Central Hypogonadism in Klinefelter Syndrome: report of two cases and review of the literature

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Abstract

Purpose: Klinefelter syndrome (KS) is characterized by late adolescence/young adulthood onset of primary hypogonadism. Hypogonadotropic hypogonadism (HH), when congenital, is usually associated with absent/incomplete puberty and low/normal gonadotropins. We report the clinical and genetic features of two subjects with KS and an unexpected HH hormone profile.

Methods: Magnetic resonance imaging (MRI) of hypothalamus-pituitary region and next generation sequencing (NGS) of congenital HH-associated genes were obtained. A narrative review of the literature was conducted.

Results: Patients were diagnosed with Klinefelter syndrome following karyotype analysis. Nevertheless, they showed unusual features: both had incomplete puberty, low gonadotropins and testosterone levels, and the first one was anosmic. Sellar lesions were excluded by MRI, and NGS was negative in both subjects. Our data add to those of the only fourteen similar cases reported so far. Unexplained HH rarely occurs in KS and is variably associated with anosmia, other pituitary hormones deficiencies and heterogeneous karyotypes. However, most cases show an early, pre-pubertal onset of hypogonadism. If the causes behind this gonadotropins defect are largely unknown, hereby we provide the first review of the literature on this topic and propose some pathogenetic hypotheses, including the coexistence of KS and congenital HH as suggested by overlapping clinical features in some of these patients.

Conclusion: HH is an exceptional occurrence in Klinefelter syndrome and is associated with heterogeneous phenotypes and, probably, aetiologies. Moreover, KS could underlie HH nonresponsive to gonadotropins. An exhaustive diagnostic workup and a tailored clinical management are advisable in these rare forms.

Keywords: Klinefelter syndrome, hypergonadotropic hypogonadism, genetics, congenital hypogonadotropic hypogonadism, Kallmann syndrome, anosmia

Introduction

Klinefelter syndrome (KS) is the most common sex chromosome aneuploidy in men, affecting 1:650 newborn males [1]. The most common form is related to the presence of an extra X chromosome (47,XXY, 80-90% cases), but various grades of mosaicism (47,XXY/46,XY) or a structurally abnormal X chromosome (e.g. X isochromosome) can be found less frequently; higher-grade X chromosome aneuploidies are rare and are characterized by more severe phenotypes [2, 3]. The classical KS presentation includes tall stature, eunuchoid body proportions, gynecomastia, small firm testes, infertility and hypogonadism [2, 4].

Despite some evidences suggest that relative testosterone deficiency may be already present during *in-utero* [5, 6] and *neonatal* stages [7], sex hormones in Klinefelter infants are within normal range [8]; likewise, puberty onset and completion occur as in the general population in most cases [9]. Testosterone levels begin to decline in late adolescence, along with an increase in gonadotropin levels, and overt hypergonadotropic hypogonadism generally presents in early adulthood [8–10].

Primary testicular damage is responsible for the sexual manifestations of the syndrome: following an initial increase in testicular volume at puberty onset, degeneration and hyalinization of the seminiferous tubules start, while Leydig cell hyperplasia is observed [9]. Despite the latter histological finding, circulating testosterone levels decrease, probably as a consequence of the unfavourable testicular microenvironment and vascular shrinkage [1, 11]. On the other hand, hypothalamus and pituitary gland are generally unaffected, and the rise of LH (luteinizing hormone) and FSH (follicle stimulating hormone) is the earliest sign of defective gonadal functions [1, 8].

Nevertheless, 12 previously published reports have described 14 patients with Klinefelter syndrome and hypogonadotropic hypogonadism (HH), variably associated with other pituitary hormones deficiencies, and in whom no organic cause could be identified to explain the hypothalamus-pituitary-gonadal axis (HPG) central defect [12–23].

In this article, we describe two patients affected with KS showing testosterone deficiency with low gonadotropin levels. Previously published research studies on hypothalamus-pituitary axes' function in KS are discussed, particularly focusing on central hypogonadism.

