

## Klinefelter's Syndrome: 18 years' experience of a pediatric endocrinology unit

*Síndrome de Klinefelter: 18 anos de experiência de uma unidade de endocrinologia pediátrica*

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### ABSTRACT

**Aims:** To describe the clinical characteristics of children and adolescents with Klinefelter Syndrome.

**Methods:** A cross-sectional retrospective study was conducted, based on clinical data of patients diagnosed with Klinefelter Syndrome and followed from January 1992 to December 2009 (18 years) at a Pediatric Endocrinology Unit of a tertiary care-level hospital in Portugal.

**Results:** In the study period 15 patients were identified. Seven had a positive prenatal diagnosis of Klinefelter Syndrome and eight had post-natal diagnosis, after investigation for psychomotor development delay, behavioral disruptions and/or suggestive phenotype (four of them only diagnosed during adolescence). Thirteen patients had a peripheral blood karyotype of 47, XXY and two presented 47, XXY/46, XY mosaicism. The median age of first visit was seven years. Onset of puberty occurred spontaneously in seven cases. Puberty induction was performed in three patients, at age of 14 years. Those who needed hormone treatment had an effective response with no side effects. Behavioral and social inadequacies were identified in two cases and moderate global motor developmental delay in nine. Hyperactivity and attention deficit disorder were diagnosed in five patients, currently treated with methylphenidate.

**Conclusions:** A global motor development delay together with physical features of Klinefelter Syndrome in a child justifies karyotyping given the high prevalence of this syndrome, especially if socialization problems and learning difficulties are present. This study highlights the need for greater awareness in diagnosis as well as the importance of multidisciplinary approach in the care and education of these patients.

**KEY WORDS:** KLINEFELTER SYNDROME; GENETIC DISEASES, INBORN; CHROMOSOME ABERRATIONS; HYPOGONADISM; DEVELOPMENTAL DISABILITIES; PRENATAL DIAGNOSIS; PATIENT CARE TEAM.

### RESUMO

**Objetivos:** descrever as características clínicas de crianças e adolescentes com Síndrome de Klinefelter.

**Métodos:** foi realizado um estudo transversal retrospectivo, com base em dados clínicos dos pacientes com diagnóstico de Síndrome de Klinefelter acompanhados entre janeiro de 1992 e dezembro de 2009 (18 anos) na Unidade de Endocrinologia Pediátrica de um hospital de cuidados terciários em Portugal.

**Resultados:** foram identificados 15 pacientes no período do estudo. Sete tiveram diagnóstico positivo pré-natal de Síndrome de Klinefelter e oito tiveram o diagnóstico pós-natal, após investigação por atraso no desenvolvimento psicomotor, distúrbios comportamentais e / ou fenótipo sugestivo (quatro deles diagnosticados apenas durante a adolescência). Treze pacientes tinham um cariótipo de sangue periférico de 47, XXY e dois apresentaram 47, XXY/46, mosaicismo XY. A idade mediana da primeira visita foi de sete anos. Início da puberdade ocorreu espontaneamente em sete casos. Indução da puberdade foi realizada em três pacientes, com a idade de 14 anos. Aqueles que precisaram de tratamento hormonal tiveram uma resposta eficaz, sem efeitos colaterais. Inadequações comportamentais e sociais foram identificadas em dois casos e atraso moderado de desenvolvimento motor global em nove. Hiperatividade e transtorno de déficit de atenção foram diagnosticados em cinco pacientes, atualmente tratados com metilfenidato.

**Conclusões:** atraso global do desenvolvimento, juntamente com características físicas da Síndrome de Klinefelter em uma criança, justifica a solicitação de cariótipo, dada a elevada prevalência dessa síndrome, especialmente se estiverem presentes problemas de socialização e dificuldades de aprendizagem. Este estudo destaca a necessidade de uma maior conscientização para o diagnóstico, bem como a importância da abordagem multidisciplinar no cuidado e na educação desses pacientes.

