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

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

\textsuperscript{a}Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa.; \textsuperscript{b}duPont Hospital for Children, Wilmington, Del.; \textsuperscript{e}Eugene McDermott Center for Human Growth and Development, and Department of Internal Medicine, The University of Texas Southwestern Medical School, Dallas, Tex.; \textsuperscript{d}Department of Pathology, The University of Texas Southwestern Medical School, Dallas, Tex.; \textsuperscript{f}The Neurodevelopment Diagnostic Center, Department of Pediatrics, The George Washington University, Washington, D.C., USA; \textsuperscript{1}Laboratoire de Biologie Hormonale, Hôpital Saint-Vincent-de-Paul, Paris, France


dpotonia 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.

Copyright © 2005 S. Karger AG, Basel

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 $-0.3 \pm 1.0$, $-0.1 \pm 1.4$, and $0.0 \pm 1.5$, respectively. Mean penile length and testicular volume SDS were $-0.9 \pm 0.8$ and $-1.1 \pm 0.8$, indicating significantly reduced penile and testicular size. Mean testosterone levels for the boys $\leq 6$ and $>6$–23 months were $128 \pm 131$ (4.4 $\pm$ 4.5 nmol/l) and $9.5 \pm 7.2$ ng/dl (0.3 $\pm$ 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

Key Words

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

Copyright © 2005 S. Karger AG, Basel
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 (± 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 SDS 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 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-
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 sim-
ilar 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 cryptorchid-
dism 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

