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ANATOMICAL AND DEVELOPMENTAL ABNORMALITIES ASSOCIATED WITH HYPOGONADISM AND INFERTILITY IN MALES

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Abstract- Infertility can be referred as the failure of conception after at least 12 months of unprotected intercourse. Male infertility means inability to induce conception in a normal woman within a year. Hypogonadism can be defined as when there is lack of physical manifestations of sexual maturation and gonadal function. The etiological factors associated with infertility and hypogonadism are anatomical/ developmental defects, seminal abnormalities, hormonal, immunological and environmental factors. The paper is aimed to highlight the anatomical and developmental abnormalities as the etiological factors associated to the infertility and hypogonadism in 119 (75 referred with infertility and 44 referred with hypogonadism) male patients, with the age ranged from 20 to 45 years (75 patients with infertility-age ranged from 21 to 45 years; 44 patients referred with hypogonadism-age ranged from 20 to 45 years).

Anatomical and developmental abnormalities were observed in 56.3% (67/119) of males with infertility and hypogonadism. Included in the 67 were 32% (24/75) with infertility and 97.72% (43/44) with hypogonadism.

In infertility, varicocele was observed in 10.66% (8/75); small testes in 8% (6/75); testicular atrophy in 5.33% (4/75) and Micropenis in 2.66% (2/75). Cryptorchidism (1), hypoplastic prostate (1), bilateral vasal aplasia (1) and seminal vesicle aplasia (1) were also observed as single cases in infertility.

In hypogonadism, small testes was observed in 59.09% (26/44); cryptorchidism and micropenis in 11.36% (5/44) and 11.36% (5/44); testicular atrophy and hypospadias in 4.54% (2/44) and 4.54% (2/44). Varicocele (1), small (1), hypoplastic prostate were observed in single cases with hypogonadism.

Chromosomal abnormality was observed in 20.83% (5/24) males with infertility and 25% (11/44) of male with hypogonadism those are associated with anatomical / developmental defects.

47,XXY karytotype was observed in all 5 males with infertility and 9 males with hypogonadism. 46,XY/47,XXY karyotype was observed in 2 males associated with hypogonadism.

It is opined that the anatomical or developmental abnormalities have an adverse effect upon the normal male reproductive function, which can lead to general inanition and deficiencies of spermatogenesis. In the counseling sessions, the patients were advised for the hormonal therapy in hypogonadism and surgical management in case of varicocele.

Keywords- karytotype, Male infertility, hypogonadism, Chromosomal abnormality

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Introduction

Infertility remains a common problem in causing a significant psychological distress to the affected couples; hence, couples are increasingly seeking medical advice. The affected couples suffer from enormous emotional and psychological trauma and it constitutes a major crisis in their life in the social context. Infertility as a public health problem varies widely in different communities according to the prevalence of the condition and importance ascribed to it by the society. Infertility accounts for about 15% of all couples attempting pregnancy with male partner responsible in approximately half the cases [1,2]. Infertility is defined as infecundity, sterility or physiological infertility defined by demographers as the incapacity 'of a man, women or couple to participate in reproduction i.e., the production of a live child [3]. In common, infertility is defined as failure to conceive after one year of intercourse without contraception. Male infertility means inability to induce conception in normal women within a year [4]. Sexual infantilism (SI) is defined as when there is lack of physical manifestations of sexual matura-

tion and gonadal function [5]. Disorders associated with sexual infantilism are grouped into hypogonadotropic hypogonadism (HH), selective or isolated gonadotropin deficiency (ISD), hypergonadotropic hypogonadism. The various factors attributing to male infertility are genetic, anatomical/developmental, seminal, immunological, hormonal, environmental and idiopathic. The anatomical/developmental factors include cryptorchidism, congenital anorchia, varicocele. Cryptorchidism, the failure of descent of testis into the scrotum is invariably associated with germinal epithelium failure. Congenital anorchia is rare and often a familial disorder, in which the testis are missing in phenotypically normal 46,XY males. Varicocele is a condition in which there is abnormal tortuoisity and dilatation of the testicular veins within the spermatic cord. The above various anatomical/developmental etiological factors are not discussed individually especially in Indian population. The present study aimed to report the suggested anatomical/developmental factors involved in male infertility and hypogonadism, which may facilitate appropriate measures in genetic counseling.

