Original Paper

HORMONE RESEARCH

Horm Res 2005;64:39–45
DOI: 10.1159/000087313

Received: February 1, 2005
Accepted: April 12, 2005
Published online: August 3, 2005

Early Androgen Deficiency in Infants and Young Boys with 47,XXY Klinefelter Syndrome

Judith L. Ross[a,b] Carole Samango-Sprouse[e] Najiba Lahlou[f] Karen Kowal[a,b] Frederick F. Elder[d] Andrew Zinn[c]

[a]Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa.; [b]duPont Hospital for Children, Wilmington, Del.; [c]Eugene McDermott Center for Human Growth and Development, and Department of Internal Medicine, The University of Texas Southwestern Medical School, Dallas, Tex.; [d]Department of Pathology, The University of Texas Southwestern Medical School, Dallas, Tex.; [e]The Neurodevelopment Diagnostic Center, Department of Pediatrics, The George Washington University, Washington, D.C., USA; [f]Laboratoire de Biologie Hormonale, Hôpital Saint-Vincent-de-Paul, Paris, France

Key Words
Klinefelter syndrome · Klinefelter syndrome, physical features · Karyotype 47,XXY · Early androgen deficiency · Testicular failure

Abstract
Background/Aims: Klinefelter syndrome (KS) is characterized by the karyotype 47,XXY. In this study, we evaluated the physical and testicular failure phenotypes of infants and young boys with KS. ***Methods:*** The evaluation included auxologic measurements, biologic indices of testicular function, and clinical assessment of muscle tone in 22 infants and young boys with KS, ages 1–23 months. ***Results:*** Mean length, weight, and head circumference in SDS were generally within the normal range at –0.3 ± 1.0, –0.1 ± 1.4, and 0.0 ± 1.5, respectively. Mean penile length and testicular volume SDS were –0.9 ± 0.8 and –1.1 ± 0.8, indicating significantly reduced penile and testicular size. Mean testosterone levels for the boys ≤6 and >6–23 months were 128 ± 131 (4.4 ± 4.5 nmol/l) and 9.5 ± 7.2 ng/dl (0.3 ± 0.2 nmol/l), respectively. High-arched palate was observed in 6/17 boys and clinodactyly (5th finger) was observed in 15/16 boys. Hypotonia was evaluated clinically and was noted to be present in 12/17 boys. ***Conclusion:*** The physical phenotype in infants and young boys with KS (1–23 months old) includes normal auxologic measurements and early evidence of testicular failure. Muscle tone was decreased in most of the boys. Testicular volume and penile length were diminished, indicating early androgen deficiency. The neonatal surge in testosterone was attenuated in our KS population. Thus, infants and young boys with KS have evidence of early testicular failure. The etiology of this failure and the clinical role of early androgen replacement require further study.

Introduction

Klinefelter syndrome (KS), first described in 1942 on the basis of testicular failure [1], occurs in 1/600–1,000 males [2–6] and is characterized by the abnormal karyotype 47,XXY [7]. The KS phenotype ranges from testicular failure manifested by small testes and penis early in infancy or childhood [8–15], to mild androgen deficiency with azoospermia in adulthood [16]. Skeletal anomalies

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–0163/05/0641–0039$22.00/0

Accessible online at:
www.karger.com/hre

Judith L. Ross, MD
Department of Pediatrics, Thomas Jefferson University
1025 Walnut Street
Philadelphia, PA 19107 (USA)
Tel. +1 215 955 1648, Fax +1 215 955 1744, E-Mail judith.ross@mail.tju.edu

associated with KS include osteoporosis, scoliosis, clinodactyly, and pectus excavatum. Motor function deficits including decreased muscle tone and decreased motor activity have also been reported in boys with KS [17, 18].

Growth of the penis in utero and during childhood represents a bioassay for the levels of endogenous testosterone as well as androgen receptor responsiveness. A burst of testosterone synthesis in the last trimester of pregnancy stimulates penile growth in the normal fetal male and, if diminished in KS males, may result in reduced penile size at birth [19–21]. KS infants also may lack the normal infant male postnatal surge in testosterone that peaks at 2–4 months of age [19–21]. Poor penile growth in early childhood implies early testosterone deficiency.

