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CASE SERIES

Rare Chromosomal Variants in Males with Hypogonadism: A Case Series From Tertiary Hospital in India

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Abstract

Male hypogonadism refers to decrease in testosterone levels due to diminished activity of testes. Hypogonadism will result in infertility, absent or poor secondary sexual characteristics and abnormal genitalia. One of the important causes of male hypogonadism is sex chromosomal abnormalities. In present study we discuss 5 cases of hypogonadism which has resulted due to rare sex chromosomal abnormalities. Identification of these abnormalities is very important in management of these patients.

Keywords: Hypogonadism, sex chromosomal abnormalities, infertility, Klinefelter syndrome

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Introduction

Male hypogonadism results from decreased activity of testes resulting in inadequate production of testosterone. In primary hypogonadism, there will be low testosterone levels with higher or normal FSH and LH levels. Main causes of primary hypogonadism include Klinefelter syndrome, anatomic causes, iatrogenic injuries, and tumors. In secondary hypogonadism, there will be low testosterone with low to low-normal LH and FSH levels. Main cause of this type of hypogonadism lies in defects related to pituitary gland. Chromosomal abnormalities resulting in altered sex hormone levels are one of the important causes of male hypogonadism. Common sex chromosomal abnormality resulting in hypogonadism is Klinefelter syndrome [1,2]. Klinefelter syndrome is the most frequent genetic cause of male infertility, and is found in 11% of azoospermic men and 4% of infertile men [3]. In consanguineous marriage, mutation in genes causing meiotic disjunction can result in chromosomal abnormalities resulting in hypogonadism. Identification of causes of hypogonadism will help clinician for hormone replacement therapy as well as to decide on assisted reproductive techniques in cases of infertility.

Case Series

We present 5 cases of hypogonadism showing rare sex chromosomal abnormalities who presented to Division of human genetics, Department of Anatomy, St. John's medical college, Bangalore from 2020-2021.Out of 5 cases, 3 cases presented as primary infertility and 2 cases presented as abnormal external genitalia. As a routine, hormonal levels were performed in these patients which showed low testosterone levels. Ethical clearance was taken from institutional ethics committee and informed consent was taken from the patients. A detailed history was taken and both general and systemic examination was carried out. The patients denied any personal history of mumps, HIV, or testicular torsion, no exposure to radiation, chemotherapy and chronic medications. This ruled out acquired causes of primary hypogonadism. Blood samples of these patients were subjected to standard protocol for karyotyping and Fluorescent in situ hybridization (FISH) to screen for chromosomal abnormalities.

Case 1

34-year-old male, born to third degree consanguineous parents, married for 3 years presented with complain of primary infertility. On examination, secondary sexual characteristics were not well developed. He had proximal hypospadias, chordee with bilateral atrophic scrotal testes. Investigation showed low levels of testosterone. Scrotal scan showed bilateral small sized testes, bilateral varicocele. His karyotype was 46,XX confirming 46,XX testicular disorder of sex development (Figure 1). Karyotype of wife was normal.

