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CASE REPORTS

A RARE CASE OF GROWTH HORMONE DEFICIENCY IN A BOY WITH KLINEFELTER SYNDROME. DIAGNOSTIC AND THERAPEUTIC CHALLENGES: A CASE REPORT

Berkan Beyti[1], Viktor Radev[1], Teodora Karamfilova[2,3], Violeta Iotova[2,3]

[1]Student, Faculty of Medicine, Medical University of Varna, Bulgaria
[2]Department of Pediatrics, Faculty of Medicine, Medical University of Varna, Bulgaria
[3]First Pediatric Clinic with NICU, St. Marina University Hospital, Medical University of Varna, Bulgaria

ABSTRACT

INTRODUCTION: Klinefelter syndrome (KS) is the most common sex chromosome disorder in males, typically associated with tall stature in adolescence, hypergonadotropic hypogonadism, and cognitive or behavioral difficulties. Growth hormone deficiency (GHD) is rare in KS and may mask or alter expected phenotypic features.

PATIENT PRESENTATION: We report a boy of 7 years and 8 months presenting with persistent short stature, selective eating habits, and mild neurodevelopmental delays. Initial evaluation revealed subtle dysmorphic features, cryptorchidism, and delayed bone age. Karyotype analysis confirmed KS (47,XXY). Two consecutive GH stimulation tests demonstrated isolated GHD (peak GH 6.92 ng/mL), and pituitary MRI was normal. The patient was initiated on recombinant human GH therapy, first daily, and later long-acting GH was administered, resulting in sustained catch-up growth over 12 months of follow-up without any adverse effects. Height improved from below the 3rd percentile to the 10th percentile, with favorable changes in growth velocity and IGF-1 levels.

CONCLUSION: This report highlights the importance of considering karyotyping not only in girls but also in boys with persistent, unexplained short stature, as coexisting disorders such as KS and isolated GHD may obscure typical clinical features. Without routine cytogenetic testing, numerical abnormalities of sex chromosomes can remain undiagnosed, delaying appropriate care. Timely diagnosis and multidisciplinary management are essential to optimize growth and long-term outcomes.

Keywords: *Klinefelter syndrome, growth hormone deficiency, short stature, growth hormone treatment, case report*

Address for correspondence:
Berkan Beyti
Faculty of Medicine
Medical University of Varna
55 Marin Drinov St
9002 Varna, Bulgaria
e-mail: b_beyti2001@abv.bg

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INTRODUCTION

Klinefelter syndrome (KS) is the most common sex chromosome disorder in males, characterized by variable phenotypic features, including tall stature in adolescence, hypogonadism, and cognitive or behavioral difficulties [1,2]. Growth hormone deficiency (GHD) is uncommon in KS, and reports of coexisting isolated GHD are rare [3,4]. Early recognition

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and management of growth failure in children with KS are essential to optimize final height and ensure appropriate developmental support. Recombinant human growth hormone (rhGH) therapy is a well-established treatment for isolated GHD, yet data on its efficacy in KS patients is limited [5,6].

Institutional Review Board Statement

Ethical review and approval were waived for this study due to receiving written informed consent from the parents.

Patient Information

A boy of 7 years and 8 months was referred to a pediatric endocrinology clinic for evaluation of growth delay after an outpatient bone age assessment revealed significant delay. He was born via Cesarean section due to maternal uterine malformation (bicornuate uterus). His birth weight and length were within the normal range, and he received only routine neonatal vaccinations, with no additional immunizations administered after that.

Family history revealed the paternal grandmother had unspecified hormonal problems, with no other known family history of chromosomal or endocrine disorders. The father's height was 180 cm and the mother's height was 157.7 cm, resulting in a mid-parental target height of 175.35 cm.

Since early childhood, the patient exhibited poor appetite with selective and monotonous eating habits and persistent growth failure. Parents reported that he rarely changed shoe size, suggesting slow linear growth. Mild delays in motor and speech development were noted, and the patient received speech therapy for dysgraphia, with partial improvement.

