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Editorial

Klinefelter syndrome: an under-diagnosed genetic condition with late diagnosis

Síndrome de Klinefelter: uma condição genética com diagnóstico tardio e sub-diagnosticada

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Klinefelter Syndrome (KS) is a chromosomal disorder that involves the X sex chromosome and occurs approximately 1 in 650 men. It is the main genetic cause of male infertility and almost all patients are azoospermic, although some may have severe oligozoospermia. Clinical features include learning difficulties, tall stature, long limbs, little body and pubic hair, hypogonadism, micropenis, gynecomastia, abdominal obesity, infertility,... Patients with KS may present comorbidities such as osteopenia, osteoporosis, metabolic syndrome, diabetes, cardiac anomalies, among others that can affect their quality of life[1]. Thus, early diagnosis of this genetic condition is essential to minimize such complications and allow treatment and implementation at an appropriate age. Two recent studies show the benefits of early diagnosis in terms of fertility preservation[2] and bone fracture prevention[3].

According to Bonomi et al.[1], the known phenotype in KS represents just the tip of an iceberg, that is, the classic phenotype was characterized only based on a small number of affected patients, precisely those who sought medical appointments and would likely exhibit a greater number of clinical features. Thus, it is very likely that the number of patients with KS is much higher, as many individuals with less severe forms and less evident symptoms may never have been diagnosed and would represent the basis of this iceberg[1].

A brief presentation of the clinical-genetic spectrum of some studies on KS is presented in Chart 1[4-6], showing substantial variability in traits presence and severity. This shows that in the literature there are few studies with this approach with a significant number of patients. A Brazilian study identified only 33 patients with KS (seven were diagnosed before the age of 20 and two before the age of 10) over a 23-year period, indicating that either patients seek little medical care, or doctors think little about this diagnosis[7]. Although this casuistry is apparently small, it is similar to that of India[6]. It is also worth mentioning that this Brazilian research was conducted at the Outpatient Clinic of the Interdisciplinary Group for the Gender Determination and Differentiation at the State University of Campinas (UNICAMP), a reference to the care of patients with chromosomal disorders[7]. In the study published in 2019[6], in the classic KS group (n=38; 86.4%), the main characteristics were hypogonadism and infertility, and behavioral problems and cardiac abnormalities were

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present in 14 (36.8%) and 6 (15.7%) of the patients, respectively. On the other hand, in the variant KS group (n=6; 13.6%), there was a relation to non-gonadal issues and the frequency of behavioral problems (83.3%, n=5) and cardiac malformations (66.6%, n=4) were extremely high. The authors described that developmental delay, cardiac malformations, behavioral problems and intellectual disabilities were common characteristics in pediatric individuals, with adult individuals more frequently presenting hypogonadism[6].

As for the etiology, KS is a chromosomal aneuploidy, and around 90% of cases exhibit the classic karyotype, that is, 47,XXY. Other chromosomal constitutions include mosaicism (46,XY/47,XXY), structural changes involving the X chromosome [47,XY,i(X)(q10)] and, less frequently, the variant SK forms (48,XXXY; 48,XXYY; 49,XXXXY). This information is summarized in Chart 1. Variant KS forms are characterized by more than one extra X chromosome and can be diagnosed earlier due to more severe phenotypes with greater intellectual impairment and dysmorphisms[1].

A recent narrative review of the literature showed cytogenetic heterogeneity regarding the possible karyotypes presented by patients with KS. In this study, a flowchart on KS diagnosis is shown, in the different phases of human development, according to the main clinical characteristics presented by the affected patients. The condition was early diagnosed in the prenatal period due to advanced maternal age and at birth when associated with chromosomopathies, especially Down Syndrome[8].

Thus, it is a consensus in the scientific literature that men with KS are frequently diagnosed in adulthood, usually around 30 years of age, during the investigation of infertility. The KS diagnosis rate is estimated to be only 25% and, therefore, it is an under-diagnosed condition. Furthermore, less than 10% of patients are diagnosed before puberty[1,6]. In summary, due to the wide and slight variation in the phenotype, KS is rarely and lately diagnosed and represents a challenge to be overcome.

A recent literature review reports that the diagnosis of KS using cytogenetics is rarely mentioned and is usually only performed as a last option[9]. It is noteworthy that the examination of the karyotype is essential to confirm the diagnosis of KS, especially when considering the phenotypic variability associated with this genetic condition.