Until recently, the diagnosis of KS was rarely made in childhood, but typically occurred in adolescence on the basis of pubertal failure. According to a recent Danish study, only one fourth of males with KS within the population were diagnosed in childhood [5]. Thus, ascertainment bias could influence perception of the KS phenotype, particularly in terms of testicular function. More recently, increasing numbers of boys with KS are detected through routine antenatal testing. Examination of this larger and younger population permits prospective evaluation of the physical phenotype in KS, including auxologic measurements, biologic indices of testicular function, and clinical assessment of dysmorphic features and muscle tone. Our results indicate that testicular failure is evident in infants and young boys with KS, consistent with reduced testicular androgen production in infancy and early childhood.

Methods

Subjects

Subjects were generally referred in infancy ($\leq$ 12 months of age) after prenatal diagnosis of KS. All had postnatal karyotypes confirming the diagnosis of KS.

The study was approved by the Human Studies Committee at Thomas Jefferson University and UT Southwestern Medical School. Informed consent/assent was obtained in 15/22 cases. For 7/22 cases, a retrospective chart review was performed and a waiver was obtained from the Thomas Jefferson Human Studies Committee for including results of the evaluation that occurred as part of standard medical evaluation in pediatric endocrinology clinic (J.L.R.).

Physical Features

Anthropometric Measurements. The clinical assessment included measurement of supine length, weight, and head circumference. In order to standardize measurements, all values were converted to SD scores, using normative, age- and gender-specific norms [22–24]. Target height SD scores were calculated for subjects from sex-adjusted mid-parental height obtained from the National Center for Health Statistics growth curve data [25].

Genitalia. We measured penile length and testicular size. Standards are available for penile growth and testicular size in childhood [22]. Testicular size was assessed with the Prader orchidometer and the measured volume was converted to SDS [26]. Values tend to cluster around the smallest bead volume of 1 ml, but may reflect variation of 0.5–1.5 ml. All measurements of testicular volume were performed by one physician (J.L.R.).

Testicular Function. Serum testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were measured by commercial assays (Esoterix Endocrinology) or as previously reported [19].

Muscle Tone. Muscle tone was evaluated clinically as normal, mildly decreased or severely decreased by one experienced clinician (J.L.R.), assessing resistance to passive movement at the elbow and knee. The degree of head lag in the infants <6 months of age was evaluated. Standing posture tone was evaluated clinically in children able to bear weight on the lower extremities by assessing the degree of pes planus and pronation of the foot.

Statistics

All results are presented as mean ± SD. Statistical comparisons included Pearson correlations and t-test comparisons. Results were considered to be statistically significant at $p < 0.05$.

Results

We studied 22 boys with KS, ages 1–23 months (mean 8.4 ± 7.2). The group included one set of monozygotic twins (boys 25 and 26). Twenty were Caucasian and 2 were African-American. Nineteen had been diagnosed prenatally. Of these 19, 17 were diagnosed by routine screening for advanced maternal age, and 2 (twins) were diagnosed because of fetal ultrasound findings including question of heart disease and choroid plexus cysts. Neither suspected finding was confirmed after birth. Of the 3 KS infants diagnosed postnatally, 1 was diagnosed on the basis of small genitalia, 1 was diagnosed because of developmental concerns, and the other was diagnosed for failure to thrive. Nineteen had a nonmosaic 47,XXY karyotype, and 3 had mosaic 46,XY/47,XXY karyotypes. One of 22 boys had received a short course (<3 months) of treatment with testosterone 12 months prior to the evaluation.

Physical Measurements (table 1)

Mean length, weight and head circumference in SDS were generally within the normal range at –0.3 ± 1.0, –0.1 ± 1.4, and 0.0 ± 1.5, respectively. The infants and young boys with KS did not show evidence of unusual tall stature or obesity. In addition, the children were not un-