During the first evaluation, the boy's height was 114.5 cm (-1.98 SDS), entirely outside the target range and below the 3rd percentile, and his weight was 18 kg (-2.39 SDS), below the 3rd percentile, both mark-

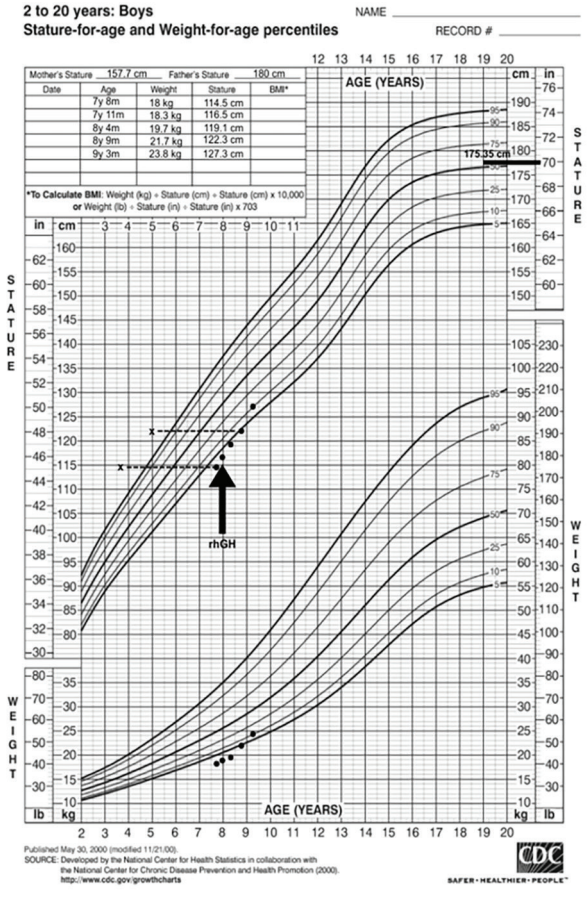


Fig. 1. Growth chart of the patient (CDC growthcharts).



Fig. 2. Bone age radiogram of the patient at 7 years 8 months of age.

edly below the target range for parental stature (Fig. 1).

The boy's BMI was 13.7 kg/m^2 (-1.53 SDS), consistent with a lean body habitus. Bone age was assessed by the Greulich & Pyle atlas, using the BoneXpert software. It was 3.69 years (-3.51 SDS), indicating a significant delay relative to chronological age (Fig. 2).

Pubertal development corresponded to Tanner stage I. The right testis had a normal prepubertal volume (2.5 mL). The left testis was palpable in the inguinal canal, consistent with unilateral cryptorchidism, and the scrotum was hypoplastic. Physical examination revealed mild facial dysmorphism, including hypertelorism, prominent auricles, and clinodactyly of the fifth fingers bilaterally. The remainder of the examination was unremarkable.

An ultrasound examination confirmed the presence of a left undescended testis with an associated indirect inguinal hernia. The patient was referred for elective orchiopexy and herniotomy, which had not yet been performed. Routine laboratory investigations and antibodies for celiac disease and autoimmune thyroiditis were within normal limits. No acute systemic illness was documented.

To exclude syndromic causes of short stature, a blood sample was obtained for karyotyping. It revealed a 47,XXY karyotype consistent with KS. Forty out of forty metaphases were analyzed for numerical abnormalities, and ten out of forty for structural abnormalities, confirming the chromosomal diagnosis.

Two months later, the patient was re-admitted for confirmatory testing and detailed endocrine evaluation. At this time, his height was 116.5 cm (-1.84 SDS), weight 18.3 kg (-2.45 SDS), and BMI 13.48 kg/m^2 (-1.81 SDS). MRI of the pituitary gland demonstrated normal sella size and configuration, a pituitary gland of normal size, shape, and homogeneous signal intensity, a normal posterior pituitary bright spot, and an infundibulum. No mass or structural abnormalities were detected.

Two stimulation tests were performed to assess growth hormone (GH) secretion. Peak GH was 6.92 ng/mL (IMMULITE), which according to the National Diagnostic algorithm and National Health Insurance requirements for GH treatment confirmed GH deficiency (accepted threshold < 10 ng/mL) (Table 1, Table 2).

Table 1. Glucagon stimulation test 0.03 mg/kg i.m.

Time point	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Blood glucose level (mmol/L)	4.56	9.0	5.66	3.8	4.7	4.4	4.1
Serum GH (ng/mL)	0.573	5.62	1.11	0.455	6.92	4.16	0.81

Table 2. Arginine stimulation test 0.5 g/kg i.v.

	0 min	30 min	45 min	60 min	90 min	120 min
Serum GH (ng/mL)	4.0	3.26	1.47	0.587	0.167	0.197

Based on the auxology findings, delayed bone age, isolated GH deficiency and lack of contraindication from the confirmed KS, the patient was approved for initiation of rhGH treatment. Somatropin was prescribed at a chosen initial dose of 0.55 mg/day (0.028 mg/kg/day) for 3 months.

At the age of 8 years and 4 months, the patient demonstrated good compliance and no adverse effects. Height increased by 2.6 cm (annualized height velocity of 8.33 cm/year) and weight by 1.4 kg, with shoe size increasing by two sizes and clothing—by one. Pubertal stage remained prepubertal, and laboratory parameters remained within normal limits.

