BRIEF REPORT

A Characteristic Cognitive and Behavioral Pattern as a Clue to Suspect Klinefelter Syndrome in Prepubertal Age

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Klinefelter syndrome (KS) with the classic 47,XXY karyotype is the most frequent chromosomal aneuploidy, with a prevalence of 1 in 700 men; although the classic clinical picture is well-known and easily recognizable, most patients remain undiagnosed. The rate of diagnosis during childhood is extremely low, and only 10% of cases are identified before puberty, with a subsequent rate of ascertainment during lifetime of 25%. The low rate of timely diagnosis is because most of the classical signs and symptoms of androgen deficiency appear in mid- to late adolescence but it is important to recognize that adult men with KS may show a great variability in clinical and physical features. A common, often underappreciated, element in young boys and children with KS is the characteristic cognitive and behavioral pattern. We describe 2 patients who were diagnosed at 7.1 and 10 years through a characteristic neurocognitive profile. Both of them showed low-normal scores when evaluated by tests of general intelligence and a behavioral profile characterized by immaturity, low self-esteem, and learning disabilities. Clinical examination showed tall stature and progressive growth acceleration between 5 and 7 years, and one of them had hypoplastic scrotum with monolateral cryptorchidism. To achieve the goal of an early diagnosis of KS, it is necessary to increase medical awareness of the disease and, in particular, to augment pediatricians' knowledge that during prepubertal age pathognomonic clinical features of KS are often lacking but a characteristic cognitive and behavioral pattern is commonly present. (J Am Board Fam Med 2012;25:745–749.)

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Klinefelter syndrome (KS) with the classic 47,XXY karyotype is the most frequent chromosomal aneuploidy, with a prevalence of 1 in 700 men,[1] and is the most common genetic form of male hypogonadism.[2] KS was first described in 1942 by Klinefelter et al[3] as a clinical entity characterized by gynecomastia, small testes, absent spermatogenesis, normal to moderately reduced Leydig cell function, and increased secretion of follicle-stimulating hormone (FSH). The classical phenotype of KS is well described in every textbook of medicine and is easily recognizable. Nonetheless, 70 years after its first description, this syndrome remains a largely undiagnosed condition.

The main reason for lack of diagnosis is that many affected patients present only discrete symptoms during their lifetime, and especially during childhood the clinical picture may be unimportant, with most of the signs and symptoms appearing only in mid to late adolescence. As a consequence, the rate of diagnosis during childhood is extremely low, with 10% of cases being identified before puberty[4]; if we consider that 10% are diagnosed prenatally and only 25% are recognized during their lifetime, we have to acknowledge that a huge percentage of KS patients remain undiagnosed. Here we describe the clinical presentation of 2 young boys who were diag-

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nosed at a young age (ie, before 10 years). The correct diagnosis was suggested by a characteristic cognitive and behavioral pattern.

Patient Presentation

Case 1

A male child, 7.1 years old, came to our outpatient clinic of pediatric endocrinology for precocious pubarche. He was born at term to nonconsanguineous parents after an uneventful pregnancy. His birth weight was 1840 g (standard deviation score [SDS], −3.4) and birth length was 49.0 cm (SDS, −0.5). The clinical history reported normal developmental milestones.

Auxological and clinical examination showed the following values: height, 126.2 cm (SDS, +0.8); target height, 167.9 cm (SDS, −1.3); weight, 28 kg; bone age, 8.3 years (Greulich and Pyle); pubic hair, P2; and testes volume, 2 mL bilaterally. Laboratory investigations were normal for routine assays and adrenocorticotropic hormone stimulation test (corticotrophin test) enabled us to exclude late-onset congenital adrenal hyperplasia as the cause of premature pubarche. One year later he showed a mild acceleration of growth velocity, a predicted final height significantly higher than target height (184.3 cm vs 167.9 cm), and a characteristic behavioral profile characterized by immaturity, insecurity, shyness, and learning difficulties. His behavioral phenotype was evaluated by a well-trained psychologist using the Children's Apperception Test (CAT-H) and the Kiddie-Sads Present and Lifetime Version interview (K-SADS-PL).

A cognitive evaluation was assessed using 3 different tests: (1) the Wechsler Intelligence Scale for Children-Revised (WISC-R) resulted in low-normal scores; in particular, the WISC full-scale intelligence quotient (FSIQ) score was 83, performance intelligence quotient (PIQ) was 85, and verbal intelligence quotient (VIQ) was 84. (2) The Developmental Test of Visual-Motor Integration (VMI) also resulted in a low-normal score of 80, and (3) the Comprehensive Test of Nonverbal Intelligence (CTONI) resulted in a score of 79. This neurocognitive pattern in association with the suggestive auxological features triggered the suspicion of KS, and karyotype analysis confirmed this diagnosis, showing the most common chromosomal pattern (ie, 47,XXY).