Materials and Methods

Clinical evaluation

The patients underwent standard interviews on pathological, physiologic, pharmacological and family history, and the physical examination was conducted with particular attention to external genitalia and secondary sexual characteristics. For this purpose, the Tanner and Marshall scales were used to stage the testicular and pubic hair development of patients [24]. In order to obtain a good approximation of the testicular volume, Prader's orchidometer was used.

Presence of gynecomastia, orofacial clefts, tooth agenesis or bimanual synkinesia was screened. Stretched penile length was measured, and the presence of micropenis was reported according to the available normative data [25, 26]. Body Mass Index (BMI) was calculated in order to identify a possible functional component for HH.

To evaluate the osmic defects, the patients were subjected to a magnetic resonance (MRI) study of the olfactory structures (olfactory bulbs, sulci and tracts) in addition to the hypothalamic-pituitary region; moreover, an olfactory functional test was performed using the Brief Smell Identification Test (BSIT Sensonic, NJ, USA).

Body proportions were measured, particularly standing height and arm span (the length between the extremities of the upper limbs measured at the fingertips, while they are parallel to the ground at shoulder height, creating an angle of 90°); eunuchoid habitus was defined as an arm span greater than the subject's height by ≥ 5 cm.

Data regarding bone mineral density (BMD) and morphometry were collected.

Hormonal evaluation

Testosterone was assayed using the Elecsys Testosterone II (Calibrator reference: 05200067190) test marketed by Roche diagnostics®. This method is standardized via isotope dilution-gas chromatography/ mass spectrometry. Elecsys Testosterone II test had a lower limit of detection of 0.087 nmol/L and a functional sensitivity of 0.4 nmol/L. The LH and FSH concentration were measured by electrochemiluminescence immunoassay 'ECLIA' from Roche Diagnostic (Roche Diagnostics GmbH). LH and FSH assays had a lower limit of detection of 0.1 IU/L and a functional sensitivity of 0.2 IU/L. The inter- or intra-assay coefficients of variation were <5% in all assays.

Genetic Analysis

Each patient underwent a genetic investigation, using a targeted Next Generation Sequencing (NGS) technique, to search for rare allelic variants. We extracted the genomic DNA of each patient from peripheral blood lymphocytes using Gene Catcher gDNA 96 _ 10 mL Automated Blood kit (Invitrogen, Life TechnologiesTM, Carlsbad, CA, USA). The congenital HH (CHH) gene panel was designed using Illumina Design Studio (San Diego, CA, USA) and included the following CHH candidate genes: *ANOS1(KAL1), FGFR1, PROKR2, PROK2, GNRHR, GNRH1, GNRH2, KISS1, KISS1R, TAC3, TACR3, HS6ST1, FGF8, CHD7, DUSP6, FEZF1, FGF17, FLTR3, IL17, SEMA3A, SEMA3E, SEMA7A, SOX2, SOX10, SPRY4, WDR11, HESX1, NELF*. The 28 CHH genes consistently represented in all sequence capture panels were assessed for the purposes of this study. Libraries were prepared using Illumina Nextera Rapid Capture Custom Enrichment kits according to the manufacturer's protocols. All regions not correctly sequenced were recovered with NexteraVR DNA Library Preparation kit (Illumina, San Diego, CA, USA). To define a "rare variant" [27, 28] we considered only the known pathogenic variants, the other rare non-synonymous or splicing-site variants (Minor Allele Frequency, MAF ≤ 0.01) and the novel non-synonymous or splicing-site variants. The frequency and the functional

annotation of the identified variants were checked in public and licensed databases (Ensembl, UCSC Genome browser, 1000 Genome project, ExAC Browser, NCBI, HGMD professional), considering the ethnic groups (Europeans). Written informed consent was obtained from the two patients for publication of their clinical details.

Results and cases description

Among 160 KS patients followed up at highly specialized endocrinological centres in Northern Italy, two patients showed hypogonadotropic hypogonadism on hormonal assessment. The patients had no previous pediatric or chronic ongoing diseases, no previous traumas or drug abuse, and no previous chemo- or radiotherapy treatments.

