromosomal compliment of 47, XXY instead of 46, XY. This additional X-chromosome is responsible for the anatomical and physiologic abnormalities in patients with KS [2]. This classical chromosomal finding of 47, XXY is seen in more than two-third of the affected patients. An estimated 20% of the patients may have more than one supernumerary X-chromosome. This complex includes 48, XXXY or a mosaic consisting of two or more cell populations, in the form of 46, XY/47, XXY [3-4]. Patients in the latter group are noticed to have a less severe phenotype than men with a 47, XXY karyotype [5-6]. The most severe of phenotypic changes and more pronounced learning difficulties are seen in patients with highest number of additional X-chromosomes (e.g. 48, XXXY) [5-6].

The search for genetic basis of KS was long and arduous. The discovery of Karyotyping was the game changer. The discovery of the inactivated gene of the supernumerary X-chromosome has laid to rest the initial controversy. Klinefelter syndrome is said to result from errors of gametogenesis in each parent and the defective sex cells are donated by each parent. Only few cases can be attributed to the errors in the stage of mitosis after Zygote formation [7]. High precision studies using DNA probes indicated paternal gametogenesis error is responsible for 53.2% of KS and maternal errors account for 43.7%. Meiotic division errors account for 34.4% and this is seen in the early phase of Meiosis and 9.3% occur in the second phase of meiosis [8]. Maternal age at the time of conception is known to affect the possibility of occurrence of the genetic abnormality in the phases of meiosis. Advanced maternal age is associated with errors in the first phase of meiosis [9].

Further study has unravelled the details of the chromosomal genetic abnormalities. The presence of the short-stature homeobox-containing gene on chromosome X (SHOX) located in the pseudo-autosomal region 1 on Xp has been pointed at as the particular culprit. The SHOX haploid-deficiency has been noted previously in Turner syndrome to be responsible for skeletal deformities and growth retardation as well as in rare conditions such as Leri-Weill dyschondrosteosis [10,11]. The tall stature due to accelerated bone growth seen in Klinefelter mosaic, 47, XXX and 47, XYY syndrome was also attributed to the same genetic disorder [12]. The cognitive impairment noted in patients with KS has been attributed to the SHOX deficiency, because the receptors for key brain neuro-transmitter, natriuretic peptide and fibroblast growth factor receptor 3 are transcriptional targets for the said insufficiency [13,14].

Patients with classical KS experience infertility, and present with small, hypoplastic testes that show evidence of seminiferous tubules hyaline degeneration on biopsy. Biochemical assessment show evidence of hypergonadotrophic hypogonadism and seminal fluid analysis show Oligo-azoospermia [7].

Although other KS related morbidities disturb patients, primary infertility is a major cause of medical consultation. Hypergonadotrophic hypogonadism results in hypoplastic testes and low serum testosterone. Testosterone replacement therapy was used to treat patients with KS to achieve many end results. It has been used to increase testicular volume and achieve relief of some of the clinical conditions that result from testosterone deficiency, such as depressive mood, decreased sex drive, easy fatigue and cognitive deficiency, especially, decreased concentration span. Testosterone therapy also improve muscle strength and limit the rate of bone demineralization [15]. Although increase

in testicular volume and penile size were noted following Testosterone replacement, no reversal in fertility status has been observed [16].

Assisted Reproductive Therapy (ART) using sperm donation was initially the most important treatment for KS related infertility. Improvement in knowledge of embryology and reproduction allowed many affected men to achieve paternity through In-vitro Fertilisation [17]. Because of Azoospermia in ejaculate, testicular sperm extraction is the preferred method of sperm retrieval. A 50% success rate has been reported for sperm retrieval via this method [17]. The younger the patient, the more likely viable spermatozoa will be obtained following testicular sperm extraction [18]. Sperm cells obtained from testicular sperm extraction has a success rate of 20-25% in achieving a successful conception after IVF [19].

2. Case Report

A 19-year old lady presented at the Surgical Out-Patient Department of State Specialist Hospital, Yobe state, Nigeria; on self-referral. She complained of bilateral, painless, groin swellings that were noticed since 10 years ago. There was no change in size or change in the skin overlying the mass. Patient is an identical twin, delivered by a 35-year-old mother following an unsupervised pregnancy. Both twin babies were said to have normal developmental milestones and developed female secondary sexual characteristics at puberty.