At the age of 11.6 years, the typical hypogonadal picture manifested with thick pubic hair and small testes, tall stature in respect of target height (SDS, +1.4 vs −1.3, respectively), predicted final stature significantly taller than target height (SDS, +2.0 vs −1.3, respectively), and eunuchoid aspect with abnormal sitting height-to-height ratio (0.499). Hormonal evaluations performed when bone age reached 12.9 years showed hypergonadotropic hypogonadism with elevated levels of both basal and stimulated (after gonadotrophin releasing-hormone test, extra volume) FSH and luteinizing hormone levels (Table 1). At the age of 13, treatment with testosterone enanthate was started at a dose of 50 mg/month intramuscularly.

Case 2

A 10-year-old male child was referred to our Department's outpatient Clinic of Pediatric Neurology and Psychiatry because of learning disabilities. He was born at term to nonconsanguineous parents via normal vaginal delivery after an uneventful pregnancy. Birth weight was 3500 g (SDS, +0.4) and birth length was 54.0 cm (SDS, +1.8). Developmental milestones were mildly delayed.

Physical examination showed the following measurements: height, 146.6 cm (SDS, +1.7); father's height, 166.0 cm (SDS, −1.8); mother's height, measurement unavailable; hypoplastic scrotum, a small left testis (1 mL) palpable in the scrotum, and the right testis palpable in the inguinal region. Because of his monolateral cryptorchidism, which surprisingly had not been reported in his clinical history, an endocrinological evaluation was requested.

The parents stated that the boy experienced unspecified academic difficulties and that special

Table 1. Hormonal and Pubertal Evolution in Our First Patient

Age, years	9.0	12.6
Basal FSH (IU/L)	1.22	9.78
Stimulated FSH (IU/L)*	4.97	35.14
Basal LH (IU/L)	<0.1	9.57
Stimulated LH (IU/L)*	3.03	45.63
Testosterone (ng/mL)	28	45
Testes volume (mL)	2	2
Pubic hair†	2	4

*Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels 60 min after stimulation with gonadotropin releasing-hormone, 100 μg intravenous.
†According to Tanner stages.

teaching support was requested by themselves and was recommended by school personnel. Therefore, the boy was administered a battery of tests as well as the WISC-R, which showed low-average scores: in particular, the WISC FSIQ score was 80, PIQ was 82, and VIQ was 82; he received a score of 80 on the Developmental Test of VMI and a score of 79 on the CTONI.

The patient also was assessed with a series of standardized tests to evaluate his language comprehension (Rustioni test) and his academic skills (IPDA), and he scored 2.0 SDS below the mean on the writing, reading, memory, and words and sentences processing tasks, thus confirming his reduced academic skills due to specific learning disorders. The psychological evaluation was completed using the CAT-H and the K-SADS-PL; the results of these tests showed a behavioral profile characterized by shyness, low self-esteem, poor judgment, and inappropriate assertive activity.

This neurocognitive profile together with genital anomalies and tall stature represented the clue to trigger the correct diagnosis. Karyotype testing revealed a 47,XXY karyotype, thus confirming the diagnosis of KS. Laboratory investigations revealed normal prepubertal levels of FSH and luteinizing hormone and normal thyroid tests, so the father was informed about the diagnosis and clinical and auxological follow-up was suggested.

Methods and Data Collection

Age at diagnosis, karyotype, clinical presentation, history of behavioral and educational problems, and parents' heights were extracted from the patients' charts. Intellectual assessment was conducted by a trained psychometrician and included the Italian translation of the WISC-R, based on a FSIQ, a VIQ, and a PIQ.[5] According to normative data, 100 has been considered the mean normal value for the FSIQ, VIQ, and PIQ, and an intelligence quotient higher than 70 (ie, SDS >-2.0 SDS) is considered normal.[6] Cognitive assessment also included the Developmental Test of VMI[7] and the CTONI.[8] Psychological and developmental evaluations were completed using a battery of tests that included the CAT-H; a semistructured diagnostic interview designed to assess diagnosis in the domain of affective, psychotic, anxiety, and behavior disorders (the K-SADS-PL); a language comprehension test (Rustioni test of language comprehension); and an academic achievement test (IPDA).[9–12] Our study design was approved by the Ethical Committee of our University and informed consent was obtained from the patients' parents.