**DESCRIPTORIOS:** SÍNDROME DE KLINEFELTER; DOENÇAS GENÉTICAS INATAS; ANOMALIAS CROMOSSÔMICAS; CARIÓTIPO ANORMAL; HIPOGONADISMO; DEFICIÊNCIAS DO DESENVOLVIMENTO; DIAGNÓSTICO PRÉ-NATAL; EQUIPE INTERDISCIPLINAR DE SAÚDE.

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This file was corrected in March 2012. The order of the first two authors was changed, moving Cláudia Costa from second to first author. A note was published in the print edition of the number 1 of volume 22, 2012, communicating this correction.

## INTRODUCTION

Klinefelter Syndrome (KS) constitutes a frequent genetic cause of human male infertility.<sup>1-2</sup> This syndrome is a chromosomal disorder in which there is at least one extra X chromosome added to the normal male karyotype 46, XY. This common aneuploidy affects one in every 660 men. Karyotype (47, XXY) is the most common form, accounting for 80-90% of all cases.<sup>3</sup> Mosaicism (46, XY/47, XXY) is observed in about 10% of cases.<sup>4</sup> A substantial number of patients remain undiagnosed because of patchiness in clinical presentation and insufficient professional awareness of the syndrome itself.<sup>2-4</sup> The prototypical phenotype of KS is traditionally described as tall, eunuchoid body proportions, with narrow shoulders, broad hips, feminine distribution of adipose tissue including gynecomastia, absent or decreased facial and pubic hair, small hyalinized testes, small penis, lower intelligence with a verbal intelligence quotient (IQ) frequently below normal, learning difficulties and androgen deficiency.<sup>5-8</sup> Elevated gonadotropins are present in all cases of KS, with a variable degree of hypogonadism.<sup>5</sup> Almost all patients have significant medical, psychological or social problems.<sup>2-9</sup> Increased incidence of osteoporosis, breast cancer, mediastinic tumors, mitral valve prolapse, diabetes mellitus, thromboembolic diseases, retention of the testes and autoimmune/rheumatologic diseases are amongst reported related comorbidities.<sup>5-9</sup> Mortality in KS is significantly increased due to diabetes and cardiovascular, respiratory and gastrointestinal diseases.<sup>9-12</sup> Early recognition, hormonal and other case-specific treatments can substantially improve quality of life, preventing serious consequences.<sup>12-13</sup> Testosterone replacement corrects symptoms of androgen deficiency but has no proved effect on infertility.<sup>13</sup> Nowadays patients with KS are no longer considered irrevocably infertile, because intracytoplasmic sperm injection offers an opportunity for procreation.<sup>14-15</sup>

As KS is characterized by multisystemic involvement, variability of presentation and high rate of comorbidities, a continuous and integrated approach in reference centers is essential to improve patients' life quality. The aim of this paper is to characterize a case series of children and adolescents with KS followed at the Pediatric Endocrinology Unit of Hospital Santa Maria in Lisbon, Portugal.

## METHODS

A cross-sectional retrospective study was conducted, based on clinical data of patients followed from

January 1992 to December 2009 (18 years). All patients were followed at the Pediatric Endocrinology Unit of Hospital Santa Maria in Lisbon, Portugal. The analyzed variables were anthropometry, demography, complete physical examination with Tanner pubertal development evaluation scale, neurodevelopmental assessment and qualitative psychological assessment, karyotype and hormone assays, comorbidities, treatment and follow-up, provided the data were recorded in the patients' charts.

The World Health Organization Growth Standards Charts for weight and height z-scores were used for analysis of anthropometric data. Weight was measured on a properly calibrated scale, without shoes, in little or no clothing on, at the nearest 0,1 kg. Height was measured in standing position at a firm vertical surface to the nearest 0,1 cm. Complete physical examination should include breast examination and Tanner pubertal development evaluation scale, comprised of axillary hair and pubic hair distribution and morphology and size of external genitals evaluated with Prader orquidometer.

Neurodevelopmental assessment was performed with Ruth Griffiths Mental Scale (at 3 year-old), Wechsler Intelligence Scale for Children (Wechsler Preschool and Primary Scale of Intelligence – WPPSI or Wechsler Intelligence Scale for Children – WISC III), applied by the same pediatric psychologist, according to age. Karyotype and hormone assays included dehydroepiandrosterone sulfate, total testosterone, follicle-stimulating hormone, and luteinizing hormone levels.

