

Genital malformation: trigger of the diagnosis of severe variants of Klinefelter syndrome

Malformación genital: disparador del diagnóstico de variantes severas de síndrome de Klinefelter

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What do we know about the subject matter of this study?

The classic form of Klinefelter Syndrome is widely known. It has infrequent variants associated to severe neurocognitive development disorders in addition to genital malformations. These patients are rarely diagnosed before middle childhood.

What does this study contribute to what is already known?

The suspicion of genetic alteration in children with genital malformation favors the early diagnosis of severe Klinefelter Syndrome variants, allowing an early intervention of the health team to mitigate the neurocognitive and socialization disorders in this population.

Abstract

Among the disorders of sexual development, Klinefelter syndrome and its variants are classified as an alteration in the number of sex chromosomes. These patients show signs of hypergonadotropic hypogonadism at puberty, however cases of severe variants also present neurocognitive and language problems from an early age. **Objective:** To describe two patients with genital malformation with genetic diagnosis of severe variants of Klinefelter syndrome, and to review clinical and therapeutic aspects. **Clinical Cases:** Case 1: Diagnosis of atypical genitalia at birth: Small and curved phallus with the urethral meatus at scrotal level, and bifid scrotum. No other somatic abnormality was observed, except for subtle clinodactyly of the fifth finger. Karyotype: 49, XXXXY. At one year of life, genitalia were reconstructed. The patient presented a global developmental delay, mainly in language, which was managed with early stimulation and speech and language therapy since he was two months old. Finally, he was able to attend kindergarten. Case 2: At one month of life, a small and severe curved phallus (more than 70°) was observed, and testicles were in the scrotum. Karyotype: 48, XXYY. At one year of life, the penile malformation was corrected. The patient presented global developmental delay, mainly in expressive language which was managed with early stimulation since the age of four months, achieving kindergarten attendance. **Conclusion:** Genital malformations led to the diagnosis of severe variants of Klinefelter syndrome, and were corrected around the year of life. The early identification of these variants allowed the intervention of the neurostimulation team, favoring the neurocognitive development and social integration of these children.

Keywords:

Klinefelter syndrome;
genital malformation;
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Introduction

In the case of a patient with severe genital alterations, a genetic evaluation is essential since sometimes, syndromes with associated pathologies of variable severity can be detected^{1,2}. If this scenario is confirmed, the patient goes from being just a carrier of a genital malformation to being a syndromic patient, with multiple effects for her or his health which needs specialized multidisciplinary management. Omission or delay in diagnosis could have relevant prognostic consequences for the future of the child^{2,3}.

A consensus conference was held in 2005, which led to the development of new terminology that has been widely adopted. It uses the term 'disorders of sexual development' (DSD) to describe the wide range of conditions involved in genital and sexual development and classifies them based on the chromosomal constitution of the patients^{4,5}.

Klinefelter syndrome and its variants are a disorder of sexual development caused by an alteration in the number of sex chromosomes. It is considered the most common defect in humans and is characterized by the presence of at least one additional X chromosome to the normal male XY karyotype. The classical form (47, XXY) is the most frequent, with a 1 in 650 incidence in males². In contrast, severe variants are extremely rare: patients 48,XXXY present a 1:18,000-1:40,000 incidence; patients 48,XXYY a 1:50,000 incidence; and patients 49,XXXXY a 1:100,000 incidence⁶.

Children carriers of these rare Klinefelter syndrome variants, in addition to showing signs of hypergonadotropic hypogonadism at puberty, have neurocognitive and language disorders, which appear as early as 18 months of age^{3,6}. Early diagnosis in these children is essential to initiate early neurostimulation therapy and improve their long-term prognosis.

In this context, the reason for this review is the exceptional presence of severe genital malformations leading to early diagnosis of Klinefelter syndrome^{6,7}.

The objective of this paper is to describe two carrier patients of genital malformation with a genetic diagnosis of severe Klinefelter syndrome variants and to review clinical and therapeutic aspects.

Clinical Cases

Case 1

Second child of non-blood related parents, with no significant morbid history, with prenatal ultrasound diagnosis of single pregnancy, female and without apparent pathology. 39-week gestational age eutocic delivery. At birth, atypical genitals were observed, thus she was referred to the Urology Service.

Physical examination revealed the presence of a small, curved penis with urethral meatus at scrotal level, penoscrotal transposition, and bifid scrotum. Both testicles of usual size for age in the scrotal sac (Figure 1). External masculinization score 3 according to the scoring system adapted by Ahmed et al.⁸. The patient also present very subtle clinodactyly of the 5th finger in the right hand, and there were no other alterations on physical examination. Abdominal ultrasound showed no signs of Müllerian ducts. When evaluated by the Genetics Service, a male karyotype was reported, with 49,XXXXY sexual polysomy. Significant neurological and cardiovascular disorders were ruled out. At 10 months, the patient presented changes in her face characterized by up-slanting palpebral fissures, ocular hypertelorism, and flat nasal bridge. From the year of life, genitalia were reconstructed in two surgeries, achieving satisfactory functional and esthetic results.

