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Phenotype and Adverse Quality of Life in Boys with Klinefelter Syndrome

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Abstract

Objectives—To characterize associations among psychosocial well-being, physical phenotype, and sex hormones in a sample of youth with Klinefelter syndrome (KS). We hypothesized that KS physical traits (phenotype) are associated with adverse psychosocial health measures and that testosterone levels are associated with adverse psychosocial health.

Study design—Forty-three boys with KS (ages 8-18 years) participated in a cross-sectional study. Participants underwent physical examination, hormone analyses, and psychosocial health questionnaires.

Results—Using an investigator-developed Klinefelter Phenotype Index Scale, the number of KS physical traits ranged from 1-13 (mean 5.1 ± 1.9). Pubertal boys presented with more KS traits compared with prepubertal boys (5.6 vs 4.2, $P = .01$). Boys diagnosed prenatally had a milder phenotype compared with those diagnosed postnatally. Gonadotropins were elevated without androgen deficiency in 45%. Psychosocial health scores indicated adverse quality of life (QOL) (67%), low self-esteem (38%), poor self-concept (26%), and risk for depression (16%) without a difference between pubertal groups. Linear regression showed that 22% of the variance in QOL ($P = .0001$) was explained by phenotype. Testosterone level was not associated with psychosocial health measures.

Conclusions—Depending on the degree of phenotypic abnormality, boys with KS may be at risk for impaired QOL. Testosterone levels were not shown to influence psychosocial health. The Klinefelter Phenotype Index Scale may be a useful tool to characterize KS features in boys.

Klinefelter syndrome (KS) is a genetic condition caused by the presence of an extra X chromosome in the male karyotype. Tall stature, gynecomastia, small testes, androgen deficiency, elevated gonadotropins, and azoospermia typically characterize the condition.[1] KS is reported to be the most common sex chromosome aneuploidy with a prevalence of

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approximately 1 in 600 male births.[2] KS is also associated with physical, neurocognitive, and psychosocial comorbidities, including infertility and high risk for the development of cardiovascular disease, diabetes, osteoporosis, autoimmune disorders, and certain kinds of cancers.[3] Only 10% of affected individuals are diagnosed during childhood. It has been estimated that approximately 25% of affected individuals are diagnosed in adulthood, usually for infertility assessment, with the remaining 65% never receiving a diagnosis in their lifetime.[4] In adults, KS is associated with reproductive, neurocognitive, and psychosocial health problems that are believed to first emerge during childhood.[5] Affected individuals require long-term medical and mental health care needs that vary according to development and life stage.[6]

Although androgen deficiency is believed to underlie many KS-related abnormalities in both physical and emotional health,[7] large studies of boys with KS are uncommon, leading to poor understanding of how this genetic disorder affects growth and development during childhood. Testosterone concentration has been suggested to be associated with many physical and psychological symptoms in adult men. We sought to explore any relationships between testosterone and psychosocial health in children. The peripubertal period is presumed to be a sentinel time for the emergence of physical and psychosocial health issues associated with diminishing production of testosterone.[8] To gain insights into the range of KS traits and their impact on quality of life (QOL) during childhood, we studied the physical phenotype, associated reproductive hormones, and psychosocial health of peripubertal boys with KS.

Methods

The Columbia University Medical Center Institutional Review Board approved the research protocol. Data were collected between April 2010 and August 2011. The inclusion criteria included boys between the ages of 8 and 18 years with a confirmed karyotype of 47,XXY, or 46,XY/47,XXY, who were English speaking and able to read at the third grade level. Subjects were recruited from a pediatric endocrine clinic at Columbia University, local KS support groups, an online study website, a professional research recruitment website, and a social media website.

The study visit consisted of 3 components: physical examination, blood collection for hormone determinations with completion of 1 demographic questionnaire by the parent, and 4 questionnaires by the youth (QOL, self-esteem, selfconcept, and risk for depression). Written informed consent was obtained from 18-year-old participants with parental informed consent; child assent was obtained from boys under the age of 18 years. Each subject received a $25 gift card as compensation for his/her time.

Clinical observations of physical traits, anthropometric measurements, and Tanner stage (TS) were assessed by 2 of the investigators, a pediatric nurse practitioner (S.C.) and a pediatric endocrinologist (I.F.). To characterize the KS physical phenotype, an investigator-developed assessment tool was used to quantify the number of KS physical traits including tall stature, eunuchoid body proportion, wide arm span, large waist circumference (WC), high body mass index (BMI), small testicular volume, short phallus, gynecomastia, skeletal

abnormalities (pectus excavatum, pectus carinatum, scoliosis), high arched palate, clinodactyly, hand tremor, and hypertelorism. The KS phenotype index (KSphI) measurement tool was created and modeled after the Mainz Severity Score Index,[9] an instrument for quantifying the Anderson-Fabry disease phenotype. The KSphI score is a summed value that reflects the presence (score = 1) or absence (score = 0) of each physical trait with a total score ranging from 0 to 13. A higher score represents the presence of more KS physical features. Quality and accuracy of these measurements was assured with 90% agreement between the 2 raters (S.C. and I.F.). Height was measured to the nearest 0.1 cm in a standing position with either a Seca (Chino, California) fixed wall-mounted or a portable Charder HM200P clinical stadiometer (Charder, Taichun City, Taiwan). Subjects were positioned using the Frankfort horizontal plane, a horizontal plane represented in profile by a line between the lowest point on the margin of the orbit and the highest point on the margin of the auditory meatus. Height was measured 3 times. The average of the height measurements was used.[10] Reliability between the wall-mount and the portable stadiometers was measured by comparing heights in cm taken from 30 adult volunteers.