The study followed the ethical principles of research involving human subjects stated in the Declaration of Helsinki of 1989 and was approved by the Directors of Pediatric Department and Pediatric Endocrinology Unit in Children and Family Department of Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Portugal. Descriptive statistical analysis was obtained using Excel 2007 version and SPSS 19.0 version.

## RESULTS

In the study period 15 patients with KS were identified, with a first appointment median age of seven years (minimum of three months and maximum of 15 years). The median period of follow-up was 11 years (minimum of three months and maximum of 13 years).

Positive prenatal diagnosis was confirmed in seven patients, five of them in the last three years of the study period. In the remaining eight, a post-natal diagnosis of KS was made following investigation for psychomotor development delay, behavioral disruptions and/or suggestive phenotype (four of which only diagnosed in adolescence). Thirteen patients had peripheral blood karyotype of 47, XXY and two 47, XXY/46, XY

mosaicism. Median maternal delivery age was 36 years (minimum 32, maximum 40).

World Health Organization z-score for height at the time of the study ranged between +2 and +3, with a z-score for height greater than target height in all patients. Gynecomastia was diagnosed in four patients (Table 1).

Onset of puberty occurred spontaneously in seven cases. Puberty induction was performed in three patients at 14 years, with enanthate ester of testosterone, whose initial dose ranged between 50 and 100 mg. Mean time of hormone treatment was 24 months (minimum six, maximum 27), with effective response and no side effects identified (Table 2).

**Table 1.** Clinical signs in patients with Klinefelter Syndrome followed at the Pediatric Endocrinology Unit of Hospital de Santa Maria in Lisbon, Portugal, from January 1992 to December 2009 (18 years).

Clinical Signs	N Found / examined patients*	(%)
Tall Stature	13/15	87
Gynecomastia	4/12	33
Small penis	3/12	25
Tests volume <3ml at >15years of age	3/5	60
Global motor developmental delay	9/12	75
Learning difficulties	8/12	67
Hiperactivity attention deficit disorder	5/12	42
Language deficits	2/12	17
Psicosocial/behavioral problems	2/15	13
Hypergonadotrophic hypogonadism	3/5	60

\* Not all data were recorded in the patients' charts.

All cases were assessed for developmental and psychological aspects, and severe mental retardation and behavioral and social inadequacy were found in two cases. Moderate global motor developmental delay was described for nine patients. Of the twelve patients with evaluation for language development, only two cases had specific deficits. Hyperactivity and attention deficit disorder was diagnosed in five patients, currently treated with methylphenidate.

## DISCUSSION

This study aimed to characterize children and adolescents with KS followed in the last 18 years at one of the five most representative Pediatric Endocrinology Units of Portugal. Over the study period, half of the patients were referenced because of a positive prenatal diagnosis, performed on the basis of advanced maternal age. Results of previous reports describe a positive correlation between advanced maternal age and this chromosomal anomaly.<sup>1-5</sup> A greater number of prenatal diagnoses in the last three years of the study period was probably related to the greatest achievement of amniocentesis and/or increasing maternal delivery age in recent years.<sup>3</sup> Four KS cases were diagnosed in adolescence, a stage where testosterone is crucial for a proper development of muscle and bone, as well as secondary sexual characters in boys.<sup>9</sup> A reasonable explanation for this delay is the lack of severe physical manifestations in these prepubertal boys, so the syndrome goes undiagnosed in most affected patients.<sup>1-5</sup> Among those with known KS,

**Table 2.** Features of 15 patients with Klinefelter Syndrome followed at the Pediatric Endocrinology Unit of Hospital de Santa Maria in Lisbon, Portugal, from January 1992 to December 2009 (18 years).