Parents noticed the bilateral groin swellings in the index patient, but, did not give it any significance due to its painlessness. Patient became worried by her failure to achieve menarche at the age of 18 years like her twin sister. She presented at the hospital on self-referral because, she thought her failure to achieve menarche may be related to the groin swellings.

3. Examination

On examination, a tall, slim lady was seen with an obvious feminine body habitus, bilateral Tanner stage three breasts and feminine distribution of pubic hair. There are bilateral ovoid groin swellings with no demonstrable visible or palpable expansile cough impulse, each about 3*4*2cm, not warm or tender, firm, smooth with well-defined margins. They were freely mobile.

Vaginal examination revealed a micro-penis, about 6cm in non-erect position, blind ended 2cm vaginal cavity and absent scrotum.

Central Nervous System examination showed a fully alert and oriented patient with excellent Mental functions and no visible speech difficulty. No cardiac or pulmonary abnormalities were noted.

4. Investigation

Abdominal USS revealed bilateral benign groin swellings in keeping with testicular tissues, absent uterus and ovaries and right renal agenesis. Buccal smear showed no Bar Bodies. Fasting Plasma Glucose measured was within normal range.

5. Surgery

Bilateral, open, groin exploration was done after an informed consent and excisional biopsy of the groin masses was done.

6. Histology

Histological assessment showed groin masses made mainly of Seminiferous tubules.

7. Out-Come

Both patient and parents opted to maintain a feminine gender despite detailed explanation of the diagnosis.

8. Objection

Although patient and parents gave consent for publication of a case report, they denied consent for taking photographs of the face or sexual organs because of their religious beliefs.

NB: The other twin sister is phenotypically female with well-developed breasts and a grossly normal uterus, ovaries and capacious vagina. She menstruates regularly [Fig. 1].

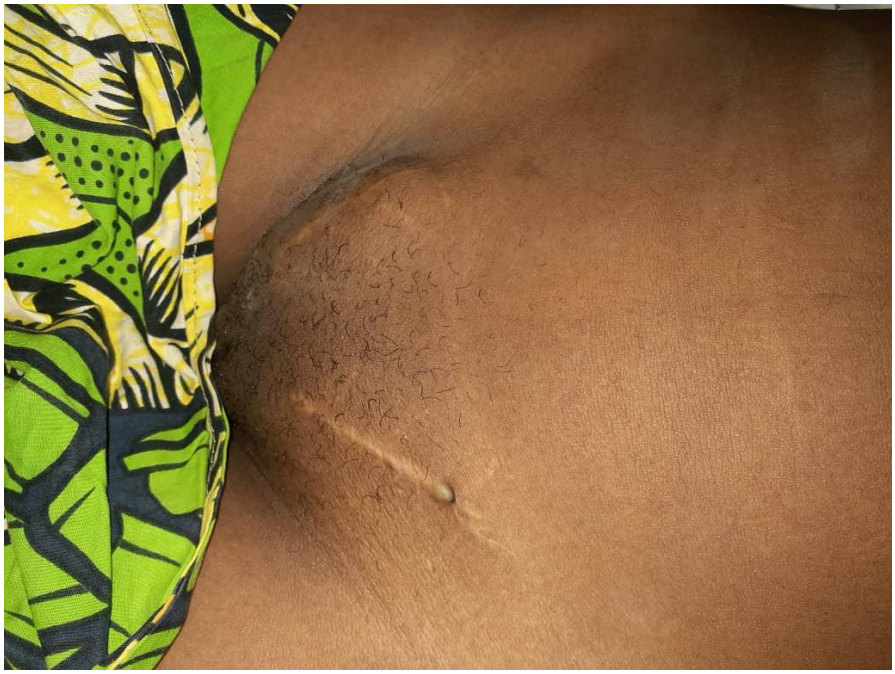

FIG. 1. Showing bilateral groin scar and Mons Pubis.