Weight was measured to the nearest 0.1 kg on a calibrated RLS (Rice Lake Weighing Systems, Rice Lake, Wisconsin) clinical digital scale (measurements at Columbia University Medical Center) or a calibrated portable UC-321 (A and D Medical, San Jose, California) digital scale (off-site measurements). Reliability between the clinical scale and the portable scale was measured by comparing weight in kg taken from 30 adult volunteers. Reliability between digital scales exceeded 98%.

WC was measured using a nonstretchable measuring tape according to the National Health and Nutrition Survey III guidelines.[11] Subjects were measured standing with legs together and arms at their sides with palms facing inward. The midpoint of the inferior margin (lowest point) of the last rib and the crest of the ilium was located. The subject was asked to exhale gently. WC was measured at just above the uppermost lateral border of the right ilium to the nearest 1 mm. Abnormal WC was defined as values $ the 90th percentile for age. BMI was calculated for height and age using the Centers for Disease Control BMI for Children online calculator.[12] BMI greater than the 85th percentile was used to determine overweight status.

Upper to lower body segment ratio (U/L) was measured with the subject in a standing position. The top of the pubic bone was palpated. The lower segment was measured from the top of the middle part of the pubic bone to the sole of the foot to the nearest 0.1 cm. The lower segment was subtracted from the total height to obtain the upper body segment measurement. The U/L was calculated by dividing upper body segment by the lower body segment. U/Ls less than 1.0 were considered abnormal.[13] Arm span was measured to the nearest 0.1 cm with the subject standing against a flat wall with arms outstretched to create a 90° angle with the torso. The distance between the tips of the right and left middle fingers were measured in cm using a nonstretchable measuring tape.[13] Hypertelorism was determined by measurement of the inner canthal distance using a disposable plastic ruler.[13] Inner canthal distance $2 SD was determined to be classified as hypertelorism.[13,14]

Sexual maturation was assessed by clinical observation of the presence and distribution of pubic hair, stretched phallic length, appearance of scrotum, and staged 1 to 5 according to the guidelines of Tanner.[15] Stretched phallic length was measured using a disposable wooden tongue blade pressed against the pubic ramus depressing the suprapubic fat pad as completely as possible.[13] Phallic length measurement to the nearest 1 mm was compared with the normal size range for chronological age using the normative measurements for age established by Schonfeld and Beebe.[16] Testicular volume was measured using Prader orchidometer beads. With the subject lying supine, testes were manually palpated and compared for size according to the technique of Prader. If testes were of different sizes, the average of the 2 testes were taken.[13] For purposes of this study, given that boys with KS characteristically have small testicular volume, the designation ofprepubertal and pubertal status was made on the basis of pubic hair distribution. Gynecomastia was assessed using TS and bimanual palpation to distinguish between presence and absence of lipomastia or glandular tissue.[17] Subjects were assessed for the presence of skeletal abnormalities such as elbow dysplasia, scoliosis, and pectus deformities. Clinodactyly was assessed by observation of the angle of the fifth finger distal interphalangeal joint.[14] The presence of involuntary hand tremor was determined by examining the subject's hands at rest on his lap while seated. Intention tremor was assessed by visual observation as subject reached for an object such as a pen from the hand of the examiner.[18] High arched palate was assessed by observation of the height of the palatal vault in relation to the alveolar ridge. When maximum palate height was greater than twice the height of the teeth, it was considered to be abnormally high.[13] Although hypotonia is frequently described in KS, it is difficult to quantify by subjective observation alone and would require the use of electromyography or muscle biopsy to objectively measure it. As the KSphI was developed with clinical observation in mind, this potential characteristic was not included in the KSphI.

A sample of approximately 25 mL of whole blood was collected from each subject prior to 10 a.m. for measurement of sex hormones. Small aliquots of serum were frozen at −80° C. All samples were batched and sent for analysis together to commercial laboratories. Hormones including testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, sex hormone binding globulin, and dehydroepiandrosterone sulfate (DHEAS) were sent to Esoterix Labs, Inc (Calabasas, California). Testosterone and estradiol were measured by high pressure liquid chromatography and tandem mass spectrometry with free testosterone by equilibrium dialysis. Interassay coefficient of variation (CV) for testosterone was 14.8% and for estradiol was 4.4%. DHEAS, LH, and FSH were performed by electrochemiluminescence with CV at 15%, 8.2%, and 11%, respectively. Sex hormone binding protein was measured by immunoradiometric assay with CV of 4.7%. Low testosterone was reported as either below the lowest expected values based upon published standard ranges by Esoterix Labs or low normal testosterone, the lowest quartile of the assay range for each TS. The lowest quartile was calculated as the midpoint between the lowest assay level and the median.