Table 1. Auxologic results in KS boys

Patient	Age months	Height SDS	Weight SDS	HC SDS	Penile length, cm	Penile length, SDS	Testicular volume, cm^3	Testicular volume, SDS	Birt weight, SDS	Birth length, SDS
5	1.5	1.11	1.06	0.84	3.3	–0.69	1	–1.52	0.816	1.273
32	1	–1.88	–0.27	–0.72	3.5	–0.87	1	–1.52	–0.474	0.306
33	1.5	0.07	–0.72	–0.78	2.9	–1.75	1	–1.52	–0.222	0.306
3	2	–0.58	0.17	–0.93	4	1.00	1	–1.52	–0.222	–0.173
4	2.5	–0.41	0.51	0.51	3.3	–0.75	1	–1.52	0.364	0.788
23	2.3	–0.96	–0.1	–0.43	3.2	–1	1	–1.52	–1.643	–1.120
43	2.3	–0.25	0.33	–1.05	2.9	–1.2	1.8	0.38	–0.324	–0.173
44	2.8	0.12	0.29	–0.74	4.7	1	1	–1.52	0.586	0.306
46	2	–0.06	1.39	0.93	2.4	–1.77	1	–1.52	1.051	1.273
22	3	0.17	0.68	1.78	2.8	–2	1	–1.52	0.308	0.788
28	5	1.21	–0.02	–0.15	3.5	–0.25	1	–1.52	–0.523	0.547
36	5.8	–1.37	–0.79	–1.99	2.3	–1.89	1	–1.52	–1.643	0.382
21	9	–0.23	–0.51	–0.93	2.5	–1.65	1	–1.52	0.474	0.788
7	8.5	0.98	1.55	2.23	3.5	–0.45	1	–1.52	1.109	2.253
48	12.5	–0.39	0.41	2.28	2.5	–1.83	1	–1.52	–0.222	0.306
19	13.8	–2.22	–3.73	–1.48	3.5	–0.87	1	–1.52	–1.178	–0.411
6	14.8	0.66	–0.01	0.82	4.2	–0.19	1	–1.52	0.531	0.788
24	17.3	–2.60	–3.92	–3.95	3	–1.35	1	–1.52	–0.813	–0.173
29	16.8	–0.02	–0.59	–0.51	4	–0.38	1	–1.52	0.199	0.306
35	17.8	1.20	0.33	0.26	3	–1.35	1.5	–0.33	0.474	1.517
25	23	–0.29	1.09	1.71	4.4	–0.53	2	0.86	–1.348	0.306
26	23	–0.17	0.63	1.36	4	–0.96	2	0.86	–1.519	–0.173

usually tall, relative to parents. The mean difference in the children's height SDS minus the mid-parental height SDS was –0.5 ± 1.4. Head circumference SDS was similar to length SDS. Mean birth weight and birth length SDS were within the normal range at –0.2 ± 0.9 and 0.5 ± 0.7, respectively.

Mean penile length and testicular volume SDS were –0.9 ± 0.8 and –1.1 ± 0.8, respectively (fig. 1). Thus, penis and testicular size were significantly reduced ($p < 0.001$) in this population. Only 1 patient had cryptorchidism in infancy.

Measures of Testicular Function (table 2)

Mean LH, FSH (mIU/ml, IU/l), and testosterone (ng/dl, nmol/l) levels were analyzed separately for boys <6 months to assess the surge of testosterone that occurs in infant boys and for boys aged >6–23 months (fig. 2). Mean testosterone levels for the boys <6 and >6–23 months were 128 ± 131 ng/dl (4.4 ± 4.5 nmol/l) and 9.5 ± 7.2, ng/dl (0.3 ± 0.2 nmol/l) respectively. The upper and lower limit for the testosterone surge in the first 6 months of life are about 580 and 120 ng/dl (20.0 and 4.2 nmol/l), respectively [19]. Thus, the levels measured