9. Discussion

The term Klinefelter Syndrome was initially a clinical description of a phenotypic appearance of a male with female body habitus, gynaecomastia, small hypoplastic testes and primary infertility. The speech and cognitive impairment is not a universal occurrence and depressive moods often begins after clinical diagnosis. (20) Karyotyping revealed the classical chromosomal abnormality of 47, XXY and the other mosaics. Some studies placed the incidence of Klinefelter syndrome in the neonatal period at 1/500-1000 and in adults at 1/2500. This study however, alleged that the incidence of KS in adults may be under-reported due to lack of life-threatening morbidities and estimated that more than 50% of cases of KS go undiagnosed. 21 The incidence among infertile patients is about 11% of azoospermic and 0.7% of oligozoospermic men with 47, XXY karyotype [22,23]. There is dearth of literature highlighting the incidence in Africa, particularly, the West African region and also the incidence among Identical Twins.

Diagnosis is often delayed, especially in Africa. This problem has been noted globally. Some reports indicated that postnatal diagnosis of XXY is often delayed, and parents are often left confused about the phenotypic appearance of their child and often perpetually anxious about some of the cognitive impairments and psychosocial disorders exhibited by the older children [24]. Even in developed nations a prenatal diagnosis of KS is often incidental following amniocentesis for other unrelated events and the babies often have other congenital anomalies that may put significant strain on the ability of parents to take decision about the fate of the pregnancy [25,26].

Our patient presented at the age of 19 years in keeping with the delayed diagnosis noted in previous reports. She failed to achieve menarche despite the presence of a female body habitus, well developed breasts and the presence of what looked like a normal vagina. The decision of the patient and her parents to reject treatment and maintain a feminine gender hampered the use of medical assistance. Many of the patients with KS improve on Testosterone Replacement Therapy (TRT) depending on the severity. Intramuscular injection of testosterone is the most common method of treatment. Although the extent of response to treatment is variable, majority show an appreciable improvement in symptoms [27]. It is generally safe and well tolerated and the Testosterone improve the development of secondary sexual characteristics. For optimal benefit, testosterone replacement therapy is best started at the age of 11 or 12 years [27]. At whatever age given, testosterone therapy has shown demonstrable benefits. It increases facial and pubic hair, muscle mass and strength, and improves sex drive [15]. It also improves their mood, behaviour and self-esteem [27]. Although It may have an effect on the size of the testicles, it has no effect on the enlarged breast tissue and infertility [16]. Intramuscular Testosterone injections have been given at 2 to 4-week interval with good results [28]. In the presence of patients' rejection of Intramuscular injection or a cogent medical contra-indication, a depo-testosterone preparation can be applied at 3-month interval. Testosterone preparations can be given orally or percutaneously where necessary [28]. The only drawback of the Oral preparations is the potential for hepatotoxicity. Irrespective of method of application, the outcome is said to be the same, as no statistically significant difference in the outcome has been observed in relation to the application method [29].

Many patients with KS have cognitive impairment characterised by learning disabilities, poor body image, poor self-esteem and difficultly in maintaining hetero-sexual relationships [27]. TRT has been shown to improve behaviour, energy level, general well-being, learning capacity and verbal fluency [30,31]. There is an assumption by many workers

that TRT may result in increase in brain volume. This assumption is hinged on a finding of a significant reduction in left temporal lobe grey matter volumes in untreated KS patients [32]. A major study over three decades, involving Caucasian male psychiatric inpatients found a frequency of KS ranging from 0 to 4.8% among schizophrenic patients and a 4- to 5-fold increase in prevalence compared to the general population [33]. Other studies reported that more boys with KS require psychiatric referrals [34] and 54% of these boys when they reach adolescence they exhibit mild to moderate psychiatric disorders. (35) Several non-randomised studies of boys and men with KS on the tendency of developing psychiatric disorders has revealed an increased tendency for developing schizotypal traits, schizophrenia, minor to major psychosis, minor to major depressive disorders, anxiety disorders, autism and attention deficit-hyperactivity disorder [36-43].

Extra care is therefore needed in handling patients with KS, especially, during adolescence and adulthood. A multi-disciplinary approach to treatment should be the goal standard. Early diagnosis of depressive or other psychiatric disorders and prompt referral to a psychiatrist will go a long way in determining an outcome.

10. Conclusion

Although KS is rare, the effect of the diagnosis on patients and their parents is enormous. One should keep a high index of suspicion to detect the cases early and activate the right treatment flow chart.

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Citation: Aliyu S, Ningi AB, Babayo UD, et al. Klinefelter syndrome in an identical twin: A case report and review of literature. Case Rep Rev Open Access. 2020;1(1):107.