We chose 4 discrete domains of psychosocial health that are well-validated in the pediatric population: QOL, selfconcept, self-esteem, and risk for depression.

In this sample of boys, the inclusion criterion of reading at the third-grade level was screened during the parent demographic interview and consenting/assenting process. Parents reported that their child was reading at the third-grade level. Child participants were asked to read portions of the consent/assent form out loud prior to signing. Each participant read the questionnaire instructions and was asked by the examiner if he knew how to respond. The questionnaires were administered in a rotating order between participants. The examiner asked participants to read the directions and first 3 questions of the first questionnaire out loud prior to continuing. The examiner was within close proximity to respond to questions about the questionnaires, if needed. Participants in this sample did not report difficulties reading or understanding questions on the questionnaires.

Health-related QOL is a construct that in most general terms reflects a person's overall sense of well-being. The Pediatric Quality of Life Inventory 4.0 health-related QOL is a validated measure that examines a child's well-being in 4 domains: physical, emotional, social, and school well-being.[19] It is a 23-item questionnaire with a possible total score of 100. A total score less than 80 indicates poorer QOL.[19] Self-esteem and self-concept are distinguished between one another within context of self. Self-concept signifies self-evaluation with regard to body and intellect in consideration of behavioral adjustment, freedom from feeling anxious, popularity, and happiness.[20] Self-esteem suggests self-value and worthiness with regard to approval or disapproval in the context of feeling competent, successful, and significant in the world.[21]

Self-concept was measured using the Piers-Harris 2 Self-Concept Scale,[20] an 80-item instrument designed for use in children between the ages of 7 and 18 years. Each item is rated by the child as "yes" or "no" based upon how he feels about himself. The instrument contains 6 domain scales: behavioral adjustment, intellectual and school, physical attributes, freedom from anxiety, popularity, and happiness. Scores are converted to standardized t scores ranging from 20-80 with higher *t* scores indicating better self-concept. Selfesteem describes the evaluation that a person makes or maintains that is an expression of approval or disapproval in the context of feeling competent, successful, significant, and worthy. Self-esteem reflects an individual's personal sense of worthiness towards him or herself.[21] Self-esteem was measured using the Coopersmith Self-Esteem Inventory. Scores range between 0 and 100 with higher scores indicating higher self-esteem.[21] Risk for depression was measured using the Children's Depression Inventory (CDI), a validated screening tool designed to assess depression risk in children between the ages of 8 and 17 years of age.[22] The CDI contains 28 items, each of which consists of 3 statements. For each item, the individual is asked to select the statement that best describes his or her feelings for the past 2 weeks. The CDI contains 5 subscales that assess negative mood, interpersonal problems, ineffectiveness, anhedonia (the inability to experience pleasure), and negative self-esteem. Mean scores were reported as standardized t scores with scores above 54 considered to be clinically significant for increased depression risk.

Statistical Analyses

The sample size was calculated based upon a moderate correlation of at least 0.40 between the clinical characteristics and psychosocial variables as observed in a study of health-

related QOL and polycystic ovary syndrome.[9] For a 2-tailed test with 80% power and alpha at 0.05, 46 subjects were required. Data were analyzed with SAS Software v 9.2 of the SAS System for Unix 2008 (SAS, Cary, North Carolina) using descriptive statistics. Data were stratified by pubertal status and compared according to KSphI score, sex hormones, and psychosocial health surveys using χ^2 and Fisher exact tests for categorical data and Wilcoxon signed rank tests for continuous data. Linear regression models were used to examine relationship between KSphI and QOL.

Results

Data were normally distributed with the exception of 2 psychosocial health subscales: the school functioning subscale of the Pediatric Quality of Life Inventory 4.0 and the interpersonal problems subscale on the CDI. Owing to these skewed subscales and the relatively small sample size, we employed nonparametric statistics.

Of the 43 subjects who participated in the study, 22 (51%) volunteers were assessed at the Irving Center for Clinical and Translational Research Pediatric Division at Columbia University Medical Center, 16 (37%) were studied at the participant's home, and in 5 cases (12%), data were collected at prearranged appointments during the 2010 Knowledge, Support, and Action Families National Conference. Characteristics of the sample are summarized in Table I. Boys ranged in age from 8-18 years with a mean of 12.5 ± 3.1 years. The majority (86%) were Caucasian with 47,XXY karyotype (90%). Over one-half were diagnosed prenatally (65.1%). Of those diagnosed postnatally (34.9%), the most common reason for ordering karyotype was for developmental delay (11.6%) or tall stature (9.3%). Other reasons for postnatal diagnosis included genital abnormalities, such as hypospadias, chordee, or undescended testis (6.9%), speech and language delay (2.3%), behavior problems (2.3%), and hand tremor (2.3).