Case	Karyotype	Age (years)	Tanner* at first consultation	Tanner* at last consultation	Tests volume at last consultation left/right (ml)	Follow-up (years)	Hormonal treatment, duration (months)
1	47xxy	16	A4P4G4	A4P4G4	10/15	2	No
2	47xxy/46xy	15	A4P4G4	A4P4G5	20/25	4	No
3	47 xxy	19	A1P1G1	A4P4G1	20/25	13	Yes, 27
4	47xxy	11	A1P1G2	A1P1G2	4/6	11	No
5	47xxy	12	A2P2G2	A2P2G2	6/8	11	No
6	47xxy	10	A1P2G2	A1P2G2	6/8	10	No
7	47xxy	8	A1P1G1	A1P1G1	<3	4	No
8	47xxy	8	A1P1G1	A1P1G1	<3	8	No
9	47xxy	15	A3P3G1	A3P4G1	3/3	0,5	Yes, 6
10	47xxy	15	A1P2G1	A3P4G2	6/8	4	Yes, >9
11	47xxy	5	A1P1G1	A1P1G1	<3	4	No
12	47xxy	12	A1P1G1	A1P2G1	<3	3	No
13	47xxy	14	A3P3G2	A4P4G2	6/8	2	No
14	47xxy	7	A1P1G1	A1P1G1	<3	0,3	No
15	47xxy/46xy	13	A3P3G3	A3P3G3	15/10	0,3	No

\* Tanner classification: A, axillary hair distribution; P, pubic hair distribution; G, morphology and size of external genitals.

many do not receive the diagnosis until the adult age.<sup>9</sup> In our study, karyotypes in children and adolescents were carried out mainly because of neurobehavioral disorders.<sup>11</sup> As described in literature, we perceived a high relative frequency of 47, XXY peripheral blood karyotype and a lower rate of mosaicism (46, XY/47, XXY).<sup>1-4</sup> Men with mosaicism are less affected and rarely diagnosed.<sup>4</sup> Gynecomastia presented in four of our boys was secondary to increasing estradiol levels and estradiol-to-testosterone ratio.<sup>5</sup> Gonadal development is particularly susceptible to each additional X chromosome, which may justify small penis in three boys, small testes in other three and spontaneously onset of puberty in seven cases.<sup>5</sup> Puberty induction needed to be performed in three of seven adolescent patients, at 14 years old, consistent with published data.<sup>13</sup>

Screening for behavioral and cognitive/learning problems is recommended in all children with KS, preferably before the age of 10 years.<sup>4-7</sup> Early detection could improve the long term prognosis, as described in the literature.<sup>1-5, 9-10</sup> Communication between medical experts, geneticists, and primary care physicians becomes essential in optimizing patient care. Prompt diagnosis and extensive discussion benefit the patient, who will receive the proper care for his special needs.<sup>9-10</sup> Most males with the 47, XXY karyotype had normal intelligence. We reported, as described in literature, a negative correlation between mental capacity and additional X chromosome: a 15 points reduction in IQ score for each supernumerary X chromosome; behavioral and social inadequacy in two cases and moderate global motor developmental delay in nine patients.<sup>6-7</sup> Concerning minor developmental and learning disabilities (academic difficulties, specific language deficits, diminished short-term memory, decreased data-retrieval skills, reading difficulties, dyslexia and attention deficit disorder), this study stated two cases of specific language deficits and five with hyperactivity and attention deficit disorder, usually seen in 70% of series studies.<sup>12</sup>

A retrospective study is always impaired by the implications of a long follow-up and previous discrepancies in the implemented methodology and in the availability of multidisciplinary approach. This study is an example of how difficult it is to achieve all the information needed to complete a case series report. Many patients didn't had all the clinical data available in their record charts.

This study describes, for the first time, a 18-year follow-up case series of KS. Half of the expected KS diagnoses were made before puberty, due to amniocentesis performed because of advanced maternal age. Comorbidities described are mostly caused by the chromosome aberration itself. Normal

functioning in children and adolescents with KS might be challenged by the risk of serious developmental psychopathology. Impairments in the areas of communication, socialization and disorganized behaviors were frequently present in this series. Clinicians should be aware of the possibility of KS in a boy with psychiatric problems. A neurodevelopmental delay with physical features suggestive of KS justifies karyotyping of a child, given the high prevalence of this syndrome, especially if socialization problems and learning difficulties are present. This study highlights the need for greater awareness in diagnosis of KS as well as to the importance of multidisciplinary approach in care and education of these patients.

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