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The Frequency and Types of Chromosomal Aberrations in the Patients with Hypogonadism

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Abstract

Objectives: Hypogonadism is the clinical manifestation of the impaired function of the testes and the ovaries, and is either due to endocrinological problems or chromosomal abnornlalities (CA). Chromosomal analysis is one important piece in the hypogonadism individuals, and becomes essential from the clinical point of view.

Design: To determine the frequency, types of CAs in a hypogonadism population.

Materials and method: The current study was a retrospective analysis to examine the CAs and prevalence in 64 cases with unexplained hypogonadism problem. The samples were cultured routinely for the karyotype analysis using G banding.

Results: A total of 64 individuals with infertility was analysed. The karyotype results were normal in 52 (81.2%) of 64 individuals. However, CAs were detected in 12 (18.8%) of all individuals. The 15.6% of these CAs was numerical aberrations, and also structural CA was 3.1%. Specifically, Klinefelter syndrome (KS) was the most common karyotype (14.1%,9 cases) among the all cases, followed by 46,XX,anoploidy; 46,Xi(Xq) and 46,XY,robt(14;15).

Conclusion: We found a high rate CAs (18.8%) in patients with hypogonadism. Therefore, cytogenetic analysis can be strongly recommended in hypogonadism individuals, and should be performed routinely in both the male and female with hypogonadism.

Keywords: Hypogonadism; Chromosome abnormalities; Klinefelter syndrome; Isochromosome Xq

Introduction

Hypogonadism is a medical term which describes a diminished functional activity of the gonads – the testes and ovaries in males and females, respectively. Certain patients have hypogonadism from birth, while others may develop the condition later in their life. The disease has different features in males and in females, before and after the onset of puberty. If onset is in pre-pubertal boys, signs and symptoms of lack of testicular function include a change of male hair distribution, including facial, chest, and axillary hair, poor development of skeletal muscles, and disturbance of bone growth resulting in abnormally long arms and legs. Blood levels of the male hormone testosterone are low. Also observed are missing laryngeal enlargement, failure of vocal chord thickening, and alterations in body fat distribution. When hypogonadism occurs in males after puberty, low concentration of testosterone in the blood causes lack of energy, weakness, lethargy and diminished sexual function, reduced bone mass and often anaemia. In girls with hypogonadism before puberty, impaired ovarian function leads to failure of progression through puberty. The absence of periods is the most common feature. Blood levels of estradiol are low. When hypogonadism occurs after puberty, irregular periods or absence of periods is the usual concern. The patients develop ovarian suppression which manifests as infertility, decreased libido, breast atrophy, and osteoporosis.

For male patients with primary hypogonadism, the most common cause is a genetic disorder, a chromosome abnormality which occurs in one case per approximately 1,000 live births. Primary hypogonadism is more common in boys than in girls because the incidence of Klinefelter syndrome (KS) is higher than the incidence of the equivalent condition for girls, Turner syndrome (TS) [1]. Hypogonadotrophic hypogonadism (HH) in men occurs more rarely. It is estimated, though, that less than five per cent of men with HH are diagnosed and are receiving hormone replacement therapy; around a fifth of men aged more than 50 years are believed to have androgen deficiency. For women with primary hypogonadism, the most common cause is a genetic disorder known as TS, a chromosome abnormality which occurs with an incidence of one case per approximately 5.000 live births. The incidence of HH in females is equal to that in males. Chromosome study in the males and females with hypogonadism becomes essential from the clinical point of view. Little is known, however, about other underlying genetic causes. Therefore, we analysed 50 boys and 14 females seen by the same physician during the childhood or adolescence for hypogonadism.

Materials and Methods

The present cases are phenotypically 50 males or 14 females with hypogonadism during the childhood, adolescence and adult. They have the underdeveloped testes, lack of penile enlargement, absence of pubic, auxiliary, facial hair, low levels of testosterone, high-normal to high levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), loss of libido, erectile dysfunction. All cases born to young healthy, non-consanguinous couple was clinically found to have hypogonadism. IQ was normal. There was no family history of any congenital anomaly. Over the past 15 yr in our laboratory, postnatal karyotyping was done in 64 patients with hypogonadism. The mean age of cases was 17.6 years (range 9–33 years). Patients with hypogonadism who were seen in the out-patient clinics of both the Paediatric and Urology Departments, Faculty of Medicine, Çukurova University. The diagnosis of the patients is made on the basis of a chromosomal analysis in Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Fifty metaphases were analyzed in all the patients, but in cases of abnormalities and mosaicism the study was extended up to 100 metaphases. All CAs were reported according to the current international standard nomenclature (ISCN, 2009).