Discussion

KS is the most common chromosomal disorder, affecting 1 in 500 to 1000 men[1,2]; it also is the most common genetic form of male hypogonadism.[2] The classic 47,XXY karyotype is present in 80% of affected individuals, whereas in the remaining 20% of patients, higher-grade chromosomal aneuploidies (48,XXXY, 48,XXYY, 49,XXXXY) or a mosaicism (46,XY/47,XXY) are present. The typical clinical picture described by Klinefelter et al[3] in 1942 is an endocrine disorder with small firm testes, gynecomastia, and hypergonadotropic hypogonadism with very high levels of FSH, absent spermatogenesis, and normal to moderately reduced Leydig cell function. This picture is well described in every textbook of medicine and is easily recognizable during physical examination, but it is fully displayed in only a small percentage of adult patients. In fact, we must acknowledge that many adult men with KS can show a lot of variability in clinical and physical features. For this reason, many patients with KS remains undiagnosed, and a Danish study reported that only one fourth of adult men with KS are recognized and the rate of diagnosis is very low during childhood, with only 10% of cases being identified before puberty.[4] Some authors found that 10% of expected cases of KS were identified prenatally, and 26% were diagnosed during childhood or adult life because of hypogonadism or infertility, leaving 64% undiagnosed.[13]

The clinical picture varies according to age, and before puberty only mild anomalies may be noticed, especially in the genital area—eg, lower than normal testicular volume, a slightly smaller penile length, and hypospadia.[14] Whether the prevalence of cryptorchidism is increased in KS is controversial,[15] but some authors demonstrated higher than the estimated prevalence in the general population[16] or a positive history for maldescended testes,[2] and these data are in accordance with our experience. In the majority of children with KS, the genitals are normal through early childhood,[14] so the physical appearance of a hypogonadal child may not differ from that of a normal boy of prepubertal

age.[17,18] In a large majority of patients with KS, some of the symptoms and signs of androgen deficiency appear during mid to late adolescence, but they often are disregarded. By late adolescence, microorchidism is quite evident in almost all cases and is not routinely identified by physicians during physical examination. Most of these patients are diagnosed only during adulthood when they seek medical consultation for infertility or decreased libido and potency.[2] A clinical feature that almost always presents during childhood is tall stature; in fact, children with KS are of average height or taller, but in any case they are taller with respect to their target height.[2] Auxological pattern is characteristic, showing a progressive acceleration in growth velocity between 5 and 8 years of age; this increase in stature before pubertal age demonstrates that it is not caused by androgen deficiency and consequently long-leggedness, but probably is related to the underlying chromosomal abnormality.[2]

One of our patients showed an atypical clinical sign—precocious pubarche—and this unusual clinical presentation in KS may confirm that some children with KS as well as many adult men with KS are not entirely undervirilized, and a mild degree of virilization does not exclude the suspicion of KS. Moreover, an atypical evolution of pubertal development characterized by a progressive increase in pubic hair and small, firm testes should strengthen this hypothesis. In fact, microorchidism, especially when associated with thick pubic hair, seems to be the only consistent physical feature that is truly almost universal.

The underdiagnosis of KS is probably because clinical suspicion is based mostly on the endocrinological and andrological features that become evident only during late adolescence. A common and often underappreciated element is the characteristic cognitive and behavioral pattern that can be observed in almost 80% of these young boys. Although the cognitive impairment in most of them is mild and unspecific, it is true that KS might be one of the most common causes of intellectual disability in prepubertal boys.[19] The typical cognitive pattern of patients with KS does not reflect a general decline in intellectual ability but indicates a deficit in very specific domains of cognition and, in particular, in language and frontal-executive functions that seem similar to those observed in cytogenetically normal dyslexic children.[20] Global intelligence (FSIQ) is generally within the normal limits, but boys with KS may demonstrate atypical neurocognitive development.[21]

In general, the cognitive phenotype is subtle and far from pathognomonic of KS,[21] but it generally is characterized by depressed performance on measures of language development, attention, and academic ability. Language difficulties are frequent and manifest both as delays in speech milestones in younger boys and significant deficits in higher aspects of expressive language, such as word retrieval and narrative formulation in older patients. Eighty percent of boys with KS may need special education support.[21–23]

In our 2 patients, the cognitive phenotype, academic difficulties, and characteristic personality triggered the suspicion and, in particular, stimulated the search for more typical signs of KS. According to our experience we believe that all boys who present before puberty with tall stature and a characteristic cognitive or behavioral pattern deserve a karyotype analysis. In fact, it has been demonstrated that early diagnosis of KS improves patients' quality of life; in particular, testosterone treatment started at a proper age is useful to correct the symptoms of androgen deficiency,[24] to improve goal-directed thinking and self-esteem, and to ameliorate mood and behavior.[25,26]

To achieve the goal of an early diagnosis in KS, it is necessary to increase medical awareness of the disease and, in particular, to augment pediatricians' knowledge that during prepubertal age pathognomonic endocrinological features of KS often are lacking but a characteristic cognitive and behavioral pattern is almost always present, especially when searched for accurately.

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