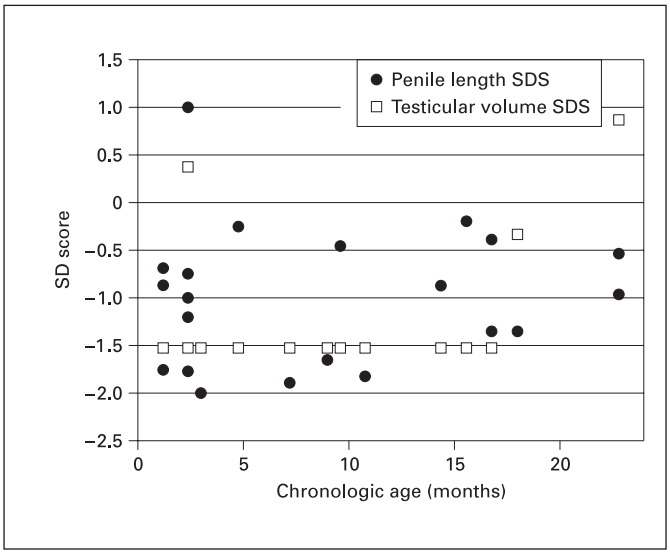

Fig. 1. Penile length SDS and testicular volume SDS versus chronologic age in KS boys.

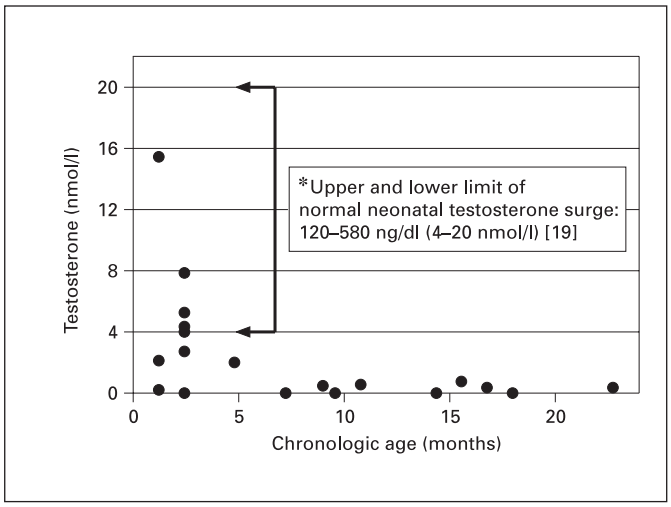

Fig. 2. Testosterone levels versus chronologic age in KS boys.

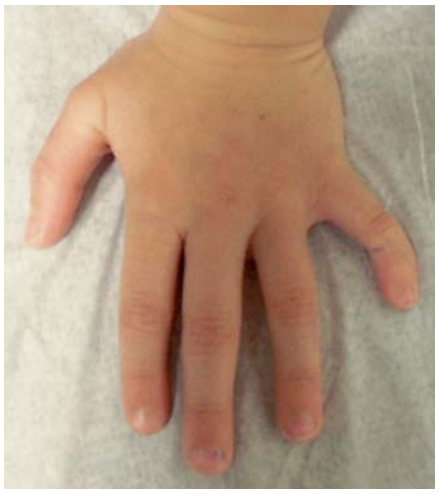

Fig. 3. Clinodactyly in KS baby.

in 11/12 of the KS subjects <6 months old were distributed in the lower range for this surge (fig. 2). Mean LH and FSH levels for the boys <6 and >6–23 months were 1.6 ± 1.5, 0.8 ± 0.8 and 0.3 ± 0.2, 0.5 ± 0.2 MIU/ml (IU/l), respectively. Thus, gonadotropin levels were in the normal range. Estradiol levels were measured in a subset of the boys and the levels were generally low (<10 pg/ml; 36.7 pmol/l).

Table 2. Hormone assay results in KS boys

Patient	Age months	LH mIU/ml (IU/l)	FSH mIU/ml (IU/l)	Total testosterone ng/dl*	Total testosterone nmol/l
5	1.5	0.5	0.7	7	0.24
32	1	1.6	2	62	2.14
33	1.5	5.7	2.4	447	15.47
3	2	0.5	0.7	152	5.26
4	2.5	2.4	0.7	79	2.73
23	2.3	1.5	2.3	116	4.01
43	2.3	1.9	1.5	228	7.89
44	2.8	1.3	1.7	127	4.39
46	2	1.5	0.6	2	0.06
22	3	0.3	0.3	not done	not done
28	5	0.8	1.6	58	2.01
36	5.8	0.7	1.0	2	0.07
21	9	0.2	0.5	15	0.52
7	8.5	0.5	0.7	2	0.06
48	12.5	0.3	0.3	17	0.59
19	13.8	0.1	0.6	2	0.06
6	14.8	0.3	0.3	23	0.80
24	17.3	0.3	0.3	12	0.42
29	16.8	0.1	0.7	10	0.35
35	17.8	0.01	0.3	2	0.06
25	23	0.3	0.4	10	0.35
26	23	0.3	0.6	10	0.35

* To convert from ng/dl to nmol/l, multiply by 0.0346.