Material and Methods

The present study is a retrospective study on consecutively referred 119 male patients with hypogonadism and infertility referred to Division of Human Genetics, Department of Anatomy, St. John's Medical College, Bangalore for cytogenetic investigations and counseling. Male patients with any seminal abnormalities such as azoospermia, oligospermia, asthenospermia, gynaecomastia, obesity, hypogonadism, absence of growth or secondary sexual characters, primary or secondary infertility, varicocele or any other congenital anomaly and without conception after marriage with their wives being normal were included in the study. Among the 119 male patients, patients referred with infertility were 63.02% (75) and with hypogonadism were 36.97% (44). The age ranged from 20 to 45 years (75 patients with infertility-age ranged from 21 to 45 years; 44 patients referred with hypogonadism-age ranged from 20 to 45 years).

Clinical profile and other information were gathered from the detailed proforma and the data was analyzed. It may be noted that at the time of the referral, patients consent has been duly obtained.

Results

The observed anatomical and developmental abnormalities associated with infertility and hypogonadism are tabulated in [Table1].

Table 1- Anatomical and Developmental abnormalities in Males with Infertility and Hypogonadism

S.no.	Abnormalities	Infertility (%, n) (32%, 24/75)	Hypogonadism (%, n) (97.72%, 43/44)
1	Small testes	25, 6/24	60.46, 26/43
2	Cryptorchidism	4.16, 1/24	11.62, 5/43
3	Testicular atrophy	16.67, 4/24	4.65, 2/43
4	Micropenis	8.33, 2/24	11.62, 5/43
5	Varicocele	33.34, 8/24	2.32, 1/43
6	Scrotum - small	-	2.32, 1/43
7	Hypospadias	-	4.65, 2/43
8	Prostate - hypoplastic	4.16, 1/24	2.32, 1/43
9	Bilateral vassal aplasia	4.16, 1/24	-
10	Seminal vesicle aplasia	4.16, 1/24	-

The anatomical and developmental abnormalities were categorized into 10 groups, which include small testes, cryptorchidism, testicular atrophy, micropenis, variococele, bifid/small/large scrotum, hypospadias, enlarged/hypoplastic prostate, bilateral vasal aplasia and seminal vesicle aplasia.

Anatomical and developmental abnormalities were observed in 56.3% (67/119) of males with infertility and hypogonadism. Included in the 67 were 32% (24/75) with infertility and 97.72% (43/44) with hypogonadism.

In infertility, varicocele was observed in 10.66% (8/75); small testes in 8% (6/75); testicular atrophy in 5.33% (4/75) and Micropenis in 2.66% (2/75). Cryptorchidism (1), hypoplastic prostate (1), bilateral vasal aplasia (1) and seminal vesicle aplasia (1) were also observed as single cases in infertility.

In hypogonadism, small testes was observed in 59.09% (26/44), cryptorchidism and micropenis in 11.36% (5/44) and 11.36% (5/44); testicular atrophy and hypospadias in 4.54% (2/44) and 4.54% (2/44). Varicocele (1), large scrotum (1), hypoplastic prostate were observed in single cases with hypogonadism.

Anatomical/developmental abnormalities versus chromosomal abnormalities are given in [Table-2]. Chromosomal abnormality was observed in 20.83% (5/24) males with infertility and 25% of male with hypogonadism. 47,XXY karyotype [Fig-1] was observed in all 5 males with infertility and 9 males with hypogonadism. 46,XY/47,XXY karyotype [Fig-2a] and [Fig-2b] were observed in 2 males associated with hypogonadism.

Table 2- Anatomical and Developmental abnormalities Vs. Chromosomal abnormalities

S. no.	Chief complaints (%, n)	Anatomical & Developmental abnormalities (%, n)	Chromosomal abnormalities (%, n)
1	Infertility (63, 75/119)	32, 24/75	20.8, 5/24 47,XXY (100, 5/5)
2	Hypogonadism (36.97, 44/119)	97.7, 43/44	25.5, 11/24 47,XXY (81.81, 9/11); 46,XY/47,XXY (18.18, 2/11)

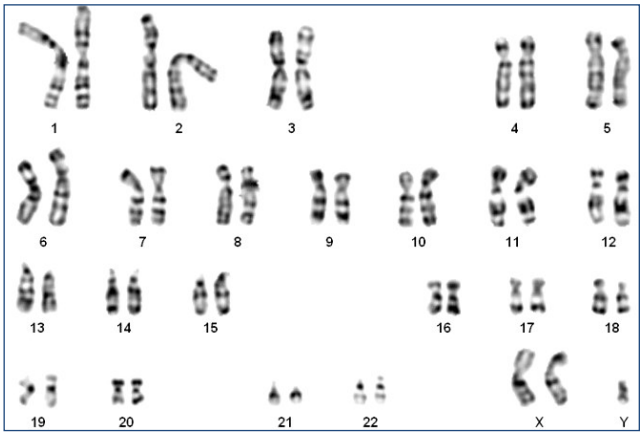

Fig. 1- KFS karyotype: 47, XXY

Discussion

Almost all significant anatomical/developmental factors have an adverse effect upon the normal reproductive function in the male, which can lead to general inanition and deficiency of spermatogenesis. The genes reported to be responsible for primary sexual dif-