Case 1

Patient 1 was born from a full-term physiological pregnancy; his parents were unrelated, and he had no familiarity for endocrine or genetic diseases and malformations. An aunt and a cousin were reported to be anosmic and both had no children, despite being adults. When he was 57 years old, he was sent to our evaluation for congenital hypogonadotropic hypogonadism in Klinefelter syndrome.

He was diagnosed with hypogonadism at the age of 53 during an hospitalization for pneumonia. Once the underlying disease was completely resolved, total testosterone levels were 1 nmol/L confirmed in two determinations, and LH and FSH were both 0.1 IU/L. The remaining hormonal evaluation was unremarkable, and blood tests showed no inflammation, normal glycemic and lipidic profile, mild microcytosis due to hyposideremia and a Prostate Specific Antigen (PSA) of 0.02 ng/mL. Abdominal ultrasound examination was reported to be normal. The karyotype, assessed in 20 metaphases from peripheral blood lymphocytes culture, was 47, XXY with no mosaicism. At diagnosis he had a Tanner stage of P2G1 and bilateral gynaecomastia (diameter 1 cm, no nodules). He presented with a eunuchoid habitus, an incompletely developed penis with no hypospadias and an apparently empty scrotum. Ultrasound showed hypoechoic descended gonads, smaller than 1 mL with no internal lesions. He complained of low libido, erectile dysfunction, and no morning erections. He claimed to be anosmic as confirmed by a BSIT evaluation (2 correct answers out of 12) and had normal BMI, while he did not report any learning difficulty.

Genetic analysis using NGS techniques found no rare variant in known CHH genes. No cardiac anomaly was recorded. The MRI with contrast enhancement of the sella turcica and hypothalamus revealed no alterations. Since the diagnosis at 53 years of age, he was treated with intramuscular injections of testosterone undecanoate, which did not provide significant gain in the grade of external genitalia virilization, despite producing moderate improvement in sexual symptoms.

BMD evaluation, performed at the diagnosis, was consistent with osteoporosis, with a femoral T-score of -5.2 (Z-score -4.7) and a lumbar T-score of -3.7 (-3.3); the morphometric study of dorsal and lumbar spine showed no vertebral fractures.

He had normal 25OH-vitamin D levels in supplementation. After three years of treatment with testosterone, BMD improved (T-scores: -4.8 in femoral neck, -2.8 in lumbar spine) but patient was still at high fracture risk. For this reason, treatment with intravenous zoledronate was started.

Case 2

A 17-year-old Caucasian boy presented to our Department for hypogonadism and a prenatal diagnosis of Klinefelter syndrome. He was born preterm at 31 weeks by caesarean section following premature rupture of membranes, after an uncomplicated pregnancy and without significant perinatal complications. He had no cryptorchidism, micropenis or hypospadias at birth. As a child, he presented learning difficulties. He had no family history of infertility, anosmia or pituitary diseases, and his parents were not consanguineous.

The patient presented spontaneous puberty onset at the age of 14; however, for incomplete pubertal progression at the age of 16, he underwent hormonal assessment which was consistent with hypogonadotropic hypogonadism (morning total testosterone 0.3 nmol/L, LH 1.7 IU/L, FSH 1.0 IU/L); for this reason, treatment with hCG 1000 IU/week for one month was attempted, which produced an increase in testicular volume from 4 mL bilaterally, to 6 mL (right) and 8 mL (left).

Upon his first referral to our center, he was obese (weight 111 kg, height 185 cm, BMI 32.4 kg/m^2) and appeared fully virilised (Tanner stage 5) except for small testes of firm consistency; gynecomastia was not present. Nocturnal penile tumescence was preserved, and the patient did not complain of erectile dysfunction. Lumbar and femoral BMD appeared normal for age on dual energy x-ray absorptiometry (femoral z-score -0.6, lumbar z-score -0.9) and normal kidneys were documented on abdominal ultrasound scan. Vitamin D deficiency (plasma 25-OH vitamin D 17.8 ng/mL) was found on biochemical assessment, requiring subsequent supplementation.

