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Klinefelter syndrome in childhood: language delay as an early warning sign for diagnosis

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ABSTRACT

Klinefelter syndrome (KS), the most common sex chromosome aneuploidy in males, is often underdiagnosed until adolescence, delaying early intervention. We describe 11 pediatric patients with KS who were followed between 2005 and 2025 to identify early markers. Three were diagnosed prenatally; the remaining eight were diagnosed at a median age of 6.1 years, mainly due to neurodevelopmental problems. Of the total of 11 patients, 9 had delayed language acquisition, followed by 8 with psychomotor delay, 5 with behavioral disorders, 3 with sleep disorders, and 2 with epilepsy. Endocrinological comorbidities were less frequent in childhood. Delayed language development emerges as a crucial early indicator. Active detection, along with other neurodevelopmental comorbidities, is essential to address underdiagnosis and enable early, multidisciplinary intervention, thereby significantly improving patients' developmental outcomes and quality of life in KS.

Keywords: *Klinefelter syndrome; child; comorbidity; language development disorders; early diagnosis.*

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INTRODUCTION

Klinefelter syndrome (KS), characterized by the presence of one or more additional X chromosomes in the male karyotype,[1] is the most common sex chromosome aneuploidy in males, with an estimated prevalence of 1 in every 500 to 1000 live male births.[2,3]

Although hypogonadism is the primary clinical manifestation of KS, this condition often remains latent until late adolescence or even adulthood.[4] The phenotypic spectrum of KS is remarkably heterogeneous and nonspecific. Associated symptoms include learning difficulties, language delay, attention deficit, hyperactivity disorder, and obesity.[3,5] However, these problems are not specific. This clinical variability contributes to a significantly high rate of underdiagnosis, with estimates suggesting that only 39% of men with KS are diagnosed,[6] and of these, only 10% receive a diagnosis before the age of 12.[7]

A late diagnosis, after the age of 18, can have devastating implications for the adolescent's psychosocial development, negatively affecting the formation of their personality. Therefore, early detection of this aneuploidy is imperative to improve the quality of life for these individuals substantially.

Patients with KS exhibit increased susceptibility to a wide range of comorbidities, including osteoporosis, metabolic syndrome, various endocrinopathies, cognitive and psychiatric disorders, as well as cardiovascular diseases and dental abnormalities.[2,3,8] Many of these problems, even those considered nonspecific, may manifest before puberty (9-10 years of age).

A deeper understanding of the comorbidity of KS during childhood, a period in which the signs of hypogonadism are often undetectable, could facilitate early diagnosis of the disease. The present study aims to investigate neurological, endocrine, and somatic disorders in a series of pediatric patients with KS to identify clinical findings that serve as early warning signs during childhood development.

CLINICAL CASES

Between January 2005 and January 2025, 11 patients with KS were treated at the Pediatric Endocrinology Unit of the Hospital San Juan de Alicante (Spain), representing 0.1% of all male newborns in our area during that period. The study was approved by the hospital's Ethics Committee (code 25/015).

In our case series, 10 of 11 patients had a 47XXY karyotype, and 1 had a 48XXXY karyotype.

Regarding the timing of diagnosis, 3 of the 11 patients were identified prenatally by amniocentesis. The indications for amniocentesis in these cases included the detection of possible fetal malformations in two patients and elective amniocentesis due to advanced maternal age (over 42 years) in the third case. The other 8 patients were diagnosed postnatally, with a median age at diagnosis of 6.1 years (range: 2.1-9.7 years). The main reason for karyotyping in 6 of the 8 children diagnosed postnatally was concerns related to neurodevelopment.

The demographic information and detailed clinical characteristics of each patient are summarized in *Table 1*. Notably, all patients in the case series had at least one neurological finding. The most prevalent neurodevelopmental disorder was delayed language acquisition, which affected 9 of the 11 patients, with expressive language onset beyond 2 years of age. In addition, 8 patients exhibited some degree of psychomotor delay. Additional neurological comorbidities included behavioral disorders, reported in 5 patients. Likewise, 3 patients had sleep disorders, and 2 were diagnosed with epilepsy.

In contrast, endocrine abnormalities were less frequent, occurring in 5 of the 11 patients. Specific endocrine manifestations included cryptorchidism (3 patients), obesity (2 patients), and gynecomastia and micropenis (each observed in 1 patient).

DISCUSSION

KS is the most common sex chromosome aneuploidy in males; it accounts for a condition that, despite its prevalence, is significantly underdiagnosed worldwide.[3] The heterogeneity and nonspecificity of its phenotypic spectrum in the early stages of life contribute substantially to this diagnostic challenge. In our case series, only 3 of the 11 patients received a prenatal diagnosis, a percentage that, although valuable, underscores the persistence of underdiagnosis relative to estimates suggesting that less than 25% of adult males with KS are ultimately diagnosed at a median age of 27.5 years.[9] This diagnostic delay has significant negative implications, not only in the management of physical comorbidities, but also in the psychosocial development and quality of life of affected individuals.

