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Artigo de Relato de experiência

Early Diagnosis of Klinefelter Syndrome: the Importance of Genetic Counseling

Diagnóstico Precoce da Síndrome de Klinefelter: a Importância do Aconselhamento Genético

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ABSTRACT

Introduction Klinefelter syndrome is associated with a numerical abnormality involving the sex chromosomes, and has an estimated prevalence of 1:660 in live male births. We present here a child with karyotype 48,XXXY/49,XXXXY diagnosed early a genetic investigation started at 2 months of age. **Case description:** Brazilian male patient, 2-month-old child of a non-consanguineous couple, uneventful pregnancy and no history of genetic disease. He was brought in for genetic consultation due to delayed psychomotor development and congenital heart disease, had low birth weight, and from the beginning he presented hypotonia, dolichocephaly, ear with low implantation, cryptorchidism, congenital heart disease and camptodactyly. The result of the GTG-banding karyotype examination revealed the mos 48,XXXY[20]/49,XXXXY[70] karyotype, which is compatible with the diagnosis of mosaic Klinefelter syndrome. The early identification of these patients has great relevance for their appropriate treatment and care, especially for minimizing the risks of infertility, feminization and the biopsychosocial implications of Klinefelter syndrome.

Keywords: G-banding; Mosaic; Sex chromosome.

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RESUMO

Introdução A síndrome de Klinefelter está associada a uma anormalidade numérica envolvendo os cromossomos sexuais e tem uma prevalência estimada de 1:660 em nascidos vivos do sexo masculino. Apresentamos aqui uma criança com cariótipo 48,XXXY/49,XXXXY diagnosticada, precocemente, com investigação genética iniciada aos 2 meses de idade. **Descrição do caso:** Paciente brasileiro do sexo masculino, filho de 2 meses de idade, de casal não consanguíneo, gestação sem intercorrências e sem histórico de doença genética. Procurou consulta genética por atraso no desenvolvimento psicomotor e cardiopatia congênita, baixo peso ao nascer, desde o início apresentou hipotonia, dolicocefalia, ouvido com implantação baixa, criptorquidia, cardiopatia congênita e camptodactilia. O resultado do exame de cariótipo de bandagem GTG revelou cariótipo mos 48,XXXY[20]/49,XXXXY[70], compatível com o diagnóstico de síndrome de Klinefelter em mosaico. A identificação precoce desses pacientes tem grande relevância para seu tratamento e cuidados adequados, principalmente para minimizar os riscos de infertilidade, feminização e as implicações biopsicossociais da síndrome de Klinefelter.

Palavras-chave: Banda G; Mosaico; Cromossomo sexual.

INTRODUCTIONS

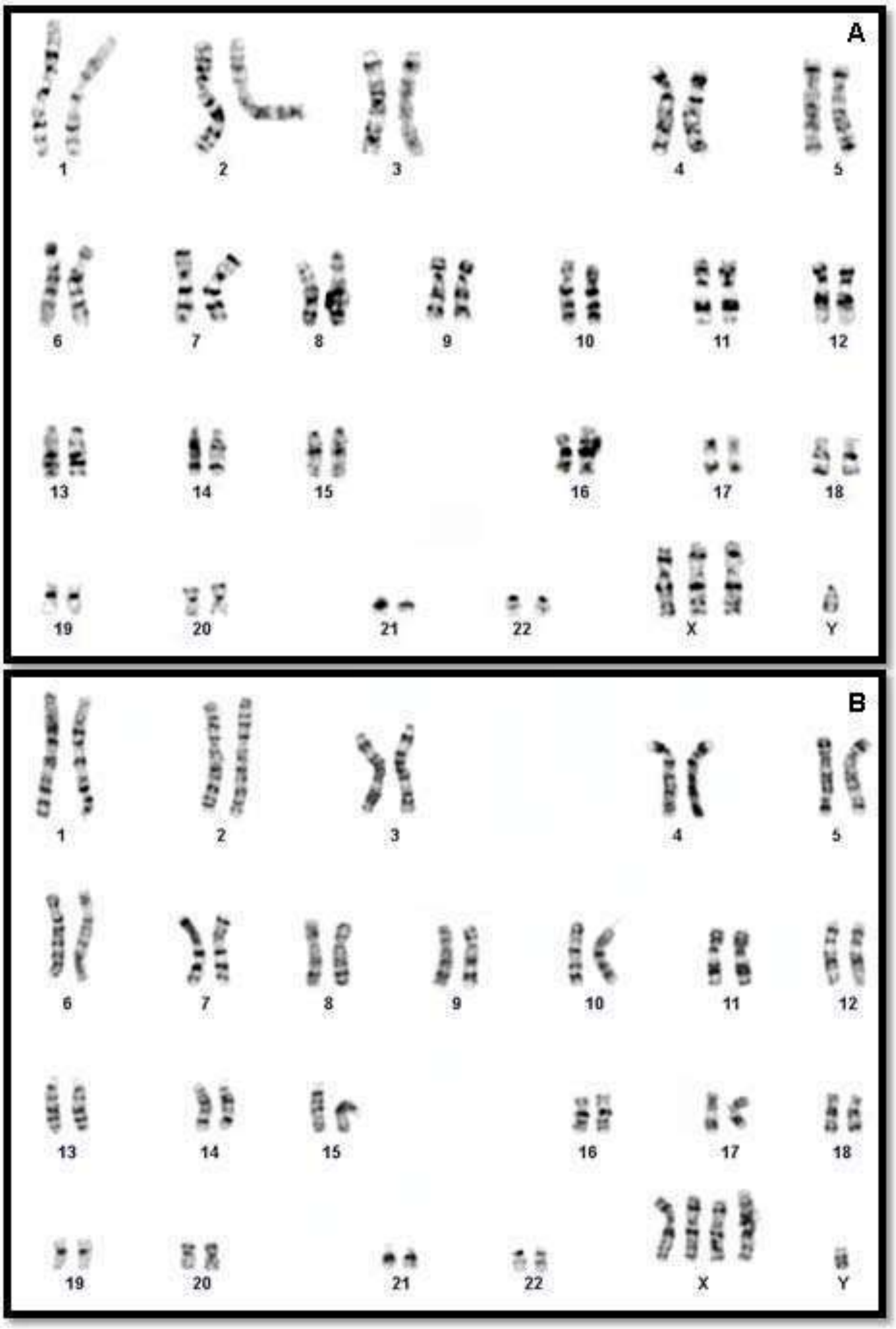
Klinefelter syndrome (KS) is a genetic condition caused by a numerical chromosomal alteration involving the sex chromosomes due to meiotic nondisjunction. Klinefelter syndrome can be diagnosed by examining the karyotype, by which it is possible to determine the chromosomal constitution of the individual from a blood sample[1] .The classic Klinefelter karyotype 47,XXY is present between 80% and 90% of cases and in the rest it is distributed among karyotypes with additional X chromosomes (48,XXXY; 49,XXXXY; 48,XXYY), structurally abnormal X chromosomes (ex: 47,X,iXq,Y) or some kind of mosaic (ex: 47,XXY/46,XY; 47,XXY/45, X/46,XY). The variability observed in the karyotype partly explains the broad clinical spectrum of the syndrome[2].