Hormonal assessments revealed hypogonadism (morning fasting total testosterone 5 and 2.1 nmol/L on two different assessments) with still inappropriately normal gonadotropins (LH 3.6 and 3.8 IU/L, FSH 1.4 and 2 IU/L). Following this finding, karyotype was assessed again and a low-grade mosaic Klinefelter karyotype was confirmed on 50 metaphases [8% (47,XXY) / 92% (46,XY)].

The patient underwent hormonal and radiological workup to exclude organic causes of central hypogonadism. The remaining pituitary hormones resulted unaffected, and hypothalamus and pituitary stalk and gland were normal on MRI; incidentally, olfactory bulbs were visible. BSIT was consistent with normosmia.

Finally, genetic analysis was obtained to screen for CHH-associated genetic variants. However, no significant variants were identified by NGS.

The patient was started on testosterone replacement therapy, which provided normalization of serum testosterone concentrations, with further suppression of gonadotropins' levels (LH <0.3 IU/L, FSH <0.3 IU/L).

Discussion

Klinefelter syndrome is the most common form of primary hypogonadism in men [1]. In this article we describe two cases of HH in two patients with KS without any identifiable cause to explain the central defect. Only 14 other similar cases have been previously reported so far (Table 1) [12–23].

Different karyotypes were associated with HH in KS, including homogeneous 47,XXY, different grades of mosaicism, and one case with an extra Xq isochromosome (Table 1), so that a clearly predisposing cytogenetic background cannot be identified for this condition. While neonatal bilateral cryptorchidism and micropenis were reported only in one patient [18], absent or incomplete pubertal maturation was evident in most previously described cases and in our 2 patients as well, indicating an early onset of hypogonadism, which is unusual in KS [8–10]. Among features associated with KS, diabetes was reported in one patient, overweight in 4, low-normal intelligence scores in 5 with behaviour problems and emotional lability in one, and venous insufficiency in lower limbs in one subject (Table 1).

HH was an isolated defect in most subjects except for the ones described by Nistal [12], Vague [13] and Wittenberg [19], who reported deficits of other pituitary hormones, with no abnormal finding on skull X-ray. Actually, in the patient described by Rabinowitz, hormonal assessment suggested an isolated FSH deficiency, while LH levels were high basally and responded normally to LH releasing hormone (LHRH) stimulation [15].

Stimulation tests were performed in 9 cases and showed variable responses of gonadotropins to both single bolus and prolonged administration of LHRH, and of testosterone to human chorionic gonadotropin (hCG) (Table 1).

There is currently no clear explanation for the finding of central hypogonadism in this subset of KS patients. Some authors have hypothesized that exhaustion of gonadotroph cells may occur following prolonged hypersecretion [14–16]; however, high gonadotropins levels are generally maintained lifelong in most KS patients, as well as in other conditions like premature ovarian insufficiency and physiologic menopause.

Alternatively, it is possible that gonadotropins deficiency outlines a rare phenotypical variant of KS with a more extensive endocrine involvement. It is estimated that only 25-40% of KS patients are currently diagnosed, and many authors correctly claim that the phenotype of up to 75% of KS subjects is still unknown [2, 29]. Mild neuroendocrine alterations were seldom previously described in KS patients. For instance, a higher frequency of LH daily pulsatility [30], a change in FSH glycosylation profile [31], an enhanced response of gonadotropins to LHRH stimulation [9, 32, 33] but a poorer rise after naloxone administration [34, 35] have been reported. A few studies addressed other hypothalamus-pituitary functions. Day-time prolactin and growth hormone secretion appeared increased in KS patients compared to healthy males [36], while an exaggerated response of TSH [37] and prolactin [37, 38] to thyrotropin

releasing hormone was observed in some studies, but not confirmed in others [39, 40]. Recently, lower circulating free thyroxine levels were outlined in KS compared to healthy men [41] and non-Klinefelter hypogonadal patients [42], possibly due to a change in thyrotrope set-point. Overall, minor changes in several endocrine systems may be present in KS, and central hypogonadism may represent a variant or one extreme of these endocrine manifestations. However, many of these reports are anecdotal, most studies date back to 1970-1980 and included a limited number of subjects, and results have not been replicated recently.