About 50% of the boys had received testosterone either as an infant or therapeutically during puberty. Of those with histories of testosterone treatment, 5 received injections prior to the age of 1 year (23%), 2 between the ages of 2 and 4 years (9%), 1 at the age 8 years (12.5%), and 13 initiating treatment between the ages of 11 and 14 years of age (59%). At the time of the study, 6 boys reported current testosterone treatment with regular adherence (27%). The remainder of the treated sample reported intermittent or nonadherence to regular therapy (73%).

A majority of the sample reported learning disabilities (69.8%), speech and language problems (67.4%), and social interaction issues (62.8%), with more than one-third reporting attention deficit disorder (37.2%).

Table II summarizes anthropometric, physical characteristics and KSphI scores of the sample stratified by pubertal group. Mean KSphI score of the sample was 5.1 ± 1.9 (range 1-10). KSphI scores were significantly lower for the prepubertal group compared with the pubertal group (4.2 vs 5.6; $P = .01$). Specific physical characteristics did not differ between prepubertal and pubertal groups with the exception of abnormal testicular volume and high arched palate, both of which were more frequent in pubertal boys (81.5% vs 50%, $P = .04$)

and (41.9% vs 18.8%; $P = .03$). Comparing KSphI scores according to time of ascertainment, milder phenotype was observed in boys diagnosed prenatally (mean = 4.5) vs postnatally (mean = 6.2) $P = .004$.

Frequencies of subjects with abnormal hormone concentrations for TS are shown in Table III. Serum testosterone values were in the low normal or low range in 4 boys (9.5%). Values above the normal range levels for TS were observed for LH in 21 boys (50%) and FSH in 18 boys (42.9%). DHEAS values were low in 16 boys (38.1%), suggesting that androgen deficiency of adrenal source does not present a common problem in early puberty in this sample. A high proportion of boys in the pubertal group showed high concentration of FSH (66.7%) and LH (59.3%) in conjunction with a low proportion of boys with low testosterone (14.8%), indicating evidence of early testicular failure without androgen deficiency.

Table IV presents frequencies of participants with adverse psychosocial health stratified by pubertal group. Overall, two-thirds of the sample (67%) showed lower QOL with total scores below the cutoff of 80. Low subscale scores were reported for all QOL domains without difference between pubertal groups. Regression models demonstrated an inverse relationship between KSphI and total QOL ($r^2 = 0.22$, $P = .0001$), including subscales for physical ($r^2 = 0.23$, $P = .001$), social ($r^2 = 0.14$, $P = .015$), and school functioning ($r^2 = 0.21$, $P = .002$). Neither testosterone nor age showed an association with QOL.

The Piers-Harris 2 Self-Concept Scale showed total t scores below the cutoff in 25.6% of the sample. Low scores were also observed for the following subscales: behavioral adjustment (18.6%), intellectual and school status (18.6%), physical attributes (11.6%), freedom from anxiety (27.9%), popularity (27.9%), and happiness (29.9%), with no differences in self-concept between pubertal groups. A trend for an inverse relationship between KSphI and total self-concept score was observed ($r^2 = 0.10$, $P = .05$) without significant relationships for the specific subscales of behavioral adjustment, intellectual/school physical attributes, freedom from anxiety, popularity, or happiness.

Thirty-seven percent of the boys in this sample had scores below the cutoff of 75 indicating low self-esteem with no differences noted by pubertal group.

Based on a total t score above 54, 16.3% of the boys met criteria for risk of depression. By subscales, the percentages of boys with risk for depression were as follows in descending order of frequency: anhedonia (25.6%), negative self-esteem (23.3%), ineffectiveness (18.6%), negative mood (16.3%), and interpersonal problems (16.3%). There were no differences in mean group scores between pubertal groups. Of note, 2 boys responded “yes” to the question, “I want to kill myself” and were referred for more comprehensive screening and consultation with a mental health professional. No significant relationships were observed between self-esteem and risk for depression with KSphI, testosterone, or age.

Discussion

Using the investigator-developed KSphI scoring tool, our results support the findings of Zeger et al,[14] who observed in a sample of 55 boys with KS between the ages of 2 and 14 years, taller childhood height, small testicular volume, reduced phallic length, gynecomastia,

clinodactyly, high arched palate, hypertelorism, and bony abnormalities. With respect to physical traits and endocrine markers, our results are similar to those of Aksglaede et al,[23] who found in a sample of 166 individuals from infancy to 80 years that patients with KS were taller in childhood with small testicular volume. Taken together with the results from earlier reports, our findings support the view that the KS phenotype can be clinically documented in children regardless of pubertal status. However, a recent study noted that out of all KS cases, only 21% were diagnosed before age 20 years and 6% before age 10 years.[24] Given our findings that the majority of youth with KS reported poor QOL with a significant minority at risk for depression and/or suicidality, greater awareness and improved education of pediatric primary care providers is needed in recognizing physical characteristics suggestive of KS in youth to improve rates of diagnosis and potential intervention.