Table 1. Neurological, endocrinological, and clinical findings in patients

Patient	1	2	3	4	5	6	7	8	9	10	11
Karyotype	47XXY	47XXY	47XXY	47XXY	47XXY	47XXY	47XXY	48XXXY	47XXY	47XXY	47XXY
Age at diagnosis (years)	8.1	0	4.7	0	9.7	2.1	7.1	8.1	0	5.7	3.4
Reason for the diagnosis	Epilepsy	Prenatal (syndactyly)	Language delay	Renatal (mother >42 years old)	Mental delay	Mental delay	Dysmorphic phenotype	Mental delay	Prenatal (fetal twin with Potter syndrome)	Overweight and micropenis	Language delay
Autonomous walking start (months)	18	14	NR	15	14	NR	13	14	18	15	15
Language onset (years)	>2	>2	4.5	2	>3	>3	3	5	>2	2	5
Mental delay	Yes (mild)	No	Yes (mild)	No	Yes	Yes	Yes	Yes	No	Yes (mild)	Yes (mild)
Attention deficit	Yes	No	Yes	No	No	No	Yes	No	No	Yes	Yes
Sleep disorders	Somniloquy, night terrors	No	No	No	No	Somniloquy	No	No	No	Night terrors	No
Behavioral disorders	No	No	No	No	Oppositional defiant	Disruptive behavior	No	Disruptive behavior	No	Emotional instability	Disruptive behavior
Epilepsy	No	No	No	No	Yes	No	No	Yes	No	No	No
Other neuropsychiatric disorders	Headache	No	Motor disorder	Migraine	Gender dysphoria	No	No	No	No	Motor disorder	No
BMI at diagnosis (km/m²) (SD)	19.6 (0.57)	NR	18.1	NR	23.5 (1.5)	15.2 (-0.93)	13.6 (-1.3)	14.6 (-1.09)	NR	22.1 (2.7)	16.8 (0.32)
Gyneco-mastia	No	No	No	Yes	No	No	No	No	No	No	No
Cryptor-chidism	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Micropenis	No	No	No	No	No	No	No	No	No	Yes	No
Other findings	Adenoid hypertrophy	Asthma Syndactyly (foot)	Interatrial communication Asthma		Primary enuresis Obesity Late teething		Escoliosis	Mild pulmonary valve dysplasia		Strabismus Obesity	Primary enuresis Genu valgum Renal ectasia

BMI: body mass index; SD: standard deviation; NR: not referred.

The primary purpose of this case collection is to provide evidence on the early presentation pathology associated with the syndrome to facilitate early diagnosis, ideally before adolescence, a critical period for intervention. Despite the limited size of our sample, which represents all children diagnosed with KS in our geographical area over the last 20 years, the observed incidence of the disease is consistent with the ranges reported in the international literature.[2,3]

In our series of 11 patients, we identified 23 distinct comorbidities, ranging from disorders most frequently associated with KS in the literature (primarily neurological and endocrinological conditions) to those less prevalent or traditionally considered (e.g., dental and cardiac anomalies).[3,10]

These findings underscore the multisystemic nature of KS and the need for a comprehensive clinical approach from the earliest stages of life.

Neurodevelopmental disorders emerge as the most prevalent and early-onset group of comorbidities in our case series, and some neurological findings were observed in all patients. These data are crucial because, although the neuropsychological phenotype of KS is known to be highly variable,[5,11] delayed language acquisition is the most specific and earliest alteration in this group in our study population. The presence of language delay in 9 of our 11 patients, with expressive language onset beyond 2 years of age, highlights its potential as an early warning marker. This finding aligns with growing evidence that language difficulties are among the earliest and most consistent challenges in children with KS; they are often the main reason for consultation and lead to diagnosis. A detailed assessment of language development should therefore be standard practice in the evaluation of any child suspected of having KS, even in the absence of other more obvious signs.

The presence of behavioral disorders, attention deficit, sleep disorders, and epilepsy in our case series also emphasizes the complex interaction of neurocognitive and psychiatric factors in pediatric KS.

In contrast to the high prevalence of neurological alterations, endocrinological manifestations were observed less frequently in our pediatric case series. The nature of the disease accounts for this: classic hypogonadism, the primary endocrinological manifestation of KS, typically becomes evident at 15-18 years of age, when small testicles and incomplete pubertal development are most noticeable. The lower frequency of prepubertal endocrinological findings, such as cryptorchidism, obesity, gynecomastia, and micropenis, underscores the fact that these manifestations may not be the first warning signs in childhood.

The main limitations of our study are its small sample size and its retrospective nature. Although this case series includes all patients diagnosed with KS in our referral area over a prolonged period, a larger sample would provide greater statistical power and broader generalizability of the results. In addition, the inherent variability of clinical follow-up in a retrospective study may have affected the completeness of comorbidity recording. Future research, preferably prospective and multicenter studies, is essential to confirm our findings and deepen our understanding of the early manifestations of KS.

In conclusion, early diagnosis of KS remains a major clinical challenge. Our study reinforces the need for careful and proactive clinical observation to identify these patients in childhood, ideally before psychological problems become established and the management of hypogonadism in adolescence becomes complicated. Delayed language development emerges as the earliest and most distinctive marker that should alert the physician to the possible presence of KS, prompting karyotyping and facilitating early, multidisciplinary intervention, which is essential for optimizing the prognosis and quality of life of these children. ■

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