Other Physical Features Associated with KS

We assessed boys for other mild dysmorphic features described in KS including high-arched palate, 5th finger clinodactyly and hypotonia. High-arched palate was observed in 6/17 boys. Clinodactyly of the 5th finger was observed in 15/16 boys (fig. 3). None had pectus excavatum.

Muscle tone was assessed in 15/22 infants and young boys. Tone was normal in 4, mildly decreased in 9, and severely decreased in 2 subjects. None of the boys with decreased tone received prior treatment with testosterone. Of the 4 boys with normal tone, 1 had received treatment with testosterone for 2 months, 1 year earlier, in the newborn period. There was no significant correlation between degree of hypotonia and level of testosterone ($r = 0.02$, $p = 0.96$) or penile length z score ($r = 0.39$, $p = 0.11$). The effect of mosaicism on tone could not be evaluated because no children with mosaic karyotypes were evaluated for tone. Six of the 22 subjects were receiving physical therapy at the time of the evaluation.

No boys had evidence of gynecomastia, pubic hair, axillary hair, or varicose veins.

Discussion

We evaluated a population of infants and young boys with KS, nearly all ascertained through routine antenatal screening, thus minimizing ascertainment bias. The physical phenotype includes normal auxologic measurements and early evidence of testicular failure. Birth weight and length of KS infants has been reported as normal [27] or low [10, 28]. In our population of KS infants, mean length, weight, and head circumference SD scores were within the normal range, as were mean birth length and weight SD scores. The tall stature previously reported in older boys and adults [6, 29] was not observed in this population of infants and young boys with KS, in agreement with Stewart et al. [8] who observed that the mean height SD score in a population of boys with KS followed longitudinally became positive during adolescence. The childhood onset tall stature in KS is likely related to the presence of three copies of the X and Y chromosome height-determining gene, SHOX, as well as delayed epiphyseal fusion on the basis of decreased testosterone levels [30].

In addition, previous measurement of KS infants revealed relatively small head circumference SD scores compared to height SD scores [31–34]. According to our results, head circumference SDS was similar to length SDS, which did not confirm previous reports of microcephaly. Findings of normal head circumference in this study may relate to the prenatal ascertainment.

The most common mild dysmorphic feature in KS was clinodactyly or curving of the 5th finger. This nonspecific finding does not have any clinical or motor significance but was noted relatively commonly in this study. Clinodactyly was also previously found in 4/8 KS boys aged 11–16 years [35].

Our finding of decreased motor tone in infancy and early childhood is consistent with previous reports of KS infants being more likely to have decreased muscle tone, psychomotor delay, decreased motor activity, and atypical movement patterns [18, 36]. This decrease in tone is most likely related to delayed motor praxis and delayed motor milestones as well as decreased muscle strength [17]. For example, KS boys have delayed onset of walking (mean age of 18 months, normal mean age is approximately 12 months) [17, 37]. Functional and static neuroimaging studies of KS have shown altered left hemisphere function [38] and reduced overall brain and amygdala volumes [36, 39], which may be related to psychopathology or behavioral dysfunction. The relationship between muscle tonus, androgen function and brain structure has not been studied but needs consideration [36].

We examined testicular function in our KS cohort and found evidence of impaired Leydig cell function and decreased levels of testosterone in the first 6 months of life, consistent with early testicular failure. Mean penile length and testicular size, biologic indices of testicular function, were also reduced in infants and young boys with KS, consistent with previous reports [12, 34, 40, 41]. Poor penile growth in early childhood implies early testosterone deficiency.

Testosterone levels in normal male infants rise, starting the first month of life, peak at 2–4 months, and decline to prepubertal levels by age 6 months [19, 42, 43]. This neonatal surge in testosterone was recently found to be attenuated in our population as well as in a similar population of KS infants [19]. Moreover, serum testosterone levels in a small number of KS infants were decreased [14, 40, 43] or low normal [44] and remained low in childhood and adulthood. Testicular failure and reduced testosterone levels with impaired Leydig cell function occurs in nearly all KS adolescent and adults [45, 46] and is accompanied by increased (castrate) levels of gonadotropins.