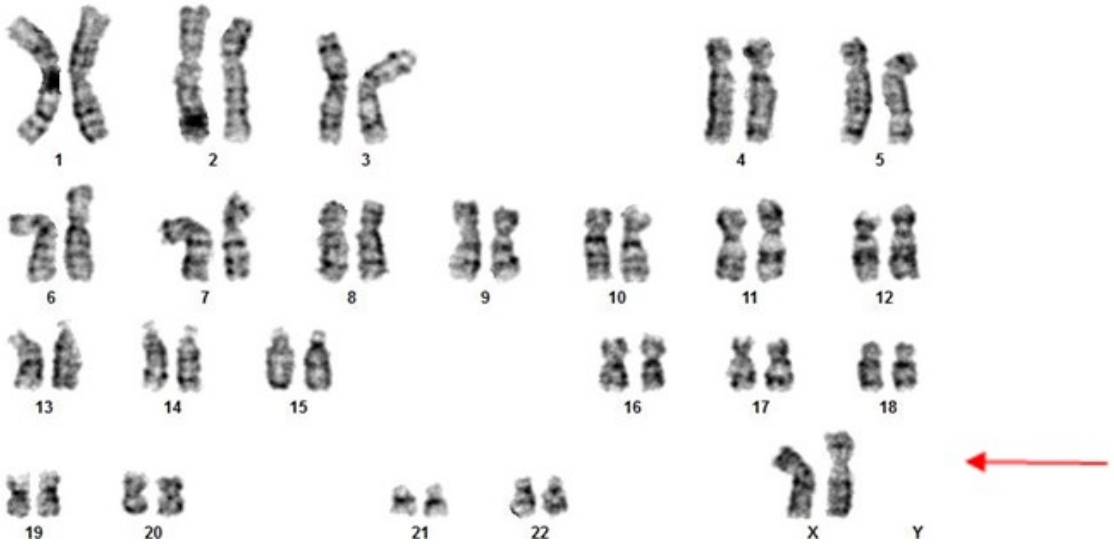


Figure 1. Karyotype of a male patient with hypogonadism showing 46,XX karyotype(Case 1).

Case 2

17-year-old male child born to a non-consanguineous marriage was referred for karyotyping with ambiguous genitalia. Hormonal profile showed low testosterone levels. Scrotal scan revealed bilateral small volume testis. Chromosomal analysis showed mosaic pattern with 29 cells with 45,X Karyotype and 21 cells showing 46,X,+mar. Marker was identified as Y chromosome with deletion on the Yq in mosaic pattern with positive SRY gene on marker. Presence of Y chromosome confirmed diagnosis of mixed gonadal dysgenesis (Figure 2).

Case 3

43-year-old male married for 7 years was referred for karyotyping with history of primary infertility. On examination he had bilateral gynecomastia and absent secondary sexual characteristics. His semen analysis showed azoospermia. Karyotyping showed mosaic variant of Klinefelter syndrome. Out of 25 metaphase spreads analysed, 4 spreads showed a normal 46,XY karyotype and 21 spreads with 47,XXY karyotype. Karyotype of wife was normal (Figure 3).

Case 4

38yr old male, married (consanguineous) for 13yrs was referred for karyotyping with history of primary Infertility. On examination he had bilateral gynecomastia and absent secondary sexual characteristics. Hormonal profile showed decreased testosterone levels with high FSH and LH levels. Semen analysis showed Azoospermia/ cryptozoospermia. Chromosomal analysis showed mosaicism with 47,XXY [33]/48,XXY,+mar[17] suggestive of Klinefelter syndrome. FISH probes (X/Y centromeric and X/Y WCP) were used to identify the marker chromosome, but both probes did not hybridize on the marker and normal signals for X and Y was seen. Y microdeletion studies was also done and it showed the presence of all the 3 regions on the Y chromosome. Spectral karyotyping was suggested to find out origin of marker chromosome. Spectral karyotyping showed

marker chromosome as a part of Chromosome 5. Karyotype of wife was normal (Figure 4).

Case 5

19-year-old male, second born to a non-consanguineous couple was referred for karyotyping with history of small sized testis and diminished secondary sexual characteristics. Hormonal profile showed increased FSH, LH and decreased Testosterone levels. Chromosomal analysis showed 48,XXYY karyotype suggestive of a Klinefelter variant. FISH studies were also done using X/Y centromeric probes - 2 green signals and two red signals indicating the presence of two X and two Y chromosomes were seen respectively (Figure 5).