According to Ferlin[10], although our knowledge about this syndrome has improved substantially in recent years, the rate of diagnosis is still very low and the “classic” phenotype affects only a minority of patients. Regarding the diagnosis of KS, in 15-20% of cases it occurs during prenatal care, 10% of individuals are diagnosed before puberty, 15% in puberty and the remaining 50-60% of cases are diagnosed during age adult, usually during fertility investigation, with some cases diagnosed even after age 50 or 60 years. However, variant SK forms tend to be diagnosed earlier when compared to 47,XXY individuals because they exhibit distinct clinical characteristics[10,11]. A recent study[10] briefly discusses general strategies for early diagnosis of the classic KS karyotype in different periods of life (prenatal, birth, childhood, prepuberty, adolescence, puberty and adulthood). The implementation of NIPT (Non-Invasive Prenatal Testing) and PGT (Preimplantation Genetic Test) techniques for the detection of aneuploidies (PGT-A) could increase the rate KS diagnosis in the prenatal period. At birth, karyotyping in newborns with bilateral cryptorchidism and micropenis could contribute to an increase in this rate. In the other stages, the authors suggest a special attention to the clinical characteristics, with emphasis on the routine analysis of the testicles of affected patients[10].

In short, it is important that health professionals, including the medical ones, especially pediatricians, endocrinologists and urologists, consider KS as a clinical suspicion, even in the absence of specific signs[7]. In this sense, it is necessary to recognize the spectrum of clinical manifestations of this syndrome, with attention to the “hidden” phenotype, aiming to reach an early diagnosis and timely treatment.

Chart 1 – General characteristics of three studies that analyzed patients with KS.

	Costa et al.[4]	**Pacenza et al.[5]**	**Asirvatham et al.[6]**
Countries	Portugal	Argentina	India
Goals	Describe the clinical characteristics of children and adolescents with KS	Establish the frequency and clinical characteristics of different forms of KS presentation at different ages in a large cohort of patients	Check the clinical characteristics and various forms of KS presentation
Number of patients with KS studied (period)	15 (January/1992 to December/2009)	98 (1982 to 2008)	44 (2007 to 2015)
Karyotypes (number of patients)	47,XXY (13) 46,XY/47,XXY (2)	47,XXY (82) 46,XY/47,XXY (7) 48,XXYY (3) 47,XXY/48,XXYY (2) 48.XXXY (1) 47,XXY[4]/48,XXXY[2]/46,XY[44] (1) 49.XXXXY[44]/48.XXXY[6] (1) 47,XXY[36]/48,XXXY[1]/46,XX[1]/46,XY[2] (1)	47,XXY (38) 48,XXYY (2) 49.XXXXY (2) 47,XXY/48,XXXY/49,XXXXY (1) 49,XXXXY/48,XXXY/46,XX (1)
Clinical signs - frequency	tall stature - 87% Gynecomastia - 33% Micropenis - 25% Global motor development delay – 75% Learning difficulties – 67% Attention Deficit Hyperactivity Disorder - 42% Language deficits – 17% Psychosocial/behavioral problems - 13% Hypergonadotrophic hypogonadism - 60%	Pediatric and adolescent patients (< 18 years) Neurodevelopmental Disorders - 44.4% PP and 53.8% P Small testicles - 16.7% PP and 76.9% P Cryptorchidism – 55.5% PP and 23% P Gynecomastia - 0% PP and 42.3% P Micropenis - 16.7% PP and 11.5% P Varicocele - 11.5% PP and 11.5% P Dysmorphism - 3.8% PP and 3.8% P <u>adult patients</u> Small testicles - 100% Infertility - 100% Eunucoid proportions - 35.2% Gynecomastia – 31.3% Erectile Dysfunction - 29.3% Reduced libido - 27.5% Varicocele - 23.3% Neurodevelopmental Disorders - 22% Micropenis - 0%	Pediatric patients/P (n=17) and adults/A (n=27) Small testicles – not available P and 59.3% A Cryptorchidism - 17.6% P and 3.7% A Gynecomastia - 0% P and 29.6% A Micropenis - 35.3% P and 11.1% A Dysmorphism - 23.5% P and 0% A Cardiac anomalies - 29.4% P and 0% A Subnormal intelligence – 58.3% P and 41.6% A Behavioral problems - 76.5% P and 22.2% A
Other relevant information	Prenatal Diagnosis - 7 Postnatal diagnosis - 8 (4 diagnosed in adolescence)	44 - < 18 years (18 < 10 years and 26 between 10 and 17.9 years) 54 - 18 years or older prenatal diagnosis - 4 cases prevalent age group at diagnosis - 11-20 years	Classic KS presentation age (n=38): > 20 years Variant KS presentation age (n=6): < 7 years

PP: prepubertal, n=18 (median age 5.07 years, range 0.75 – 9.28 years); P: puberty, n = 26 (median age 14.3 years, range 10.1 – 17.7 years)

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