It can be further hypothesized that acquired conditions like late onset hypogonadism, great obesity requiring nutritional rehabilitation, metabolic and systemic diseases can modulate negatively the hypothalamus-pituitary-gonadal axis even in KS subjects, as in the general male population, and consequently determine a decrease in circulating gonadotropins levels. Iwatsuki and colleagues found that LH and FSH concentrations were negatively correlated with BMI in KS [43], even if both persisted above normal in this series.

As one last hypothesis, coexistence of KS and isolated CHH could be considered in this setting. CHH is a rare condition characterized by the deficient secretion or action of gonadotropin releasing hormone (GnRH); age of onset is variable, and it can manifest with micropenis and cryptorchidism in a newborn male, with incomplete pubertal maturation in an adolescent male, or with infertility and hypogonadism at adult age [44–46]. Kallmann syndrome is diagnosed when CHH is accompanied by olfaction defects due to a common development of GnRH (gonadotropin-releasing hormone) and olfactory neurons, but also other features, such as facial midline defects, have been associated to this syndrome [44–46]. Hazard and colleagues described a 25 year-old man with anosmia, bilateral cryptorchidism, micropenis and cleft palate at birth, absence of spontaneous puberty, and a 47,XXY karyotype [18] thus demonstrating the co-occurrence of KS and Kallmann syndrome. This may also be the case of the 57-year-old man we have described in the present series (case 1), as anosmia and a positive family history are present as well; negative genetic analysis cannot exclude the diagnosis of Kallmann syndrome and it is not surprising indeed, as a genetic defect can be found only in 40-50% of patients with CHH [47, 48]. To the best of our knowledge, we are the first to report the genetic characterization of HH in KS. If we suppose that there are no interferences between CHH and KS, considering a frequency of 1:650 and 1:30,000 for KS [1, 4] and CHH [49] respectively, co-occurrence of these two conditions is expected in 1:19,500,000 newborn males. Coexistence of KS and HH would also explain the higher prevalence of cryptorchidism and micropenis among these patients when compared to pure Klinefelter population. Indeed, early GnRH deficiencies, often associated with absent minipuberty, leads to impaired penis development and testicular descent [50].

The above-mentioned variable association with other pituitary insufficiencies and the possible dissociations of FSH and LH levels in KS, suggest that all the different forms of congenital hypogonadotropic hypogonadism (i.e. also multiple pituitary hormone deficiencies and isolated FSH deficiency) can combine with an underlying Klinefelter syndrome.

This combination may impact the diagnosis and treatment of patients with congenital HH (CHH). In fact, if KS patients are usually studied with a full hormonal evaluation of the HPG axis, conversely patients with CHH not always perform a karyotype. This could lead to overlook a possible underlying cause of testicular damage, which could determine an absent or lesser response to treatment with gonadotropins, in terms of testicular volume increase or induction of spermatogenesis. On the basis of our observations and the above-mentioned review of the literature, we therefore suggest an alert regarding the evaluation of karyotype even in CHH, especially in those subjects who show clinical features suggestive, even if not exclusive, of KS, like bilateral gynecomastia, fully virilized external genitalia but low bitesticular volume, or patients who are resistant to restoration therapies aimed to increase the endogenous production of testosterone. The timely recognition of both conditions is paramount considering the increased morbidity and mortality associated with KS and male hypogonadism.

Finally, it has to be mentioned that, besides these rare cases, germ cell tumours [51–54], craniopharyngioma [55] and pituitary adenomas [56–59] have been reported in Klinefelter syndrome as causes of acquired hypopituitarism; therefore, an exhaustive diagnostic workup is always recommended in presence of HH to exclude organic diseases of the sellar region.

