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Klinefelter: Which Sexuality?

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ABSTRACT

Klinefelter syndrome (KS) was described by Klinefelter, Reifenstein, and Albright in 1942, who described 9 adult males with gynecomastia, small and firm testes, azoospermia, and increased serum FSH with functional Leydig cells. In 1959, using cytogenetics, Jacobs and Strong described the existence of an extra X chromosome in a male with Klinefelter syndrome The International Consensus Conference organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology in 2006 included KS in disorders of sexual development. Klinefelter syndrome is also characterized by a genetic dysfunction of the entire gonad that affects germ cells from early fetal life and Sertoli and Leydig cells from mid-puberty. Today we know much more. In this article, we have delved into the social, relational, and sexual quality of life of patients with KS, going beyond fertility studies.

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Introduction

It is a matter of fact that the scientific bibliography has been much concerned with infertility in patients with Klinefelter syndrome (KS), much less so with sexual experience in general, including that of the partners. It has moved over time from the first description connoted by gynecomastia, tall stature with eunuchoid body proportions, small testes, infertility, and hypergonadotropic hypogonadism to a broad spectrum of phenotypes, occupations, incomes, and socioeconomic status [1]. But KS may also be associated with an increased risk of systemic diseases including malignancies, venous thromboembolism, diabetes, cardiovascular and metabolic diseases, and osteoporosis [2]. In addition, a large percentage of patients with KS suffer from verbal impairment, disturbances in attention span, relational and language response and an introverted personality [3,4]. Not to mention a predisposition to psychiatric disorders: depression and anxiety [5]. Klinefelter syndrome is the most common chromosomal abnormality in humans, with an estimated prevalence of 1 in 600 live births in males [3]. However, the condition is usually underdiagnosed, with about 25 percent of the expected number of patients being diagnosed and only a minority being diagnosed during childhood This could be because Klinefelter syndrome was initially a clinical diagnosis of adult males classically described as tall, with gynecomastia, small testes, azoospermia, sparse body hair, narrow shoulders, and wide hips. XXY males who lack these typical features are probably not detected, as is the case with nearly 90% of prepubertal patients in whom the diagnosis of hypogonadism is usually delayed until puberty [6]. These clinical premises have conditioned patients' judgement of health care providers as being insensitive and uncaring with regard to the pathology and its consequences for the quality of life of the individual and the partner.

What Sexuality do KS Patients Experience?

Early studies reported that individuals with KS experience insipid sexuality tend to marry older women, and often divorce because of their sex lives. Sexually, they appear less active and report limited autoerotic activity from adolescence and scarcity of sexual intercourse in adulthood more recent studies have, on the other hand, revealed hyper sexuality, paraphilic behavior, and gender dysphoria, mediated by obsessive-compulsive and autistic traits [7-9]. Disorders of desire and a high incidence of Premature Ejaculation. Indeed, it is well known that testosterone (T) plays a physiological role in various aspects of the male sexual response, starting with sexual desire, arousal, orgasm, and ejaculation. Corona has reported in patients with KS the presence of severe erectile dysfunction (ED), hypoactive sexual desire (HSD), and premature and/or delayed ejaculation [1].

However, these associations disappeared when patients with KS were compared with age, smoking habit, and T-matched controls, allowing the authors to conclude that sexual dysfunction in KS is mainly related to the underlying hypo gonadal state. The fact remains however, that patients often see the anthologist primarily because of infertility and not because of sexual dysfunction. In fact, the desire to have a child seems to be the basic motivation of KS patients, and often, having achieved parenthood, sexuality again becomes infrequent and with poor erotic traits.

Depression and SK

But there is more a survey conducted in Denmark, of 832 patients with KS and 4033 controls, showed an increased risk of hospitalization for psychiatric disorders (HR 3.65) [10]. Other studies have reported a high prevalence of depression, between 19 and 24% [11]. Whether depressive symptoms are specifically associated with genotypic alterations in KS or are consequences of physical and emotional traits due to the syndrome has been questioned [12]. Van Rijn et al. reported increasing emotional agitation and difficulty in identifying and verbalizing emotions [13].

The organic basis for this could be traced to alterations in the amygdala and other limbic structures involved in emotion regulation, as well as in aggressive and impulsive behaviors. Another factor could be the higher cortisol levels during states of anxiety and depression [14]. A relationship between hypogonadism and depression has also been proposed. Two population-based studies showed a hazard ratio of 4.2 for hypo gonadal depression and 1.55-2.71 for depressed hypogonadism [15]. In fact, the evidence on this topic is conflicting: some studies have reported improvement in depression in KS undergoing TRT, while others have not [16]. However, the link between hypogonadism and depression could be considered in light of the shared symptoms. Regarding anxiety however, a study by Tartaglia examined the behavioral characteristics of 57 KS: 25% reported pathological coefficients or had risk scores in the areas of anxiety, depression, and somatic complaints. Fifty percent stated little interest in social activities and relationships [17].