Although those affected with KS have hypergonadotrophic hypogonadism, the time course of gonadal failure remains uncertain. A longitudinal study by Wikstrom et al observed normal TS development associated with the expected rise in testosterone that remained normal over the study period.[25] In contrast, Zeger et al found that 75% had testosterone levels below the 25th percentile for TS—a much higher frequency than observed in our current study or by Wikstrom et al. Findings from our study showed that even though a preponderance of boys (90.5%) had normal testosterone levels for their age, gonadotropins were elevated beginning in early puberty. An explanation for this may be found in a study that examined testicular biopsies, showing that the onset of puberty was associated with accelerated germ cell depletion.[26] The depletion of germ cells impairs the testicular response to gonadotropin stimulation, resulting in an initial elevation of FSH followed by elevation of LH. Thus, during puberty, although testosterone production appears to be normal, there is evidence that testicular fibrosis and impending testicular failure are well underway. Taken together, the evidence to date suggests that early gonadal failure involving spermatogenesis is a common finding in boys with KS, but conflicting evidence remains about whether peripubertal boys are androgen-deficient.

Studies of the neuropsychiatric and social profile of KS in children have been limited. A high prevalence of neurocognitive deficit exists in KS with estimates of intelligence in the low-normal range.[27] There is, however, wide variability in the phenotype. Tartaglia et al reported that 36% met criteria for an attention deficit hyperactivity disorder diagnosis with 25% showing increased risk for social difficulties.[28] Cordeiro et al[29] found that although participants with KS scored better than those with other genetic abnormalities, all affected groups scored in the severe range of social responsiveness compared with the Social Responsiveness Scale normative sample. Ross et al[30] showed that parental ratings on the Child Behavior Checklist fell within the normal range with no increased risk for depression on the CDI. This contrasts with the depression risk in our sample using the same measure. Alternatively, the earlier report noted 12% of the KS group had positive results for autism screening. This is consistent with parent-reported results of autism in 14.6% of the boys in our study.

Herlihy et al[31] showed poor outcomes on measures of wellbeing, body image, self-esteem, mental health, social support, and general health for men with KS compared with a general

male population. Turriff et al[32] found that 68.8% had clinically significant levels of depressive symptoms and that emotion-focused coping, perceptions of stigma, perceived negative consequences of KS, and the importance of having children in the future all correlated significantly with depressive symptoms.

The KSphI measure showed that a higher number of KS-related physical features was inversely associated with QOL and self-concept. A possible explanation for these linear relationships is that the cumulative number of physical features is a proxy measure for severity. There may be typologies or severity levels of KS that can account for variabilities in phenotype and clinical characteristics. In this sample, the KSphI showed a range of 1-10 KS characteristics demonstrating large variability. Although we observed that boys diagnosed prenatally appeared to have a milder phenotype, we must interpret this with caution as none of the boys diagnosed postnatally were in the prepubertal group. KSphI includes measures and clinical observations that are related to growth and development. As puberty progresses, there is a higher probability that boys entering a period of increasing testicular failure may be older and might exhibit signs of gynecomastia and low testicular volume.

Questions remain to what extent, if at all, androgen or androgen deficiency plays a role in neurocognitive function or psychosocial health. Our study showed a fairly low percentage of boys with androgen deficiency (9.5%) as defined by our cutpoints, and we did not observe associations between testosterone and psychosocial health. One explanation for this may be attributable to effects of the supernumerary X on brain structure and neurodevelopmental interactions with physical and social environment, although this is has yet to be studied.

Results from this study must be interpreted within the context of methodological limitations. This study was cross sectional without a comparison group. Findings are descriptive and are limited only to questions of association. Questionnaire data were obtained by boys' self-report and possibly subject to recall and social desirability bias. Although 65% of the sample was diagnosed prenatally, developmental problems and other postnatal reasons for diagnosis in the remainder of the sample may have contributed to ascertainment bias in sample selection. The principal investigator served as primary data collector and carried out unblinded assessments of clinical phenotype. This was partially mitigated by a second health care provider who conducted data collection and compared accuracy of measurements with the primary collector. The KSphI tool was developed by the investigator, and although guided by current research on KS and in consultation with pediatric endocrinologists, was not previously tested for reliability and validity. Because the KSphI is still in development, it is not ready to be used as a tool for characterizing phenotype in a clinical setting.

Pediatric primary care practitioners should increase awareness of the physical phenotype associated with KS and initiate diagnostic testing when suspicions are raised. Because a large proportion of boys with KS remain undiagnosed during childhood, many boys with undetected KS grow up feeling different and struggling with neurocognitive and social issues. For those who are diagnosed, attention to self-esteem, self-concept, depression risk, and QOL are important aspects of health care. Early neurocognitive and behavioral

interventions for children who have psychosocial vulnerabilities would seem warranted to prevent or diminish life-long issues with psychiatric and social morbidities.