Results

A total of 64 individuals with infertility was analysed. Karyotype results were divided into two categories: numerical and structural CAs were shown in Table 1. The karyotype results were normal in 52(81.2%) of 64 individuals. However, CAs were detected in 18.8% (12) of all individuals.

Cytogenetic category	Karyotypes	No. of cases	Frequency in all cases (%)	Clinical findings
Normal	46,XX or 46,XY	52	81.2	
Abnormal	Numerical and structural chromosome abnormalities	12	18.8	
	Total	64		
Numerical chromosome abnormalities				
Klinefelter syndrome	47,XXY	6		Prepubertal
Klinefelter syndrome with isochromosome	47,Xi(Xq)Y	2		underdeveloped testes, lack of penile enlargement, absence of pubic, auxiliary, facial hair
X long arm abnormalities	46,XY/47,XXY(20%)	1		Postpubertal
Klinefelter syndrome with mosaic	46,XX, anoploidy (15%)	1		delayed puberty, constitutional delay, infertility, low levels of testosterone, high-normal to high levels of LH and FSH, loss of libido, erectile dysfunction
	Total	10	15.6	
Structural chromosome abnormalities	46,Xi(Xq 46,XY,robt(14;15)	1 1		
	Total	2	3.1	

Table 1: The frequency and types of chromosomal abnormalities in a hypogonadism population.

The 15.6% of these CAs was numerical aberrations, and also structural CAs were 3.1%. Specifically, Klinefelter syndrome was the most common karyotypes (14.1%,9 cases) among the all cases, followed by 46,XX,anoploidy (15%); 46,Xi(Xq) and 46,XY,robt(14;15).The incidence of abnormal karyotype was higher in males than females (the male-female ratio=3.0) (Table 1).

Discussion

The genetic causes of infertility are varied and include CAs, single gene disorders and phenotypes with multifactorial inheritance. The complex organization and regulation of the human hypothalamic–pituitary–gonadal axis render it susceptible to dysfunction in the face of a variety of genetic insults, leading to different degrees of HH. Despite the major genetic advances in understanding HH over the past 20 years, a pathogenic genetic defect can be found in around 30% of cases, suggesting that many mutations remain to be discovered which may give new insights into the organisation of the neurocircuitry regulating GnRH secretion. In the past decade, the rate of genetic discovery has dramatically accelerated, with defects in more than 10 genes now associated with HH [2]. Chromosome study in the cases with hypogonadism becomes essential from the clinical point of view. Bhagavath et al. [3] karyotyped 76 HH patients and identified a sporadic male patient with complete HH and hyposmia who had a balanced chromosome translocation, reported as 46,XY,t(10;12)(q26.3;q13.1). Four cases reported of (X;Y) translocations with a derivative Y. All involved a portion of Xp22 and Xq28 translocated to Yq11, and all patients had normal stature, hypogonadism with hypoplastic male external genitalia or ambiguous genitalia, mental retardation, and various dysmorphic features [4,5]. In the present study, retrospective analysis of cytogenetic results in 64 cases revealed CAs in 18.8% of all cases with hypogonadism. The 15.6% of these

karyotype anomalies were carriers of numerical aberrations, and 3.2% were carriers of structural (Table 1).

The most frequent chromosome-related causes of HH are sex CAs. Among men with infertility, the most frequent cytogenetic findings are 47,XXY and 47,XXY/46,XY karyotypes. We also identified 9 males with 47, XXY (KS) and variants, which accounted for the majority of the abnormalities, and the sex CA was the most common finding in male cases, accounting for about 3.4% (Table 1). Hypogonadism and gynecolnastia are the clinical manifestations of KS and its variants [6,7]. However, KS is the most common genetic cause of hypogonadism in men, and our study also reconfirmed this conclusion. The most common genotype is 47,XXY, but mosaicism (46,XY/47,XXY) is also frequently seen. The patients have small firm testes and are generally infertile because of tubular damage. Testosterone concentrations in serum are low, but patients might present with concentrations at the lower end of the normal range and have a normal male phenotype. Some men with mosaicism have normal testicular size and spermato genesis at puberty, but germ cells are progressively lost over time [8]. The conclusion from all this information, phenotypic anomalies such as hypogonadism have been attributed to sex-chromosome mosaicism.