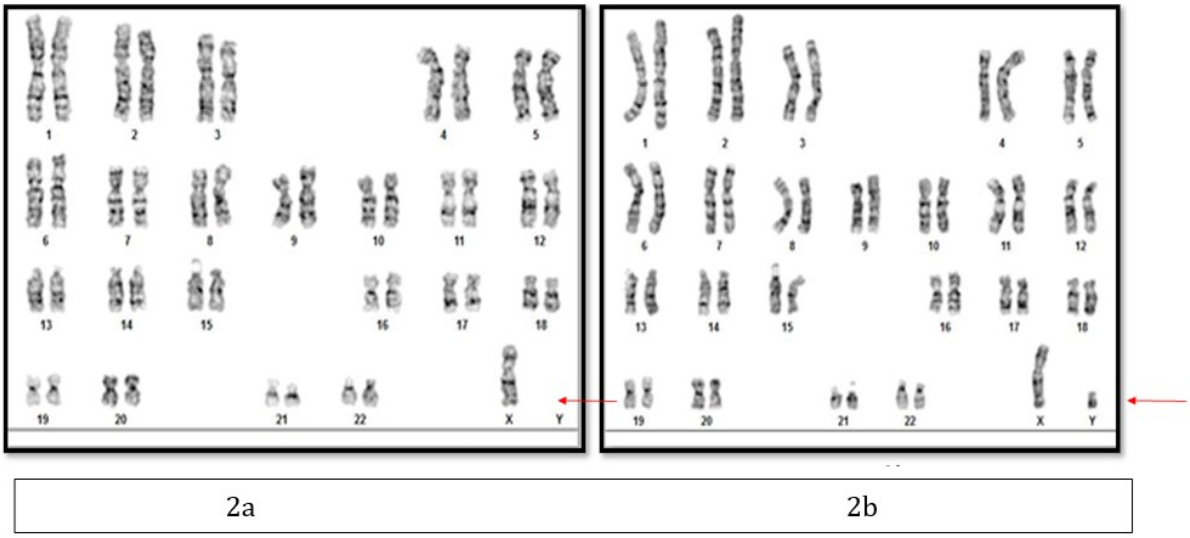


Figure 2. Karyotype showing mosaic chromosomal variant with mixed gonadal dysgenesis in hypogonadism, 2a showing 45,X karyotype, 2b showing 46,X,+mar karyotype(Case 2)