Individuals with KS have tall stature, decreased secondary sexual characteristics, small testicles, gynecomastia, and suffer from infertility[3]. Clinical heterogeneity causes this condition to be underdiagnosed and its clinical findings are usually nonspecific during childhood. Only 25% of the expected number of patients are diagnosed and, of these, a minority are diagnosed before puberty[1,4]. Any type of treatment would be more effective if started earlier in life[5]. Thus, our objective was to describe a case of Klinefelter syndrome diagnosed in early childhood.

CASE DESCRIPTION

The study was approved by the Ethics Committee of the Amazonas State University (UEA), under approval No. 2.949.936. The informed consent form (ICF) was given to the patient's parents/legal guardians, and was completed and duly signed. The cytogenetic examination performed by the Cytogenetics Laboratory of the Amazonas State University. Male patient, 2-month-old child of a non- consanguineous couple, pregnancy without complications, cesarean delivery at 36 weeks. He was born weighing 2,385 g, 48 cm, APGAR score: 8 (1 min), was premature, and had no history of familial genetic disease. He was referred to the outpatient clinic for pediatrics and neonatal screening at the Policlínica Codajás, Manaus, Amazonas, Brazil for consultation with a geneticist due to delayed psychomotor development and congenital heart disease. Physical examination showed hypotonia, dolichocephaly, ear with low implantation, cryptorchidism, congenital heart disease, camptodactyly and hypertelorism. A Karyotype examination was requested for the initial investigation of Edwards' syndrome. He was also sent for a follow-up with a cardio pediatrician. Classic cytogenetic analysis by GTG-banding according to Seabright[6] karyotype examination revealed the mos 48,XXXY[20]/49,XXXXY[70] karyotype with two cell lines (Figure 1), which is compatible with the diagnosis of mosaic Klinefelter syndrome.

Figure 1. Representative karyotype of the two lineages found via GTG-banding. Figure A lineage 48, XXXY and Figure B lineage 49, XXXXY.



DISCUSSION

KS is the most common chromosomal abnormality in men, but it remains largely underdiagnosed. Only 25% of the estimated cases are diagnosed and these are rarely identified in childhood[1,7]. Clinical evaluation and diagnosis of patients with KS are a challenge, especially before puberty. Although baseline determinations of the hormones Luteinizing Hormone, Follicle Stimulating Hormone, the sex steroids testosterone and/or estrogen, markers of gonadal function, including inhibin B and anti-Müllerian hormone, are useful in diagnosis, they are applied only at specific ages[8]. Early detection of this syndrome is recommended in order to be able to offer treatment and intervention at the appropriate age and stage of development of the disease, and thus offer prevention of the different clinical conditions related to the disease[9].