Regarding her development, at the age of two months, she started treatment with early kinesics and speech and hearing stimulation. The 3-year follow-up evaluation showed an overall developmental delay according to the Child Development Observation Tool (IODI, Ministry of Health of the Argentine Republic)⁹, mainly in language, with good understanding and very little verbal fluency. However, the support of the early stimulation team allowed her to be integrated into a kindergarten, resulting in the social inclusion of the patient.

Case 2

Healthy, non-blood related parents who due to infertility underwent assisted fertilization treatment (ICSI) through egg donation. Prenatal ultrasounds reported single male fetus with no abnormalities. Eutocic delivery at week 38, with perinatal evolution showing no special features. In his first month of age, the pediatrician noticed an 'atypical penis' and referred the patient to a pediatric urologist, who found a small, severely curved penis (more than 70°) with apparent meatus at the glans level and very little ventral skin. Normal scrotum with both testicles in scrotal sac, with the right one of smaller size. (Figure 2). External masculinization score 7⁸. No other significant dysmorphia was observed. The Genetics Service reported a male karyotype with 48,XXYY sexual polysomy. Abdominal ultrasound showed no special features or evidence of Müllerian ducts. At one year of age, genitalia were surgically corrected, achieving a straight penis with normal meatus appearance and location in glans.

Regarding development, at four months of age, he started treatment with early kinesics and speech and hearing stimulation. At the age of two, he had an overall developmental delay according to the IODI, with

good comprehension and difficulty in verbal expressive language. He started his integration in a kindergarten assisted by a therapeutic companion.

Discussion

The 48,XXYY, 48,XXXY, and 49,XXXXY syndromes are abnormalities of sex chromosome aneuploidy that lead to testicular dysgenesis and appear as alterations in the genital and reproductive sphere (depending on the hypogonadism degree). Due to this observation, they are considered variants of Klinefelter syndrome. However, these patients also show delayed neurological and cognitive development, speech disorders, behavioral and socialization problems, and various skeletal malformations, casting doubts on the consideration of these disorders as variants of classic Klinefelter syndrome^{6,10,11}.

In general, patients with 48,XXYY at birth do not show distinctive features. In isolation, as in case 2, they present genital alterations that may vary from cryptorchidism or communicating hydrocele to severe malformations such as hypospadias, and small or curved penises. Other physical signs may include clinodactyly of the 5th finger (in 70% of cases), flat foot, dental problems, hypertelorism with up-slanting palpebral fissures and epicanthus, and rarely have heart disease^{6,12}. Radioulnar synostosis and food or respiratory allergy are also described as part of the syndrome¹¹.

If there are no genital or skeletal alterations, the first symptoms appear after 18 months of age, with mild hypotonia in 75% of cases. They may also show

language developmental delay (especially expressive) and varying degrees of psychomotor and cognitive delay. All patients present difficulty in learning at school age, with an IQ around 70-80. Regarding social development, they are generally docile and submissive, but cases of extreme aggression have been described^{6,13}.

49,XXXXY syndrome was first described in 1960 by Fraccaro et al.¹⁴. It is known as the most severe variant of Klinefelter syndrome due to the presence of hypergonadotropic hypogonadism associated with a combination of skeletal, neurological, cognitive, genital, and heart malformations.

Published data on newborn patients with 49,XXXXY syndrome are very limited. The presence of several non-specific congenital anomalies such as low birth weight, microcephaly, bifid uvula, cleft palate, hypotonia, clinodactyly of the fifth finger, patent ductus arteriosus, or genitalia malformations has led to the diagnosis of this syndrome at an early age¹⁵. Facial features are almost a pathognomonic sign (ocular hypertelorism, up-slanting palpebral fissures, and flat nasal bridge), however, it is not possible to identify it until 9-12 months of age^{3,16}. Phenotypes change as the child grows into adulthood, therefore, certain clinical characteristics of postpubescent teenagers are not clear in younger children⁷. They are patients of low height (unlike the other variants) and may present other skeletal alterations such as radioulnar synostosis, genu valgum, pes cavus, scoliosis, and hypotonia with joint laxity.

The IQ usually ranges from 20 to 60, with great difficulty in learning. Cognitive and language developmental delay severely affects the socialization of these children. They tend to be shy, friendly, with occasional



Figure 1. Appearance of external genitalia of the patient with 49, XXXXY syndrome.



Figure 2. Appearance of external genitalia of the patient with 48, XXYY syndrome.

irritability and temper tantrums, low tolerance for frustration, and difficulty adapting to changing routines.

The variability in the clinical features of these syndromes is thought to derive from the manifestation of three factors: the genetic defect severity (X numbers), androgen deficiency, and androgen receptor sensitivity. The more altered these factors are, the more severe the phenotypic expression will be^{1,2}.

Conclusion

In these clinical cases, the presence of a severe genital malformation led to the suspicion of an underlying genetic disorder, which was confirmed through clinical and genomic evaluation.

Genital malformations were the trigger for the diagnosis of severe Klinefelter syndrome variants, and they were resolved around one year of age by the Urology Service. The early identification of these syndromes enabled the prompt intervention of the early stimulation team (speech and hearing therapists, kinesiologists, educational psychologists, neurologists, psychiatrists, etc.), promoting the neurocognitive and speech and hearing development of these patients, with a positive impact on their social integration.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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