ferentiation are SRY (Sex determining region Y on Yp11.31), SOX 9 (Sex determining region Y box 9 on 17q23), SF1 (Steroidogenic factor) and DAX 1 (Dosage sensitive sex reversal, adrenal hypoplasia critical region on X21.3).

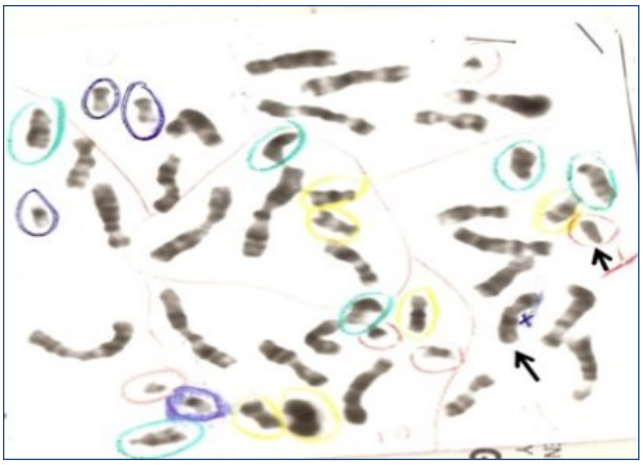

Fig. 2a- KFS: Metaphase spread: X-mosaicism: 46,XY (*Arrows indicate X & Y*)

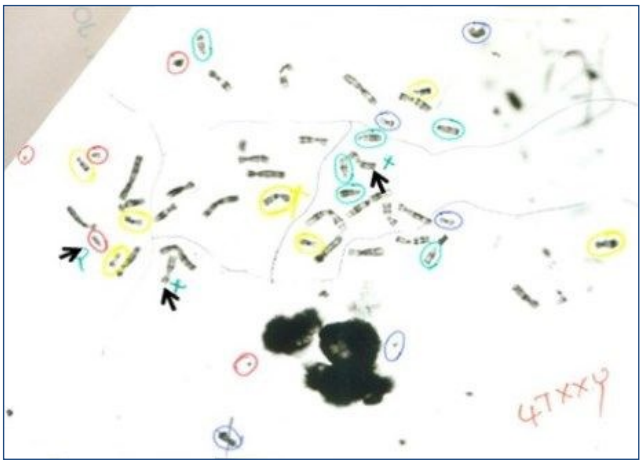

Fig. 2b- KFS: Metaphase spread: X-mosaicism: 47,XXY *Arrows indicate X & Y*

In the present study, it was observed that, urogenital system has manifested its features more frequently, which may be due to developmental, hormonal and point mutations of the genes involved in the primary sexual determination. Most of the findings from the present study are discussed with the findings from the literature.

In the present study, small testes were observed in 8% (6/75) and testicular atrophy in 5.33% (4/75) of male with infertility. On the other hand, in male referred with hypogonadism, small testes was noted in 59.09% (26/44) and testicular atrophy in 4.54% (2/44).

Absent gonads may reflect failure of gonad formation or failure of gonad retention. Loss of testicular function after critical phase of male differentiation results in anorchia, a syndrome characterized by normal male differentiation both internally and externally with micropenis without structural abnormalities of genital tract, but no gonadal tissue. The presence of normal male genitalia and absence of mullerian duct derivatives implies that fetal testicular function was normal. Grumbach and Styen [5] cautiously deferred laproscopic exploration of males with presumed true anorchia as phenotypic males with no palpable testis, elevated gonadotropin levels and no rise plasma testosterone concentration. Mc Clure [6] reported that testes may have been lost due to testicular torsion, trauma, vascular injury or infection. Pinsky, et al [7] opined that the possibility of testicular torsion or strangulation was may be due to lack of stabilizing ligamentous attachments of the testes and atrophy in-utero would be the likely consequence of testicular demise due to torsion or strangulation.

In the present study, in one male with infertility, cryptorchidism (1) was observed and in hypogonadism, it was observed in 11.36% (5/44) of cases.