These findings were confirmed by Bruining in a study of 50 KS: depressive disorder was reported in 24% and anxiety disorders in 32% [18]. Anxiety and depression condition difficult social interactions; in particular, KS show social anxiety and problems in relationships with peers, social impulsivity and shyness However, brain volumetric differences in KS (global and regional) in addition to preliminary findings of functional brain alterations related to auditory, motor, language and social processing should not be underestimated. The combination of cognitive, psychological and social challenges negatively affects the quality of life of these patients [19].

Mind and Body

Morphological and functional studies focusing on the brain have in fact shown important differences in the brain structure of subjects with KS. Several psychiatric disorders such as schizophrenia, autism, attention deficit hyperactivity disorder, depression, and anxiety have been frequently reported in patients with KS according to a wide spectrum of phenotypes.

T supplementation (TRT) was unable to improve psychotic disorders in men with KS with or without overt hypogonadism [20]. Decreased gray matter volume in the hippocampus, Para hippocampal cortex, and amygdala is associated with memory impairment and mood dysregulation; in particular, involvement of the amygdala may be related to atypical temperament, passivity, and reduced sex drive; decreased left inferior frontal area and motor fascia, particularly on the left side, are related to muscle weakness in the trunk and shoulders [21,22]. In contrast, increased gray matter volume in the sensorimotor and occipital regions in KS appears to be associated with sensorimotor deficits. Finally: ventricular volume is inversely related to verbal processing speed and verbal executive function [23].

Gender Incongruence and SK?

But there is more Although observational studies have potentially shown a higher prevalence of Klinefelter syndrome among presumed male trans individuals at birth than rates in the general population, the link between the conditions remains unclear [24]. The existing literature alludes to a twofold explanation behind the predisposition to gender incongruence. First, a fetus with Klinefelter syndrome is exposed to less androgen, which could contribute to different gender identity development. Second, typical features of Klinefelter syndrome such as gynecomastia and sparse body hair may be perceived as eminine. Some studies have suggested that this may make the individual more vulnerable to doubts surrounding their male identity [25]. The fact remains that clinical studies in this regard are scarce and the literature often underestimates this phenomenon.

The Timing of Diagnosis

Although in infants the frequency of KS is between 1/500 and 1/700 it seems that 64% of KS cases go undiagnosed. Abnormally low levels of testosterone blood values are very common in this syndrome. In such cases, androgen replacement therapy should be started (ideally at age 11-15 years) In order to prevent osteoporosis and to improve secondary sexual characteristics. In the 1960s and 1970s, systematic screenings in psychiatric hospitals found 1.3% KS among hospitalized boys, which is 10 times more than in the general population, and between 0.6 and 1% KS among hospitalized men. In addition to this: boys presenting with KS are usually described as shy, with little energy, little social motivation and few friends. They cry more often than peers. Neuropsychological studies show significantly lower verbal IQ than controls, while performance IQ is generally normal and global IQ is within the normal range, with wide individual variations. Language acquisition is always delayed. However, aggression does not increase.

Scientific studies in recent decades have found more psychiatric disorders among patients with KS, compared with groups of hypo gonadal patients at first examination (mean age = 27 years). Several hypotheses have been proposed to explain the psychological aspects of KS such as low androgen levels during fetal and childhood development, personality disorder related to hypogonadism, and delayed mitosis of cells with an extra X chromosome, but none of them can explain the specificity of psychological problems associated with KS [26]. Among others, studies by Liberato D. et al. analyzed 58 adult patients with KS with the classic karyotype 47, XXY. A structured clinical interview for Axis II disorders was evaluated to assess DSM IV personality disorders, in addition to the use of the MMPI-2 questionnaire. Fluid intelligence was tested using Raven's Standard Progressive Matrices (SPM) test. Blood concentration of testosterone was measured by CMIA. The results showed the prevalence of PD in 31%. Four altered MMPI scales (social responsibility, dominance, ego strength and repression) were found in more than 40% of patients. Hyper controlled Hostility and MacAndrew Alcoholism Scale-Revised scales were only altered in the PD group. The Biz-Odd Thinking and Post-Traumatic Stress Disorder scales were

associated with the presence of personality disorders. The raw SPM score was 44 ± 10.8 with no significant correlation with testosterone. Finally: the prevalence of Parkinson's disease in KS patients was higher than in the general population [27].