We report 2 cases (3.1%) of a very rare variant form of KS [47,Xi(Xq)Y] that resulted in hypogonadism. Isochromosome Xq is a struc¬tural rearrangement frequently observed in Turner syndrome, but it is apparently rare in males [9]. It is suggested that the most probable origin of an Xq isochromosome is misdivision of the centromere or sister chromatid exchange of one X chromosome. Due to the limited number of cases, the prevalence of this KS is still unclear. Up to the present, 21 patients with i(Xq) have been reported in the literature, and reports on KS with an isochro¬mosome Xq have been discussed briefly in the literature; therefore, genetic counseling is difficult for such cases [10]. In general, all 47,Xi(Xq)Y patients have been reported to exhibit the main clinical features of KS, including reduced androgenization, small testes, azoospermia, gynecomastia, and ele¬vated FSH and LH levels. In general, all 47,Xi(Xq)Y patients have been reported to exhibit the main clinical features of KS, including reduced androgenization, small testes, azoospermia, gynecomastia, and ele¬vated FSH and LH levels.The only clinical difference between the 47,XXY and 47,Xi(Xq)Y KS patients is normal-to-short stature in the latter. The height of the patient in our cases is compati¬ble with the previous reports.

However, X-chromosome deletions are usually sporadic, although familial cases have been reported. Deletions affecting the short arm of the X chromosome at band p11.2 result in ovarian failure in about half of women, and the other half experience menstrual irregularities. We also detected one female (1.6%) with isochromosome Xq, and trisomy Xq resulting from an isochromosome X long arm abnormalities [46,Xi(Xq)] (Table 1). The 46,Xi(Xq) karyotype is found in 7% to 17% of individuals with TS [11,12]. Some reports [13-15] have indicated that patients with the 46,Xi(Xq) karyotype have characteristics similar to those observed in classical TS. Patients with i(Xq) have similar characteristics to those with classical 45,X. However, patients with a deletion of Xp have short stature and congenital malformations Sybert and McCauley4 have reported the 46,Xi(Xq) karyotype in 7% of patients with TS. The clinical anomalies in the i(Xq) type TS are cardiac disease, renal malformation, menstrual disorders, mental retardation, and edema. We observed no mental retardation in this case. We found that the isochromosome i(Xq) form of TS was generally milder than classic TS. A female with short stature and hypogonadism but without typical clinical findings of TS, should be evaluated for this chromosomal form.

Kallmann syndrome is a disease clinically characterized by the association of hypogonadotropic hypogonadism and anosmia or hyposmia. The hypogonadism is due to insufficient release of gonadotropin releasing hormone from the hypothalamus [16]. The KAL-1 gene structure for X-linked Kallmann syndrome revealed the presence of 14 exons spanning approximately 210kb on Xp22.3 and shown to encode a protein sharing homology with molecules involved in neuronal migration and axonal pathfinding [17,18]. Kallmann syndrome rarely occurs as the result of a deletion involving only the KAL-1 gene [19,20]. Deletions of this gene are most frequently observed in males with a contiguous gene syndrome, including the loss of genes for ichthyosis, chondrodysplasia punctata, mental retardation and short stature in the distal short arm of the human X chromosome [21-25]. Thus, deletions of one short arm of the X chromosome in our case may be cause of hypogonadism. In the here reported the patient, cytogenetic analysis demonstrated a Robertsonian translocation between chromosomes 14 and 15 associated with hypogonadism.

Conclusions

The results suggest that CAs were a major cause of hypogonadism in humans. Therefore, cytogenetic analysis can be strongly recommended in hypogonadism individuals, and should be performed routinely in both the male and female with hypogonadism. Hypogonadism have been attributed to sex-chromosomes. These findings will could be used widely in the clinical genetics and will be an effective tool for genetic counseling and reproductive guide.

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