Cryptorchidism exists in 0.7 to 8% of adult men and 2 to 3% of new born and 6% of infertile men. Descent of testes is essential for normal function, because spermatogenesis requires the lower temperature that is present in scrotum. Maldescent testes occur in more than 40 human congenital defects including hypogonadism and lack of androgen synthesis. Griffin and Wilson [8] reported additional sequelae of cryptorchidism that include increased susceptibility of the cryptochid testis to undergo torsion, particularly after puberty and an increased incidence of herniation of intra abdominal contents through the opening of processes vaginalis. The other etiological factors include mutations in 5α-reductase and/or androgen receptor gene. Caldamone, et al [9], Marshall, et al [10] reported that cryptorchidism is associated with infertility. 30% of men with unilateral cyrptorchidism are infertile, implying bilateral effect which implies irreversible sterility.

In the present study, in male with infertility, micropenis was observed in 2.66% (2/75) and in hypogonadism, in 11.36% (5/44) of cases.

Micropenis refers to anatomically correct penis nevertheless, extremely small in size. Any defect in hypothalamo-pituitary gonadal axis can result in micropenis. Sultan, et al [11] opined that micropenis may be due to inadequate testosterone production or action and also mutation within the 5α-reductase gene and/or androgen receptor gene.

In the present study, hypospadias were observed in 4.54% (2/44) in male referred with hypogonadism.

Hypospadias is incomplete fusion of penile urethera, with an incidence of 4 to 8/1000 male live births. It can be found as an isolated defect of fetal virilization or accompanied by micropenis or cryptorchidism. Grumbach, et al [12] and Sultan, et al [11] stated the possible reason that can be implied for hypospadias is the incomplete masculanization of external genitalia that implies either subnormal Leydig cell function in-utero, a mild degree of androgen resistance of 5α-reductase deficiency or a transient action of dihydroxytestosterone on the primordial of external genitalia.

In the present study, in infertility, varicocele was observed in 10.66% (8/75) of cases and in only one case referred with hypogonadism.

Varicocele is a condition, in which there is abnormal tortuosity and dilatation of the testicular veins within spermatic cord. The incidence of varicocele is 10 to 15% of male population. Varicocele is one of the commonest causes of infertility. Lipschultz and Naglar [13] and Dublen and Amler [14] reported the incidence of varicocele in infertility as 4 to 39%. The pathophysiology of varicocele on infertility remains unclear; however, the association of varicocele

with decreased testicular size, abnormal testicular histology is reported. Stewart [5] and Lewis and Harrison [16] opined that the temperature is increased over the affected testicle in presence of varicocele, impaired Leydig-cell function resulting in decreased androgen production thereby Sertoli cell dysfunction, may be cellular abnormality accounting for decreased spermatogenesis.

In the present study, bilateral vasal aplasia was observed in 1 male referred with infertility. Mimic, et al [17] reported that approximately 1% of infertile males show congenital bilateral absence of vas deferens. Genetic analysis showed a strong association of vasal aplasia with mutations and splice variants in cystic fibrosis transmembrane conductance regulator gene.

Froland, et al [18] in his study of 78 males referred with hypogonadism, 68 had 47,XXY karyotype, 2 had X-mosaicism and 8 had KFS variant karyotype. Foresta, et al [19] reported in 2 cases with infertility associated with 47,XXY karyotype. Kamischke, et al [20] reported that 47,XXY karyotype was observed in 309 patients with infertility and hypogonadism. In the present study, Chromosomal abnormality was observed in 20.83% (5/24) males with infertility (75) and 25% of male with hypogonadism(44). 47, XXY karytotype [Fig-1] as observed in all 5 males with infertility and 9 males with hypogonadism. 46,XY/47,XXY karyotype [Fig-2a] and [Fig-2b] were observed in 2 males associated with hypogonadism.

Interpretation from the Observations of the Present Study

In males with infertility, increased percentage of occurrence was observed for testicular hypertrophy, varicocele and hypoplastic prostate; on the contrary, the percentage occurrence seemed to be increased in hypogonadiam for small testes, cryptorchidism and micropenis.

Infertility was associated to small and hypospadias; which were not observed in the hypogonadism. Hypogonadism was associated to the bilateral vasal aplasia and seminal vesicle aplasia and these two features were not observed in infertility.

A high percentage of chromosomal abnormality in males with hypogonadism reflected the higher occurrence of anatomical/ developmental abnormalities in sexual infantilism.

Conclusion

The findings of the present study could delineate anatomical and developmental abnormalities as one of the etiological factors associated with infertility and hypogonadism.

Extensive analysis of SRY gene, Androgen receptor gene and 5α-reductase 2 gene mutations may further highlight the above hypothesis and help for appropriate measures of genetic counseling.

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