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Glossary

BMI	Body mass index
CDI	Children’s Depression Inventory
CV	Coefficient of variation
DHEAS	Dehydroepiandrosterone sulfate
FSH	Follicle stimulating hormone
KS	Klinefelter syndrome
KSphI	Klinefelter syndrome phenotype index
LH	Luteinizing hormone
QOL	Quality of life
TS	Tanner stage
U/L	Upper to lower body segment ratio
WC	Waist circumference

References

1. Bojesen A, Gravholt CH. Klinefelter syndrome in clinical practice. Nat Clin Pract Urol 2007;4:192–204. [PubMed: 17415352]
2. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. J Clin Endocrinol Metab 2003;88:622–6. [PubMed: 12574191]
3. Bojesen A, Gravholt CH. Morbidity and mortality in Klinefelter syndrome (47,XXY). Acta Paediatr 2011;100:807–13. [PubMed: 21414026]
4. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn 1997;17:363–8. [PubMed: 9160389]
5. Boada R, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. Dev Disabil Res Rev 2009;15:284–94. [PubMed: 20014369]

6. Ryan S The adolescent and young adult with Klinefelter syndrome: ensuring successful transitions to adulthood. Pediatr Endocrinol Rev 2010;8(Suppl 1):169–77. [PubMed: 21217609]
7. Visootsak J, Graham JM Jr. Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. Dev Disabil Res Rev 2009;15: 328–32. [PubMed: 20014367]
8. Wikstrom AM, Dunkel L. Klinefelter syndrome. Best Pract Res Clin Endocrinol Metab 2011;25:239–50. [PubMed: 21397196]
9. Whybra C, Kampmann C, Krummenauer F, Ries M, Mengel E, Miebach E, et al. The Mainz Severity Score Index: a new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet 2004;65:299–307. [PubMed: 15025723]
10. Hall J, Froster-Iskenius U, Allanson J. Handbook of Normal Physical Measurements. Oxford, UK: Oxford Medical Publications; 1989.
11. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr 2004;145:439–44. [PubMed: 15480363]
12. CDC. BMI Percentile Calculator for Child and Teen Metric Version, http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric. Accessed October 2009-August 2010.
13. Hall JG, Froster-Iskenius UG, Allanson JE. Handbook of normal physical measurements. Oxford: Oxford University Press; 1995.
14. Zeger MP, Zinn AR, Lahlou N, Ramos P, Kowal K, Samango-Sprouse C, et al. Effect of ascertainment and genetic features on the phenotype of Klinefelter syndrome. J Pediatr 2008;152:716–22. [PubMed: 18410780]
15. Tanner JM. Growth and endocrinology of the adolescent In: Gardner L, ed. Endocrine and genetic disease in childhood. 1st ed. Philadelphia: W.B. Saunders; 1969 p. 19.
16. Schonfeld WAB, Beebe GW. Normal growth and variation in the male genitalia from birth to maturity. J Urol 1942;48:759–77.
17. Johnson RE, Murad MH. Gynecomastia: pathophysiology, evaluation, and management. Mayo Clin Proc 2009;84:1010–5. [PubMed: 19880691]
18. Baughman FA Jr. Klinefelter's syndrome and essential tremor. Lancet 1969;2:545.
19. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–12. [PubMed: 11468499]
20. Piers EV. Piers-Harris Self-Concept Scale: Manual. Los Angeles: Western Psychological Services; 1984.
21. Coopersmith S CSEI Sampler. Menlo Park (CA): Mindgarden, Inc; 2002 p. 1–38.
22. Kovacs M Rating scales to assess depression in school-age children. Acta Paedopsychiatr 1980;46:305–15.
23. Aksglaede L, Skakkebaek NE, Almstrup K, Juul A. Clinical and biological parameters in 166 boys, adolescents and adults with nonmosaic Klinefelter syndrome: a Copenhagen experience. Acta Paediatr 2011;100: 793–806. [PubMed: 21362037]
24. Tincani BJ, Mascagni BR, Pinto RD, Guaragna-Filho G, Castro CC, Sewaybricker LE, et al. Klinefelter syndrome: an unusual diagnosis in pediatric patients. J Pediatr (Rio J) 2012;88:323–7. [PubMed: 22915094]
25. Wikstrom AM, Dunkel L, Wickman S, Norjavaara E, Ankarberg-Lindgren C, Raivio T. Are adolescent boys with Klinefelter syndrome androgen deficient? A longitudinal study of Finnish 47,XXY boys. Pediatr Res 2006;59:854–9. [PubMed: 16641204]
26. Wikstrom AM, Raivio T, Hadziselimovic F, Wikstrom S, Tuuri T, Dunkel L. Klinefelter syndrome in adolescence: onset of puberty is associated with accelerated germ cell depletion. J Clin Endocrinol Metab 2004;89:2263–70. [PubMed: 15126551]
27. Rovet J, Netley C, Keenan M, Bailey J, Stewart D. The psychoeducational profile of boys with Klinefelter syndrome. J Learn Disabil 1996;29:180–96. [PubMed: 8820203]

28. Tartaglia N, Cordeiro L, Howell S, Wilson R, Janusz J. The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). Pediatr Endocrinol Rev 2010;8(Suppl 1): 151–9. [PubMed: 21217607]

29. Cordeiro L, Tartaglia N, Roeltgen D, Ross J. Social deficits in male children and adolescents with sex chromosome aneuploidy: a comparison of XXY, XYY, and XXYY syndromes. Res Dev Disabil 2012;33:1254–63. [PubMed: 22502852]

30. Ross JL, Roeltgen DP, Kushner H, Zinn AR, Reiss A, Bardsley MZ, et al. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. Pediatrics 2012;129:769–78. [PubMed: 22412026]

31. Herlihy AS, McLachlan RI, Gillam L, Cock ML, Collins V, Halliday JL. The psychosocial impact of Klinefelter syndrome and factors influencing quality of life. Genet Med 2011;13:63242.