The diagnosis of KS can be confirmed through cytogenetic analysis using lymphocyte karyotyping, but in some cases when the karyotype result is negative and is associated with a suggestive clinical picture, a FISH (fluorescence in situ hybridization) study is performed with specific probes for the X and Y chromosomes in at least 100 interphase nuclei. It is recommended that routine karyotypic examination should be performed in all adolescents and young people with small testicles, hypergonadotropic hypogonadism, and those diagnosed with non-obstructive azoospermia[10]. However, this type of examination is generally carried out only to confirm a suspected diagnosis or when other examinations have already been carried out and the professional uses cytogenetics as one of the last diagnostic options[1].

In our study, we present a male patient, who at 2 months of age was referred for consultation with a medical geneticist due to him presenting several types of dysmorphia, developmental delay and congenital heart disease under investigation; thus, a karyotype examination was requested. Cytogenetic analysis revealed a karyotype with the two cell lines mos 48, XXXY[20]/49, XXXXY[70], classified as a variant of KS. A study conducted in 2019 by Asirvatham and collaborators[11], which analyzed 103 individuals with KS, found a single mosaic case for KS with karyotype mos 47,XXY/48,XXXY/49,XXXXY and 6 (13.6%) individuals classified as KS variants, since they present more than one extra X chromosome in the karyotype. In 2015, Milani et al.[12] described relevant neurological alterations associated with a patient with mosaic 48,XXXY/49, XXXXY. Generally, variant forms are associated with severe intellectual disability and dysmorphisms. Variations were observed mainly in children with a minimum diagnostic age of 12 to 84 months. The main associated clinical complications were behavioral problems (84%) and cardiac alterations (67%). In the present report, the authors also draw attention to these more frequent clinical signs in children and adults, which can help in the early and correct diagnosis of this genetic condition.

Men who have chromosomal mosaicism usually have moderate clinical symptoms, and the testicles may have normal sizes. Endocrine abnormalities are also attenuated, and the presence of gynecomastia and azoospermia are less common. In Klinefelter syndrome with X chromosome polysomy, the phenotype progressively deviates from normal as the number of X chromosomes increases, with variant 49,XXXXY often described as the most severe variant of the spectrum[12,13]. One of the cell lines presented here was 49,XXXXY, which is considered quite rare. It has an incidence of 1:85,000 to 1:100,000 and, in addition, is described as the most severe variant of KS[14]. A recent literature review1 based on 30 articles presented a survey of possible karyotypes for KS, and pointed out that karyotype 49,XXXXY was identified in only three case-report studies[15,16,17]. In one of them, the patient was identified only in adulthood (at 19 years of age)[16], while in the other two, the diagnosis was very early (prenatal and at 16 months)[15,17].

The extra X chromosomes in this variant accumulate during maternal meiosis I and II and are the product of a double nondisjunction event[18]. In women, an X chromosome randomly undergoes inactivation in embryonic tissues; it seems that a similar mechanism occurs in men with polysomy of the X chromosome. The non-inactivation of the extra X chromosome, in men with KS, may be largely associated with the pathology presented by them, although the exact mechanism still remains unknown. Clinical features of the syndrome are a crude face with microcephaly, hypertelorism, flat nasal bridge, oblique eyelid fissures, bifid uvula and/or cleft palate, skeletal abnormalities including radioulnar synostosis, genu valgum, cavus feet, or clinodactyly, short stature with hypotonia, hyperextensive joints, and underdeveloped genitalia with hypergonadotropic hypogonadism[19]. As for behavioral issues, sufferers of KS are described as shy to friendly, but show a low tolerance to frustration and thus irritability[20].

As stated, KS is a genetic disorder that involving multiple organs and affects patients far beyond testicular insufficiency[21]. This makes KS patients need regular medical follow-up, with special attention to comorbidities that, among them, may have a risk factor that leads to increased mortality[2]. This follow- up requires the attention of multiple specialties, such as endocrinologists, pediatricians, urologists, geneticists, andrologists, infertility specialists, psychologists, speech therapists, and physiotherapists, among others, though always aiming at the quality of life of the individual[9]. One of the recommended therapies is testosterone replacement (TRT) and the sooner treatment is started the better the achieved results will be[22].

CONCLUSION

We warn of the importance of early diagnosis in order to carry out genetic counseling, especially for patients with KS who wish to be fertile. They must undergo medical treatment (during the transition to adulthood) that focuses on fertility preservation and testosterone replacement; however, we reinforce the need for a multidisciplinary approach. While there are still patients with KS who do not want to reproduce, they should consider improving their quality of life. Even in this scenario, there is little information regarding the relevance of cytogenetic tests for infertile individuals. On the other hand, the literature that is focused on the genetics of KS shows the advantage of cytogenetic studies in infertile men with small testicles and azoospermia, and also considers endocrine alterations. Cytogenetics is an important tool in the diagnosis of KS and should be implemented as a neonatal screening test, and should be conducted to prevent comorbidities and improve the health and quality of life of the individual.

Conflito de interesses:

Contribution of the authors:

DCB: Contribuição no planejamento, execução, na obtenção das amostras, análise dos dados e redação.

VMGP: Contribuição no planejamento, execução, na obtenção das amostras, análise dos dados e redação.

CF: Contribuição no planejamento, execução, na obtenção das amostras, análise dos dados e redação.

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