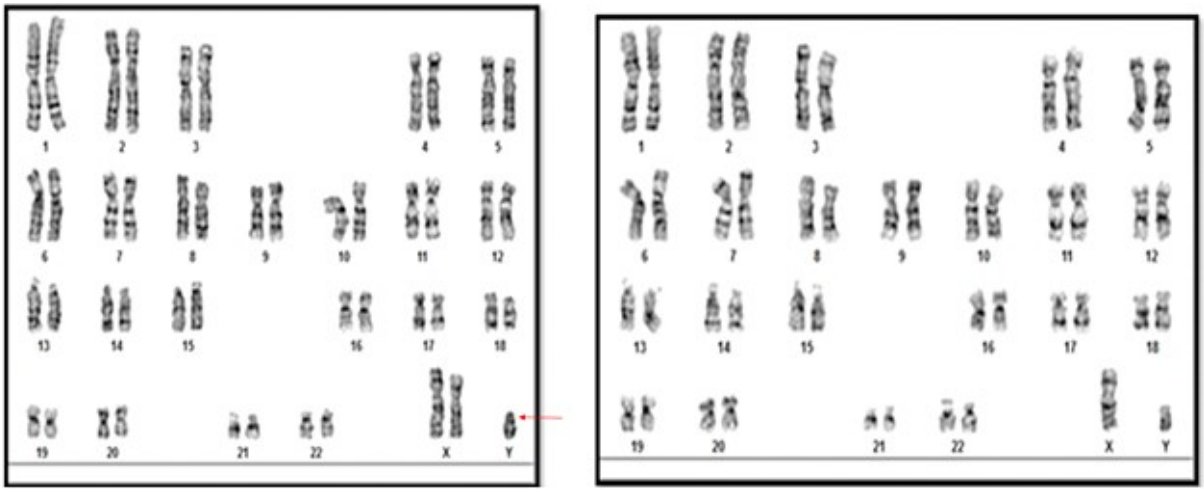
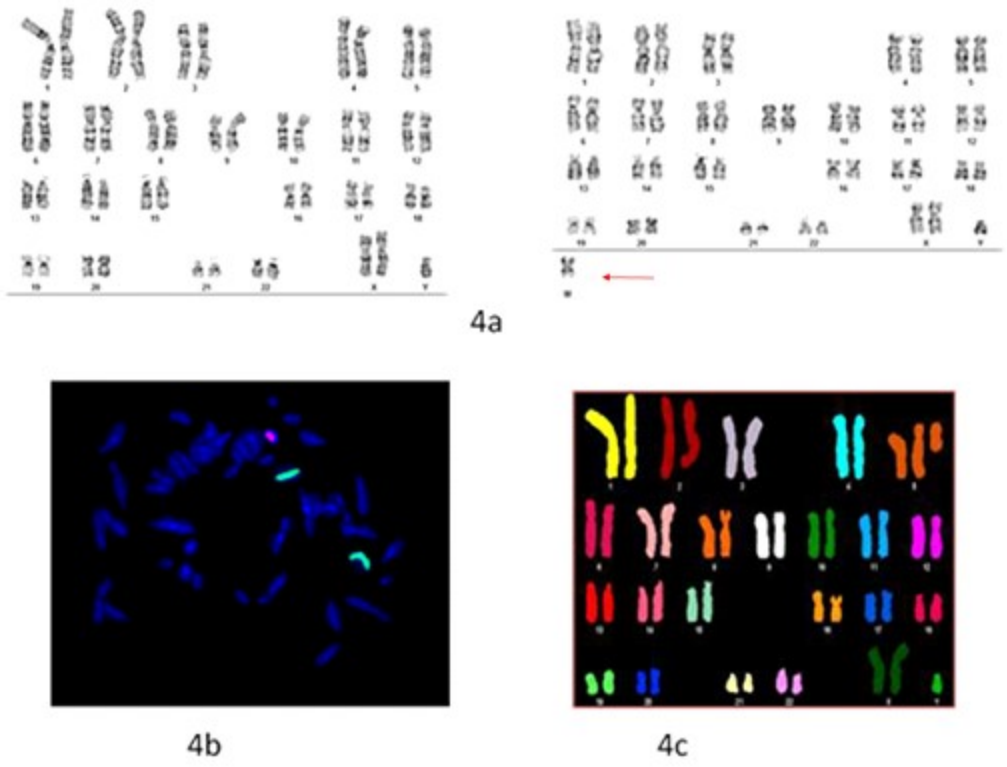
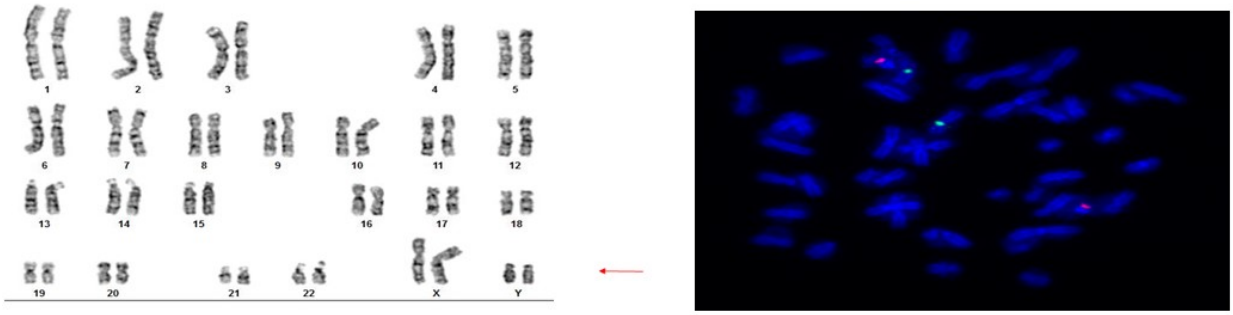


Figure 3. Karyotype of a male patient showing mosaic pattern for Klinefelter syndrome-21 spreads with 47,XXY karyotype (3a) and 4 spreads showed normal 46,XY karyotype (3b) (Case 3)



4a 4b 4c

Figure 4. Karyotype (4a) was 47,XXY[33]/48,XXY,+mar[17] suggestive of Klinefelter syndrome. Metaphase (4b) FISH showing 2 green (X) & 1 red (Y) signal. In High SKY (4c) marker got confirmed as derivative of chromosome 5 (Case 4).