Given the favorable initial response, the therapy was transitioned at the age of 8 years and 5 months to a long-acting weekly GH formulation, Somatrogon 13 mg/week (0.60 mg/kg/week) to improve adherence.

At age 8 years and 9 months, approximately five months after the previous measurement, the patient showed further height gain of 3.2 cm and weight increase of 2 kg were observed. The patient's height was between the 3rd and 10th percentiles for chronological age, with an increased growth velocity indicating effective catch-up relative to bone age. Bone age did not progress and corresponded to 5 years (SDS -3.77). During follow-up, clinical signs of adrenarche (specifically the development of axillary odor) were observed. This manifestation most likely reflected the patient's age-appropriate physiological maturation of the adrenal axis. However, it is possible that recombinant human GH therapy may have accelerated this process potentiating the effect of the adrenal androgens. Cognitive and behavioral development remained stable, and mild dysgraphia continued to be managed successfully by speech therapy.

Following reassessment by the multidisciplinary team (MDT) at the age of 8 years and 10 months, the dose of weekly GH was increased to 14.5 mg/week (0.66 mg/kg/week). Over the subsequent six months, the patient achieved a total height gain of 5 cm and weight gain of 1.8 kg, reaching 127.3 cm (-1.27 SDS), 23.8 kg (-1.59 SDS), and a BMI of 14.68 kg/m^2 (-1.23 SDS) at the age of 9 years and 3 months. Growth velocity improved to 10.44 cm/year, and the height percentile rose to the 10th, consistent with favorable catch-up. Appetite remained unstable, and no major adverse effects were observed. Mild irritability and occasional headaches were reported, primarily in the morning or after school.

Since the initiation of GH therapy, the patient has shown a total height gain of 10.8 cm over approximately 1 year and 3 months of treatment. This corresponds to an annualized height velocity of ~8.7 cm/year, indicating a sustained and effective catch-up growth response.

Pubertal evaluation showed prepubertal gonadotropin and testosterone levels as follows: LH 0.11 IU/L (reference range 0.8–7.6 IU/L), FSH 1.01 IU/L (reference range 0.7–11.1 IU/L), testosterone <0.69 nmol/L (reference range 0–1.04 nmol/L), consistent with expected hypogonadotropic status at this age. Following a further review, GH therapy was continued with a dose adjustment to 16 mg/week (0.65 mg/kg/week), maintaining good clinical and auxological response (Fig. 3).

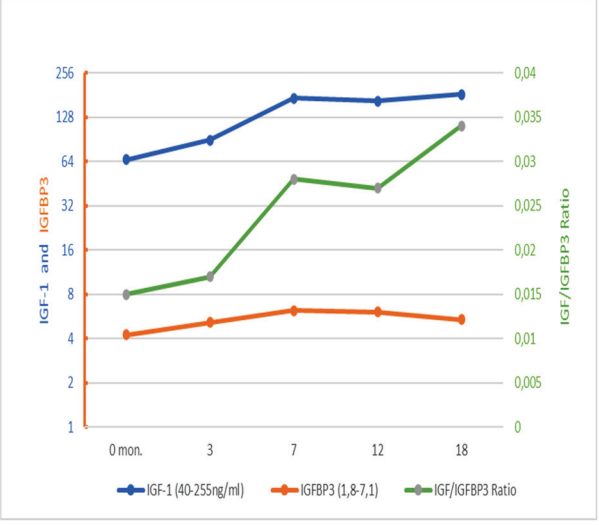


Fig. 3. Dynamics of growth factors during rhGH treatment.

IGF-1—insulin-like growth factor 1; IGFBP-3—insulin-like growth factor binding protein 3

The patient continues on weekly rhGH therapy with 6-month monitoring of growth velocity, pubertal development and yearly evaluation of bone maturation. Future management plans include ongoing surveillance for autoimmunity, hypogonadism, and initiation of sex steroid replacement at the appropriate age, alongside continued cognitive and developmental support.

DISCUSSION

Klinefelter syndrome often remains unrecognized during childhood due to its variable and frequently subtle clinical manifestations. Early symptoms may include hypotonia, delayed motor development, speech and language delays, as well as social or learning difficulties. Cryptorchidism or micropenis can be present, but it is not universal. In preschool years, affected boys are often distinguished by long limbs, reduced muscle strength and poor coordination [7,8]. During adolescence, the classic signs of testicular failure and androgen deficiency become obvious, including small, firm testes, gynecomastia, reduced body hair, delayed puberty, and elevated follicle-stimulating hormone and luteinizing hormone

levels, all in the presence of low testosterone levels [9,10].