Gonadotropin levels (LH, FSH) in our sample were normal, similar to levels recently reported [19], and were not elevated in the castrate range as in girls with gonadal dysgenesis [47]. This finding early in KS perhaps reflects initial intact Sertoli cell function in infancy. Plasma LH concentrations rise until the 3rd month of life and decline to prepubertal levels by the 12 months of age [42]. Levels of inhibin B and anti-mullerian hormone were reported as normal [19], suggesting intact early Sertoli cell function in KS infants and young boys. Serum gonadotropins and inhibin B levels became abnormal during mid-puberty, indicating that these particular measurements are not markers of the early testicular failure [48].

The development of germ cells in KS has been examined. Testicular biopsies of KS infants demonstrate decreased or absent germ cells [49, 50] and abnormal seminiferous tubules, starting in infancy [50] and evident in adolescence [34]. Prepubertal and early pubertal KS boys lacked meiotic germ cells and germ cells were depleted or absent [40]. Although mouse studies have called attention to meiotic germ cell loss triggered by an unpaired sex chromosome [51], the evidence from humans indicates that germ cell deficiency in KS begins well before the onset of meiosis, implying that abnormal X chromosome gene dosage also contributes to germ cell loss. Indeed, the X chromosome is highly enriched for genes expressed in male germ cells compared to autosomes [52].

In summary, testicular failure was evident early in life in infants and young boys with KS, aged 1–23 months. Both mean testicular volume and penile length SDS were diminished. Testosterone levels were also low and the typical neonatal surge in testosterone was attenuated, indicating testosterone deficiency in infancy. Thus, infants and young boys with KS have phenotypic evidence of early testosterone deficiency. The etiology of this failure and the clinical implications of early androgen replacement merit further study.

Acknowledgement

Supported in part by Institut de Recherche Endocrinienne et Métabolique (Paris, France).

References

1 Klinefelter H, Reifenstein EC, Albright F: Syndrome characterized by gynecomastia, aspermatogenesis, without A-Leydigism and increased excretion of follicle stimulating hormone. J Clin Endocrinol Metab 1942;2:615–627.

2 Jacobs PA, Hassold TJ, Whittington E, Butler G, Collyer S, Keston M, Lee M: Klinefelter's syndrome: An analysis of the origin of the additional sex chromosome using molecular probes. Ann Hum Genet 1988;52:93–109.

3 MacLean J, Harnden DG, CourtBrown WM: Abnormalities of sex chromosome constitution in newborn babies. Lancet 1961;2:7199, 7406.

4 Nielsen J, Wohlert M: Sex chromosome abnormalities found among 34,910 newborn children: Results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser 1990;26:209–223.

5 Bojesen A, Juul S, Gravholt CH: Prenatal and postnatal prevalence of Klinefelter syndrome: A national registry study. J Clin Endocrinol Metab 2003;88:622–626.

6 Visootsak J, Aylstock M, Graham JM Jr: Klinefelter syndrome and its variants: An update and review for the primary pediatrician. Clin Pediatr (Phila) 2001;40:639–651.

7 Bradbury J, Bunge RG, Boccabella RA: Chromatin test in Klinefelter's syndrome. J Clin Endocrinol Metab 1956;16:689.

8 Stewart DA, Bailey JD, Netley CT, Park E: Growth, development, and behavioral outcome from mid-adolescence to adulthood in subjects with chromosome aneuploidy: The Toronto Study. Birth Defects Orig Artic Ser 1990;26:131–188.

9 Stewart DA, Netley CT, Park E: Summary of clinical findings of children with 47,XXY, 47,XYY, and 47,XXX karyotypes. Birth Defects Orig Artic Ser 1982;18:1–5.

10 Stewart DA, Netley CT, Bailey JD, Haka-Ikse K, Platt J, Holland W, Cripps M: Growth and development of children with X and Y chromosome aneuploidy: A prospective study. Birth Defects Orig Artic Ser 1979;15:75–114.