5a 5b

Figure 5. Karyotype (5a) - 48,XXYY. Metaphase spread (5b) showing 2 green (X) & 2 red (Y) signal (Case 5)

Discussion

Main pathophysiology behind the chromosomal abnormalities is mutation in genes during meiotic disjunction. This will result in either additional X or Y chromosome or translocation of genes within chromosomes in germ cells. During conception, if these germ cells fertilize, resulting embryo will have chromosomal abnormalities. In all above cases there were

features of hypogonadism like gynecomastia, underdeveloped gonads, and low testosterone levels. Also, most of these cases presented with infertility. Systemic examination of cardiovascular, respiratory and nervous system was normal. Ambiguity in genitalia was limited to small size of testis and in one case hypospadias was present.

First case had 46,XX testicular disorder of sex development. Incidence of such cases is one in 20,000 male births. Alteration in location of SRY gene is main reason for 46,XX testicular disorder. During spermatogenesis, as a random event there is translocation of SRY gene to X chromosome. If fertilization occurs with sperm having X chromosome with SRY gene the fetus will develop as male even if Y chromosome does not exist. This usually happens in 80% of patients and is termed as SRY positive cases. In rest 20% there is SRY negative reason for which is not known. If Y chromosomal material is detected in such cases there are higher chances of neoplastic transformation. Hence surgical removal of gonads is suggested [4]. Tulsi Sharma et al., reported a case of male hypogonadism with 46,XX karyotype and one of the X chromosomes had an apparent deletion of Xp22.33 to Xpter and addition of chromatin material. FISH analysis demonstrated that the male sex-determining region of the Y chromosome, SRY, is present on the short arm of X chromosome [5].

Another important case which presented with hypogonadism was a case of mixed gonadal dysgenesis (case 2). Here karyotype was 45,X/46,X,+mar with underdeveloped external genitalia. In these cases, it is very important to identify status of gonads whether it is testis or streak ovaries. According to literature, risk of development of germ cell tumor in these patients is 15-35%. During providing treatment options, certain issues like malignancy risk, infertility, gender identity and dysphoria, family dynamics, social adaptation and coping skills should be considered [6,7].

Presence of extra X chromosome in males attributes to diagnosis of Klinefelter syndrome [8]. In present study we had three cases out of five who had chromosomal variants of Klinefelter syndrome. According to literature, Klinefelter syndrome is most common cause for hypogonadism. In study done by Osman et al karyotype of total of 64 individuals with hypogonadism was analysed. Chromosomal abnormalities were detected in 18.8% of all individuals. Klinefelter syndrome was the most common sex chromosomal abnormality [9]. In mosaic type of Klinefelter syndrome (case 3) there were few cells had normal male karyotype and few cells had extra X chromosome. In these individuals it is very important to conduct a testicular biopsy to confirm level of mosaicism in gonads to plan management especially in terms of infertility. Artificial reproductive techniques can help in these patients if sperms are of good quality. We had a rare type of variant of Klinefelter syndrome (case 4) with marker chromosome 5. Even with presence of marker chromosome, patient had no dysmorphism and had only presented with hypogonadism and infertility.

Another case with 48,XXYY (case 5) had features similar to classical

Klinefelter syndrome. The incidence of 48,XXYY syndrome is 1/18000–1/40000 [10]. Patients with 48,XXYY syndrome was widely studied by Tartaglia et al. In their study, they reported wide range of medical conditions with varying presentations in these patients. Almost all patients with 48,XXYY syndrome received aid for speech problems as well as intellectual disabilities [11]. Hanley et al., compared MRI scans of 25 subjects with 48,XXYY karyotype with normal male individuals and concluded that XXYY males have smaller brain than normal males and more often XXYY have abnormalities in white matter and in the ventricular system [12]. In above case MRI brain and psychologist opinion was suggested to the patient for further treatment.

It is evident from above cases that karyotyping and FISH plays very important role in diagnosis and management of patients with hypogonadism. Early diagnosis will help in better management with appropriate surgical and medical treatment along with hormonal therapy. Genetic counseling will help patient and his family to plan for future options. With regards to fertility, patient can opt for artificial insemination or in vitro fertilization using donor sperm or deciding on adoption.

Conclusion

Detection of sex chromosomal abnormalities by karyotyping and FISH plays vital role in early management of cases who are diagnosed with hypogonadism.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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