32. Turriff A, Levy HP, Biesecker B. Prevalence and psychosocial correlates of depressive symptoms among adolescents and adults with Klinefelter syndrome. Genet Med 2011;13:966–72. [PubMed: 21799429]

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Table I.

Characteristics of the sample

Characteristics	Total, N = 43	Prepubertal, N = 16	Pubertal, N = 27	*P* value
Child's age (y) *	12.5 ± 3.1 (8-18)	9.5 ± 1.2 (8-12)	14.3 ± 2.4 (11-18)	**.01** †
Boys <10 y = 7 (16%)				
Karyotype, N (%)				.62‡
47,XXY nonmosaic	39 (90)	14 (87)	25 (92.6)	
46,XY/47,XXY mosaic	4 (9.3)	2 (12.5)	2 (7.4)	
Race, N (%)				1.0‡
Caucasian	37 (86.0)	14 (87.5)	23 (85.2)	
Non-Caucasian	6 (14)	2 (12.5)	4 (14.8)	
Diagnosis timing, N (%)				**<.001**‡
Prenatal	28 (65.1)	16 (100)	12 (44.4)	
Postnatal	15 (34.9)	0	15 (55.6)	
History of testosterone therapy, N (%)	22 (51.1)	5 (31.3)	17 (62.9)	.06§
History of learning and behavior problems, N (%)				
Learning disabilities	30 (69.8)	7 (43.7)	23 (85.2)	**.01**‡
Speech and language difficulties	29 (67.4)	9 (56.3)	20 (74.1)	.32§
Social interaction problems	27 (62.8)	7 (43.8)	20 (74.1)	.06§
Attention deficit hyperactivity	16 (37.2)	4 (25)	12 (44.4)	.33§
Psychiatric diagnosis	9 (20.9)	0	9 (33.3)	**.02**‡
Autism spectrum disorder	6 (14.6)	1 (6.3)	5 (18.5)	.39§

Significance >.05 shown in bold.

*Presented as mean ± SD (range).

†*t*-Test.

‡Fisher exact test.

§χ^2 test.

Table II.

KSphI criteria by pubertal group

Physical characteristic	KSphI criteria		Presence of the characteristic: Total sample, N = 43, n (%)	Prepubertal, N = 16, n (%)	Pubertal, N = 27, n (%)	*P* value*
Tall stature	0 = <90th percentile	1 = ≥90th percentile	16 (37.2)	6 (37.5)	10 (37.0)	1.0
Eunuchoid: upper to lower	0 = non-eunuchoid stature	1 = eunuchoid stature	22 (51.2)	8 (50.0)	14 (51.9)	1.0
height ratio	(ratio ≥0.95)	(ratio ≤0.94)				
Arm span	0 = ≤4.9 cm of height	1 = (exceeds height by 5 cm)	10 (23.3)	2 (12.5)	8 (29.6)	.28
WC	0 = <90th percentile	1 = ≥90th percentile	11 (25.8)	2 (12.5)	9 (33.3)	.17
BMI	0 = ≤85th percentile	1 = >85th percentile	19 (44.2)	4 (25.0)	15 (55.6)	.06
Testicular volume by TS†	0 = normal volume TS I: 2 mL TS II: 3 mL TS III: 10 mL TS IV: 20 mL TS V: 29 mL	1 = abnormal volume TS I: <2 mL TS II: <3 mL TS III: <10 mL TS IV: <20 mL TS V: <29 mL	30 (69.8)	8 (50.0)	22 (81.5)	**.04**
Phallic length/genital	0 = normal range	1 = short (minus 1 SD)	16 (37.2)	7 (43.8)	9 (33.3)	.53
abnormalities for age		8-12 y ≤4.9 cm 13 y ≤6.1 cm 14 y ≤6.6 cm 15 y ≤9.1 cm 16 Adult ≤10.8 cm				
Gynecomastia	0 = not present	1 = present	5 (11.6)	0	5 (18.5)	.14
Skeletal abnormalities	0 = not present	1 = present	4 (9.3)	0	4 (14.8)	.28
High-arched palate	0 = not present	1 = present	18 (41.9)	3 (18.8)	15 (55.6)	**.03**
Clinodactyly	0 = not present	1 = present	23 (53.5)	8 (50.0)	15 (55.6)	.76
Hand tremor	0 = not present	1 = present	15 (34.9)	4 (25.0)	11 (40.7)	.34
Hypertelorism	0 = not present	1 = present	0	0	0	N/A
Mean KSphI ± SD			5.1 ± 3.1	4.2 ± 0.98	5.6 ± 2.1	**.01**

N/A, not applicable.

*Fisher exact test. Significance <.05 shown in boldface.