11 Stewart DA, Bailey JD, Netley CT, Rovet J, Park E, Cripps M, Curtis JA: Growth and development of children with X and Y chromosome aneuploidy from infancy to pubertal age: The Toronto study. Birth Defects Orig Artic Ser 1982;18:99–154.

12 Laron Z, Hochman IH: Small testes in prepubetal boys with Klinefelter's syndrome. J Clin Endocrinol Metab 1971;32:671–672.

13 Salbenblatt JA, Bender BG, Puck MH, Robinson A, Faiman C, Winter JS: Pituitary-gonadal function in Klinefelter syndrome before and during puberty. Pediatr Res 1985;19:82–86.

14 Ratcliffe SG: The sexual development of boys with the chromosome constitution 47,XXY (Klinefelter's syndrome). Clin Endocrinol Metab 1982;11:703–716.

15 Hatch TR, Moore RJ: Klinefelter syndrome in identical twins. Urology 1985;26:396–397.

16 Kamischke A, Baumgardt A, Horst J, Nieschlag E: Clinical and diagnostic features of patients with suspected Klinefelter syndrome. J Androl 2003;24:41–48.

17 Salbenblatt JA, Meyers DC, Bender BG, Linden MG, Robinson A: Gross and fine motor development in 47,XXY and 47,XYY males. Pediatrics 1987;80:240–244.

18 Samango-Sprouse C: Mental development in polysomy X Klinefelter syndrome (47,XXY; 48,XXXY): effects of incomplete X inactivation. Semin Reprod Med 2001;19:193–202.

19 Lahlou N, Fennoy I, Carel JC, Roger M: Inhibin B and anti-mullerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. J Clin Endocrinol Metab 2004;89:1864–1868.

20 Forest MG, Sizonenko PC, Cathiard AM, Bertrand J: Hypophyso-gonadal function in humans during the first year of life. 1. Evidence for testicular activity in early infancy. J Clin Invest 1974;53:819–828.

21 Main KM, Schmidt IM, Skakkebaek NE: A possible role for reproductive hormones in newborn boys: Progressive hypogonadism without the postnatal testosterone peak. J Clin Endocrinol Metab 2000;85:4905–4907.

22 Jones DL: Smith's Recognizable Patterns of Human Malformation, ed 5. Philadelphia, Saunders, 1997.

23 Hall JG, Froster-Iskenius, Ursula G, Allanson JE: Handbook of Normal Physical Measurements. Oxford, Oxford University Press, 1995.

24 McKusick VA: Heritable Disorders of Connective Tissue. St Louis, Mosby, 1972.

25 Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM: Physical growth: National Center for Health Statistics percentiles. Am J Clin Nutr 1979;32:607–629.

26 Zachmann M, Prader A, Kind HP, Hafliger H, Budliger H: Testicular volume during adolescence. Cross-sectional and longitudinal studies. Helv Paediatr Acta 1974;29:61–72.

27 Robinson A, Puck M, Pennington B, Borelli J, Hudson M: Abnormalities of the sex chromosomes: A prospective study on randomly identified newborns. Birth Defects Orig Artic Ser 1979;15:203–241.

28 Ratcliffe SG, Axworthy D, Ginsborg A: The Edinburgh study of growth and development in children with sex chromosome abnormalities. Birth Defects Orig Artic Ser 1979;15:243–260.

29 Ratcliffe SG, Butler GE, Jones M: Edinburgh study of growth and development of children with sex chromosome abnormalities. IV. Birth Defects Orig Artic Ser 1990;26:1–44.

30 Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, Muroya K, Binder G, Kirsch S, Winkelmann M, Nordsiek G, Heinrich U, Breuning MH, Ranke MB, Rosenthal A, Ogata T, Rappold GA: Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 1997;16:54–63.

31 Ratcliffe SG, Tierney I, Nshaho J, Smith L, Springbett A, Callan S: The Edinburgh study of growth and development of children with sex chromosome abnormalities. Birth Defects Orig Artic Ser 1982;18:41–60.

32 Ratcliffe SG, Murray L, Teague P: Edinburgh study of growth and development of children with sex chromosome abnormalities. III. Birth Defects Orig Artic Ser 1986;22:73–118.