Identity Cards of Couples with KS Syndrome and Their Partners

What characteristics do these couples exhibit? What psychological, emotional and relational traits do their partners show? B. Ottonicar et al [28]. Tested the personality traits of 17 men with KS syndrome and their partners by comparing them with 16 couples with idiopathic infertility and 17 fertile couples. The data were collected through a medical history interview and by subjecting the couples to the SSG (attitudes toward pregnancy, labor, sexuality) and MMP2 (personality questionnaire) questionnaire. Raven's matrices, on the other hand, were used only for couples in the first group. The data showed that men with KS syndrome and their partners did not differ from couples with idiopathic infertility in the nature of schizoid personality and negative attitudes toward pregnancy, labor, and sexuality. There are many differences with fertile couples. Couples with KS syndrome show a far lower quality of social life and with more personality disorders that may influence the outcome of clinical treatment for fertility and sexual dysfunction. In addition, hypoactive desire and sleep disorders are more detectable in couples with KS syndrome, with reduced sleep quality (48.5%), insomnia (sleep latency 70 minutes), delayed sleep and severe sleep apnea [29]. Other studies have shown ultimately that patients with KS and metabolic syndrome have symptoms of left ventricular dysfunction [30].

Hyper Sexuality: Of a Few or of Many KS?

Kingsley Okolie, a general practitioner, published a case study of hyper sexuality in a 44-year-old KS syndrome patient employed as a supermarket checkout clerk [31]. He had presented in 2014 with a long history of erectile dysfunction, lethargy, low mood and poor concentration. He reported daytime fatigue, did not shave regularly, and reported a markedly increased libido characterized by uncontrollable urges to masturbate and a need for frequent heterosexual encounters. With one partner, he had problems with erection and ejaculation, but achieved benefits with the cGMP-specific phosphodiesterase type 5 inhibitor, sildenafil. Alongside symptoms of sexual dysfunction and low androgenization, he denied endocrine symptoms suggestive of pituitary, adrenal, or thyroid gland disease. His excessive libido had detrimental effects on his quality of life. At the age of 17, he had been convicted of sexual offenses against a minor (a 9-year-old girl). Psychological counseling had diagnosed a "hidden pedophile" syndrome. Further denied by the patient. From age 20 he described sexual relations with more than 1800 partners, most (>95%) prostitutes. He presented regularly for screening for sexually transmitted infections (more than 3 times in the last year) and had been treated several times for genital warts with imiquimod cream. He believed he was suffering from "sexual addiction" being unable to control his desires and behaviors. He had a history of learning and behavioral difficulties. He stated that as a child he had played alone and had been diagnosed with autism for which he had not received treatment. He showed learning difficulties in school, particularly with language and more specifically with comprehension. He had begun a degree program in pharmacy but had discontinued the course because he found it too difficult. How generalizable is this tendency? This patient's antisocial personality disorders (involving passive-aggressive tendencies, criminal behavior, and paraphilia) have been linked to KS, but this clinical history seems scarcely generalizable [32]. Given that Klinefelter Syndrome involves a low libido condition hypersexual desire in this patient appears very unusual. Only the studies by Sinha et al. described a 22-year-old KS patient with similar problems [33,34]. The hypersexual desires in this other man clearly interfered with his social and academic functioning. Both cases met Kafka's criteria for hypersexual desire: a pattern of strong, repetitive sexual urges, desires, and behaviors that lead to clinically significant distress, adverse consequences, or impaired function [35]. The few cases described in the literature refer us to a broader concept of the diagnosis of hyper sexuality. This disorder is conceptualized primarily as a nonparaphilic sexual desire disorder with an impulsivity component. Specific polythetic diagnostic criteria are proposed, as well as the dysregulation of sexual arousal and desire, sexual impulsivity, sexual addiction, and sexual compulsivity.

Conclusion

We know from scientific research that there is no significant reduction in life expectancy in males with KS; however, the highest risk areas remain osteoporosis, cardiovascular disease, and breast cancer [36]. Ongoing follow-up is important not only from an endocrine and metabolic perspective, but also for emotional, psychological, and fertility support. It would be important to establish specialized services for adult KS with a multidisciplinary team to accompany KS children from childhood and adolescence through to adult services to provide care throughout the growth and maturity process. This approach could produce benefits for the physical, psychological, and relational well-being of these patients. Not forgetting the approach to diagnosis for parents of KS children. Especially when the diagnosis is reported by telephone or with an "anomalous" mode of communication. Parents should be met with an individualized prognosis, which does not induce guilt, inadequacy, or a pathological view of the child's growth process. In this regard, there is still much to be done in the clinic and in research so as not to compromise the sensitivity and adequacy of individuals and their families.

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