In conclusion, HH is an exceptional occurrence in KS and is associated with heterogeneous phenotypes and, probably, aetiologies. In this setting, a correct diagnostic workup and a tailored clinical management are advisable.

Compliance with Ethical Standards

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

This study was exempt from ethical approval procedures being a case report study that describes the clinical course and outcome of two patients who were referred to our outpatient clinic. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The participants have consented to the submission of the case reports to the journal.

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	Age (ys)	Kariotype	Family history	Neonatal phenotype	Puberty	Physical examination	Anosmia	Other syndromic features	Hormonal assessment	Comorbidities	Testicular histology
Nistal 1980 [12]	53	47,XXY	N/A	N/A	Female distribution of pubic hair	Testes 1.5x2 cm, bilateral gynecomastia, normal body proportions, overweight	NO	Intelligence quotient 64, venous insufficiency in lower limbs	HH LHRH test: no LH and FSH response. hCG test: no T response Other pituitary hormones: possible GH, ACTH and TSH deficiency	NO	Severe fibrosis of seminiferous tubules mostly with no cell within, immature Leydig cells
Vague 1963 [13]	45	(46,XY), (47,XXY)	N/A	N/A	Poor androgenization	Small soft testes, normal penile size, no gynecomastia, eunuchoid body proportions, normal body weight	N/A	Low-normal intelligence quotient	Clinical and ex juvantibus diagnosis of pan-hypopituitarism	Pulmonary tuberculosis	Hyaline sclerosis
Cherian 2015 [14]	31	47,XXY	N/A	N/A	Poor androgenization	Firm testes 2 mL, bilateral gynecomastia, eunuchoid body proportions	NO	NO	Hypergonadotropic hypogonadism at diagnosis, but later development of HH Other pituitary hormones: normal	NO	N/A
Rabinowitz 1975 [15]	18	(45,X0), (46,XY), (47,XXY)	Primary infertility	N/A	Delayed but complete, no nocturnal sperm emission	Testes 3x1.8 cm, normal penile size, no gynecomastia, normal body proportions	NO	N/A	Isolated FSH deficiency LHRH test: normal LH but no FSH response hCG test: no T response Other pituitary hormones: normal	NO	Hyaline sclerosis
Carter 1977 [16]	70	47,XXY	Negative	N/A	Incomplete	Soft testes 1x0.5 cm, bilateral gynecomastia, eunuchoid body proportions, mild obesity	N/A	N/A	HH LHRH test: normal LH and FSH response Other pituitary hormones: normal	Diabetes	N/A
Advani 1991 [17]											
Patient 1	28	47,XXY	N/A	N/A	Incomplete	Soft testes 3-4 mL, eunuchoid body proportions, underweight	N/A	N/A	HH	N/A	N/A
Patient 2	45	47,XXY	N/A	N/A	N/A	N/A	NO	N/A	HH (assessed one month after last T injection)	N/A	N/A