†TS determined by distribution of pubic hair.

Table III.

Frequencies of abnormal reproductive hormone levels

Abnormal hormone findings according to TS			Total, N = 42*, frequency (%)	Prepubertal, N = 15*, frequency (%)	Pubertal, N = 27, frequency (%)	*P* value†
Mean age in y (range)			12.6 ± 1.3 (8-18)	9.5 ± 1.3 (8-12)	14.3 ± 2.4 (11-18)	<.0001
Testosterone ng/dL‡ (below or in the lowest quartile for TS)						
Age	TS	Range	4 (9.5)	0	4 (14.8)	.54
<9.8	1	<3-10				
9.8-14.5	2	18-150				
10.7-15.4	3	100-320				
11.8-16.2	4	200-620				
12.8-17.3	5	350-970				
FSH mlU/mL (above)						
Age	TS	Range	18 (42.9)	0	18 (66.7)	**<.001**
<9.8	1	0.26-3.0				
9.8-14.5	2	1.8-3.2				
10.7-15.4	3	1.2-5.8				
11.8-16.2	4	2.0-9.2				
12.8-17.3	5	2.6-11.0				
LH mlU/mL (above)						
Age	TS	Range	21 (50.0)	5 (33.3)	16 (59.3)	.19
<9.8	1	0.02-0.3				
9.8-14.5	2	0.2-4.9				
10.7-15.4	3	0.2-5.0				
11.8-16.2	4-5	0.4-7.0				
Estradiol (above)						
Age	TS	Range	3 (7.1)	0 (0)	3 (11.1)	.54
<9.8	1	5.0-11				
9.8-14.5	2	5.0-16				
10.7-15.4	3	5.0-25				
11.8-16.2	4-5	10-36				

Abnormal hormone findings according to TS			Total, N = 42*, frequency (%)	Prepubertal, N = 15*, frequency (%)	Pubertal, N = 27, frequency (%)	*P* value†
Sex hormone-binding globulin nmol/L (below)						
Age	TS	Range	5 (11.9)	0	5 (18.5)	.14
<9.8	1	72-220				
9.8-14.5	2-5	16-100				
DHEAS mg/dL (below)						
Age	TS	Range	16 (38.1)	1 (6.7)	15 (55.6)	**.002**
<9.8	1	13-83				
9.8-14.5	2	42-109				
10.7-15.4	3	48-200				
11.8-16.2	4	102-385				
12.8-17.3	5	120-370				

The lowest quartile was calculated as the midpoint between the lowest assay level and the median. All reproductive biomarker normal standard values for pediatric age and TS ranges by Esoterix Labs (Calabasas, California, 2010).

*One subject removed from analysis due to missing data.

†Fisher exact test. Statistically significant values are shown in boldface.

≠Low testosterone was defined as values below the range of normal for, including those within the lowest quartile of normal range for age.

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Table IV.

Subjects with adverse psychosocial health scores

Psychosocial health	Total, N = 43, frequency (%)	Prepubertal, N = 16, frequency (%)	Pubertal, N = 27, frequency (%)	P value*
QOL				
Total score	29 (67.4)	9 (56.3)	20 (74.1)	.32
Physical	26 (60.5)	9 (56.3)	17 (62.9)	.75
Psychosocial	34 (79.1)	12 (75.0)	22 (81.5)	.71
Emotional	30 (69.8)	12 (75.0)	18 (66.7)	.73
Social	25 (58.1)	8 (50.0)	17 (62.9)	.53
School	36 (83.7)	11 (68.8)	25 (92.6)	.08
Self-concept				
Total *t* score	11 (25.6)	4 (25.0)	7 (25.9)	1.0
Behavioral adjustment	8 (18.6)	3 (18.8)	5 (18.5)	1.0
Intellectual and school problems	8 (18.6)	3 (18.8)	5 (18.5)	1.0
Physical attributes	5 (11.6)	1 (6.3)	4 (14.8)	.63
Freedom from anxiety	12 (27.9)	3 (18.8)	9 (33.3)	.48
Popularity	12 (27.9)	3 (18.8)	9 (33.3)	.48
Happiness	12 (27.9)	4 (25.0)	8 (29.6)	1.0
Self esteem				
Total score	16 (37.2)	9 (56.3)	18 (66.7)	.53
Risk for depression				
Total *t* score	7 (16.3)	3 (18.6)	4 (14.8)	1.0
Negative mood	7 (16.3)	4 (25.0)	3 (11.1)	.39
Interpersonal problems	7 (16.3)	3 (18.8)	4 (14.8)	1.0
Ineffectiveness	8 (18.6)	2 (12.5)	6 (22.2)	.69
Anhedonia	11 (25.6)	3 (18.8)	8 (29.6)	.49
Negative self-esteem	10 (23.3)	3 (18.8)	7 (25.9)	.72

Cut-offs determined by published data normed for each instrument: Pediatric Quality of Life Inventory 4.0 poor QOL raw score <80, Coopersmith Self-Esteem raw score <75, poor Piers-Harris 2 Self-Concept *t* score <39, CDI *t* score ≥58.

*Fisher exact test.