The patient in this report presents a rare combination of KS and isolated GHD, resulting in significant short stature from early childhood. Unlike the typical tall stature observed in KS adolescents, this child experienced early growth failure due to GH deficiency, confirmed by two stimulation tests and markedly delayed bone age [5,6]. Pituitary MRI was normal, excluding structural anomalies and indicating a functional deficiency. Early initiation of rhGH therapy, first with daily and subsequently with a long-acting preparation, led to persistent catch-up growth. Laboratory monitoring demonstrated an appropriate IGF-1 response, and treatment was well tolerated.

The current patient highlights several important clinical considerations. Although routine karyotyping is currently mandatory in girls with unexplained short stature to exclude Turner syndrome (TS), in boys it is often considered optional or secondary. However, numerical chromosomal abnormalities are not uncommon in boys with unexplained growth concerns, indeed, other sex-chromosome aneuploidies are often detected during evaluation. Although TS classically affects females, cases of 45,X/46,XY mosaicism in phenotypic males have been described—some presenting with short stature and Turner-like features—further supporting the need for systematic cytogenetic testing in boys with persistent growth failure [11,12].

In this patient, cytogenetic analysis unexpectedly revealed KS (47,XXY), a finding that would likely have been delayed or missed without early karyotyping. This observation supports the concept that karyotyping should be considered an essential, rather than optional, part of the diagnostic work-up in boys with otherwise unexplained growth failure. Early genetic evaluation allows timely diagnosis, appropriate follow-up, and targeted multidisciplinary care.

Taken together, this patient provides clinical evidence supporting the need to expand current diagnostic algorithms and consider routine karyotyping in boys with persistent, unexplained short stature, in order to avoid underdiagnosis of sex chromosome aneuploidies and improve long-term outcomes.

The coexistence of KS and isolated GHD may obscure typical syndromic features, such as tall stature in adolescence. Long-acting rhGH formulations may improve adherence and quality of life, particularly in children requiring long-term therapy. Furthermore, multidisciplinary management—including pediatric endocrinologist, genetics and developmental support—is essential to address the complex needs of these patients [13]. Published reports of KS with associated GHD remain limited, and mechanistic hypotheses include dysregulation of the hypothalamic-pituitary axis or the coincidental occurrence of two independent conditions. Further studies are required to better understand the prevalence, natural history, and optimal management strategies for this rare combination [14,15].

An additional point of clinical relevance is the child's low gonadotropin levels. In KS gonadotropins generally remain within the normal prepubertal range throughout childhood and begin to rise only with the onset of puberty, around early-to-mid adolescence [16,17]. Testicular function in KS demonstrates high variability, with considerable interindividual differences in testicular volume, gonadotropin secretion, and testosterone production, which can influence the timing and progression of pubertal development [18,19]. In this prepubertal patient, still low LH and FSH therefore raise concern for a possible coexisting central gonadotropin deficiency. Reports have documented rare cases of KS presenting with a hypogonadotropic profile, highlighting the need for vigilance when evaluating atypical hormonal patterns [20]. If gonadotropins fail to rise appropriately with advancing age, this would suggest more complex pituitary involvement rather than isolated GH deficiency. Early recognition of this potential trajectory is essential to ensure that pubertal development is not delayed or mismanaged due to an assumption of primary testicular failure typical of classic KS, and warrants regular gonadotrophin follow-up.

A limitation of this case work-up is the absence of available advanced molecular genetic analysis so far to assess the pituitary function comprehensively. While the 47,XXY karyotype confirms KS, it does not provide a causative link for GHD. To contemporary understanding, the coexistence of KS and GHD in this patient represents a coincidental occurrence

of two distinct genetic conditions, which could be challenged by future scientific developments.

CONCLUSION

The presented patient illustrates a rare coexistence of KS and isolated GHD, leading to significant early growth failure and masking the typical auxological profile of KS. The unexpected cytogenetic diagnosis underscores the importance of including karyotyping in the evaluation of boys with short stature. Early genetic testing enables timely diagnosis and appropriate follow-up. In addition, long-acting GH formulations provided effective and well-tolerated treatment, supporting their role in children requiring long-term therapy. Ongoing monitoring of gonadotropin dynamics remains essential, as evolving central hypogonadism could indicate broader pituitary involvement with implications for pubertal management. Awareness of such atypical presentations is critical to improving diagnostic accuracy and long-term outcomes in children with complex endocrine disorders. Multidisciplinary care remains a cornerstone for optimal management. Further studies are warranted to better understand the relationship between KS and GH deficiency and its implications for clinical practice.

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Informed Consent Statement

Written informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

Data Availability Statement

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

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