Hazard 1986 [18]	25	47,XXY	Negative	Bilateral cryptorchidism, micropenis	Absent	Left testis in scrotum, 15 mm, micropenis, no gynecomastia, eunuchoid body proportions, normal body weight	YES	Cleft palate	HH LHRH test: no LH and FSH response after single infusion, but pulsatile response of gonadotropins after GnRH pump administration for 21 days hCG test: no T response Other pituitary hormones: normal	NO	No hyaline sclerosis, Sertoli cells and immature germ cells present, immature Leydig cells
Wittenberg 1988 [19]	16	47,XXY	N/A	Normal	Delayed and incomplete; short stature and reduced growth velocity	Firm testes 2 cm, penile size 4.5 cm, bilateral gynecomastia, eunuchoid body proportions, normal body weight	NO	High arched palate, large ears; hypotonia and psychomotor delay, behaviour problems, emotional lability, subnormal intelligence	HH LHRH test: normal LH but no FSH response hCG test: partial T response Other pituitary hormones: possible GH deficiency	N/A	N/A
Smals 1977 [20]	38	47,XXY	N/A	N/A	Poor androgenization	Firm testes 1x1 cm, penile size 3 cm, bilateral gynecomastia, eunuchoid body proportions	N/A	N/A	HH LHRH test: subnormal LH and normal FSH response Other pituitary hormones: possible TSH deficiency	N/A	N/A
Sabbaghian 2011 [21]	33	47,X,i(Xq),Y	Negative	N/A	Poor androgenization	Testes 1.9-2.1 mL, no gynecomastia, eunuchoid body proportions, overweight	NO	NO	HH hCG treatment: normal T response Other pituitary hormones: normal thyroid axis	NO	Sertoli cells only, Leydig cells hyperplasia
Shirai 1974 [22]	74	(46,XY), (47,XXY)	Negative	N/A	Poor androgenization	Testes <1 mL, penile size 4.3 cm, no gynecomastia, underweight	N/A	N/A	HH LHRH test: poor LH and FSH response, no T increase	Arterial hypertension; recurrent urinary tract infections	No hyaline sclerosis, Sertoli cells only
Rodríguez de Ledesma 1994 [23]											
Patient 1	31	47,XXY	N/A	N/A	Male distribution of pubic hair	One testis in scrotum, 1 cm, normal penile size, bilateral gynecomastia, overweight	N/A	Intelligence quotient 70	HH Other pituitary hormones: normal prolactin	N/A	Hyaline sclerosis, no mature Leydig cells
Patient 2	53	47,XXY	N/A	N/A	Female distribution of pubic hair	Testes 1.5 cm, bilateral gynecomastia, overweight	N/A	Intelligence quotient 64	HH Other pituitary hormones: normal prolactin	N/A	Hyaline sclerosis, no

											mature Leydig cells
Features previously described in KS (%) [1, 2, 4]		• *47,XXY (80-90)* • *Higher-grade aneuploidies, structurally abnormal X chromosome or mosaicisms (10-20)*	*NO*	• *Decreased penile size (10-25) but rare micropenis* • *Cryptorchidism (27-37)*	• *Increased height (>30)* • *Decreased beard growth and pubic hair (30-80)*	• *Low bilateral testicular volume (> 95)* • *Gynecomastia (28-75)* • *Abdominal adiposity (50)*	*NO*	• *Congenital malformations (heart, cleft palate, inguinal hernia) (increased risk)* • *Verbal disorders (>40-80)* • *Learning disability (>75)* • *Mental retardation (4.2)* • *Autism spectrum disorders (30-50)* • *Thrombosis and pulmonary embolism (2.3-4.7)*	• *Low T (>75)* • *Increased gonadotropin levels (>75)*	• *Metabolic syndrome and diabetes (10-46)* • *Osteopenia (40), osteoporosis (10), fractures (increased risk)*	
Features Previously described in CHH (%) [45, 46, 60, 61]		• *46,XY* • *Involvement of CHH genes (50)*	*YES*	• *Micropenis (20-40)* • *Cryptorchidism (30-50)*	• *Absent or incomplete puberty*	• *Low bilateral testicular volume (> 95)* • *Gynecomastia in untreated patients*	*YES*	• *Hearing loss (0-8)* • *Orofacial clefting (4-15)* • *Renal agenesia (0.5-15)* • *Bimanual synkinesia (0-30)*	• *Low T (100)* • *Low or normal gonadotropin level (100)*	• *Osteopenia, osteoporosis (12.5)*	

Table 1. Review of previously published reports of hypogonadotropic hypogonadism in Klinefelter syndrome (KS).

Ys, years. N/A, not assessed. HH, hypogonadotropic hypogonadism. T, total testosterone. LH, luteinizing hormone. FSH, follicle stimulating hormone. LHRH, LH releasing hormone. hCG, human chorionic gonadotropin. GH, growth hormone. ACTH, adrenocorticotropin. TSH, thyroid stimulating hormone. CHH, congenital hypogonadotropic hypogonadism.