33 Ratcliffe SG, Masera N, Pan H, McKie M: Head circumference and IQ of children with sex chromosome abnormalities. Dev Med Child Neurol 1994;36:533–544.

34 Caldwell PD, Smith DW: The XXY (Klinefelter's) syndrome in childhood: Detection and treatment. J Pediatr 1972;80:250–258.

35 Salbenblatt JA, Bender BG, Puck MH, Robinson A, Webber ML: Development of eight pubertal males with 47,XXY karyotype. Clin Genet 1981;20:141–146.

36 Simpson JL, De La Cruz F, Swerdloff RS, Samango-Sprouse C, Skakkebaek NE, Graham JM Jr, Hassold T, Aylstock M, Meyer-Bahlburg HF, Willard HF, Hall JG, Salameh W, Boone K, Staessen C, Geschwind D, Giedd J, Dobs AS, Rogol A, Brinton B, Paulsen CA: Klinefelter syndrome: Expanding the phenotype and identifying new research directions. Genet Med 2003;5:460–468.
37 Robinson A, Bender BG, Linden MG: Summary of clinical findings in children and young adults with sex chromosome anomalies. Birth Defects Orig Artic Ser 1990;26:225–228.
38 Itti E, Gaw Gonzalo IT, Boone KB, Geschwind DH, Berman N, Pawlikowska-Haddal A, Itti L, Mishkin FS, Swerdloff RS: Functional neuroimaging provides evidence of anomalous cerebral laterality in adults with Klinefelter's syndrome. Ann Neurol 2003;54:669–673.
39 Warwick MM, Doody GA, Lawrie SM, Kestelman JN, Best JJ, Johnstone EC: Volumetric magnetic resonance imaging study of the brain in subjects with sex chromosome aneuploidies. J Neurol Neurosurg Psychiatry 1999;66:628–632.
40 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;89:2263–2270.
41 Ratcliffe SG, Bancroft J, Axworthy D, McLaren W: Klinefelter's syndrome in adolescence. Arch Dis Child 1982;57:6–12.
42 Forest MG, Cathiard AM, Bertrand JA: Evidence of testicular activity in early infancy. J Clin Endocrinol Metab 1973;37:148–151.
43 Topper E, Dickerman Z, Prager-Lewin R, Kaufman H, Maimon Z, Laron Z: Puberty in 24 patients with Klinefelter syndrome. Eur J Pediatr 1982;139:8–12.
44 Sorensen K, Nielsen J, Wohlert M, Bennett P, Johnsen SG: Serum testosterone of boys with karyotype 47,XXY (Klinefelter's syndrome) at birth. Lancet 1981;ii:1112–1113.
45 Smyth CM: Diagnosis and treatment of Klinefelter syndrome. Hosp Pract (Off Ed) 1999;34:111–112, 115–116, 119–120.
46 Robinson A, Bender BG, Linden MG, Salbenblatt JA: Sex chromosome aneuploidy: The Denver Prospective Study. Birth Defects Orig Artic Ser 1990;26:59–115.
47 Conte FA, Grumbach MM, Kaplan SL: A diphasic pattern of gonadotropin secretion in patients with the syndrome of gonadal dysgenesis. J Clin Endocrinol Metab 1975;40:670–674.
48 Christiansen P, Andersson AM, Skakkebaek NE: Longitudinal studies of inhibin B levels in boys and young adults with Klinefelter syndrome. J Clin Endocrinol Metab 2003;88:888–891.
49 Ferguson-Smith M: The prepubertal testicular lesion in chromatin positive Klinefelter's syndrome (primary micro-orchidism) as seen in mentally handicapped children. Lancet 1959;i:219–222.
50 Muller J, Skakkebaek NE, Ratcliffe SG: Quantified testicular histology in boys with sex chromosome abnormalities. Int J Androl 1995;18:57–62.
51 Burgoyne PS, Baker TG: Meiotic pairing and gametogenic failure. Symp Soc Exp Biol 1984;38:349–362.
52 Wang PJ, McCarrey JR, Yang F, Page DC: An abundance of X-linked genes expressed in spermatogonia. Nat Genet 2001;27:422–426.