---

**Table 1. Auxologic results in KS boys**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (months)</th>
<th>Height SDS</th>
<th>Weight SDS</th>
<th>HC SDS</th>
<th>Penile length, cm</th>
<th>Penile length, SDS</th>
<th>Testicular volume, cm³</th>
<th>Testicular volume, SDS</th>
<th>Birth weight, SDS</th>
<th>Birth length, SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.5</td>
<td>1.11</td>
<td>1.06</td>
<td>0.84</td>
<td>3.3</td>
<td>–0.69</td>
<td>1</td>
<td>–1.52</td>
<td>0.816</td>
<td>1.273</td>
</tr>
<tr>
<td>32</td>
<td>1</td>
<td>–1.88</td>
<td>–0.27</td>
<td>–0.72</td>
<td>3.5</td>
<td>–0.87</td>
<td>1</td>
<td>–1.52</td>
<td>–0.474</td>
<td>0.306</td>
</tr>
<tr>
<td>33</td>
<td>1.5</td>
<td>0.07</td>
<td>–0.72</td>
<td>–0.78</td>
<td>2.9</td>
<td>–1.75</td>
<td>1</td>
<td>–1.52</td>
<td>–0.222</td>
<td>0.306</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>–0.58</td>
<td>0.17</td>
<td>–0.93</td>
<td>4</td>
<td>1.00</td>
<td>1</td>
<td>–1.52</td>
<td>–0.222</td>
<td>–0.173</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>–0.41</td>
<td>0.51</td>
<td>0.51</td>
<td>3.3</td>
<td>–0.75</td>
<td>1</td>
<td>–1.52</td>
<td>0.364</td>
<td>0.788</td>
</tr>
<tr>
<td>23</td>
<td>2.3</td>
<td>–0.96</td>
<td>–0.1</td>
<td>–0.43</td>
<td>3.2</td>
<td>–1</td>
<td>1</td>
<td>–1.52</td>
<td>–1.643</td>
<td>–1.120</td>
</tr>
<tr>
<td>43</td>
<td>2.3</td>
<td>–0.25</td>
<td>0.33</td>
<td>–1.05</td>
<td>2.9</td>
<td>–1.2</td>
<td>1.8</td>
<td>0.38</td>
<td>–0.324</td>
<td>–0.173</td>
</tr>
<tr>
<td>44</td>
<td>2.8</td>
<td>0.12</td>
<td>0.29</td>
<td>–0.74</td>
<td>4.7</td>
<td>1</td>
<td>1</td>
<td>–1.52</td>
<td>0.586</td>
<td>0.306</td>
</tr>
<tr>
<td>46</td>
<td>2</td>
<td>–0.06</td>
<td>1.39</td>
<td>0.93</td>
<td>2.4</td>
<td>–1.77</td>
<td>1</td>
<td>–1.52</td>
<td>1.051</td>
<td>1.273</td>
</tr>
<tr>
<td>22</td>
<td>3</td>
<td>0.17</td>
<td>0.68</td>
<td>1.78</td>
<td>2.8</td>
<td>–2</td>
<td>1</td>
<td>–1.52</td>
<td>0.308</td>
<td>0.788</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td>1.21</td>
<td>–0.02</td>
<td>–0.15</td>
<td>3.5</td>
<td>–0.25</td>
<td>1</td>
<td>–1.52</td>
<td>–0.523</td>
<td>0.547</td>
</tr>
<tr>
<td>36</td>
<td>5.8</td>
<td>–1.37</td>
<td>–0.79</td>
<td>–1.99</td>
<td>2.3</td>
<td>–1.89</td>
<td>1</td>
<td>–1.52</td>
<td>–1.643</td>
<td>0.382</td>
</tr>
<tr>
<td>21</td>
<td>9</td>
<td>–0.23</td>
<td>–0.51</td>
<td>–0.93</td>
<td>2.5</td>
<td>–1.65</td>
<td>1</td>
<td>–1.52</td>
<td>0.474</td>
<td>0.788</td>
</tr>
<tr>
<td>7</td>
<td>8.5</td>
<td>0.98</td>
<td>1.55</td>
<td>2.23</td>
<td>3.5</td>
<td>–0.45</td>
<td>1</td>
<td>–1.52</td>
<td>1.109</td>
<td>2.253</td>
</tr>
<tr>
<td>48</td>
<td>12.5</td>
<td>–0.39</td>
<td>0.41</td>
<td>2.28</td>
<td>2.5</td>
<td>–1.83</td>
<td>1</td>
<td>–1.52</td>
<td>–0.222</td>
<td>0.306</td>
</tr>
<tr>
<td>19</td>
<td>13.8</td>
<td>–2.22</td>
<td>–3.73</td>
<td>–1.48</td>
<td>3.5</td>
<td>–0.87</td>
<td>1</td>
<td>–1.52</td>
<td>–1.178</td>
<td>–0.411</td>
</tr>
<tr>
<td>6</td>
<td>14.8</td>
<td>0.66</td>
<td>–0.01</td>
<td>0.82</td>
<td>4.2</td>
<td>–0.19</td>
<td>1</td>
<td>–1.52</td>
<td>0.531</td>
<td>0.788</td>
</tr>
<tr>
<td>24</td>
<td>17.3</td>
<td>–2.60</td>
<td>–3.92</td>
<td>–3.95</td>
<td>3</td>
<td>–1.35</td>
<td>1</td>
<td>–1.52</td>
<td>–0.813</td>
<td>–0.173</td>
</tr>
<tr>
<td>29</td>
<td>16.8</td>
<td>–0.02</td>
<td>–0.59</td>
<td>–0.51</td>
<td>4</td>
<td>–0.38</td>
<td>1</td>
<td>–1.52</td>
<td>0.199</td>
<td>0.306</td>
</tr>
<tr>
<td>35</td>
<td>17.8</td>
<td>1.20</td>
<td>0.33</td>
<td>0.26</td>
<td>3</td>
<td>–1.35</td>
<td>1.5</td>
<td>0.33</td>
<td>0.474</td>
<td>1.517</td>
</tr>
<tr>
<td>25</td>
<td>23</td>
<td>–0.29</td>
<td>1.09</td>
<td>1.71</td>
<td>4.4</td>
<td>–0.53</td>
<td>2</td>
<td>0.86</td>
<td>–1.348</td>
<td>0.306</td>
</tr>
<tr>
<td>26</td>
<td>23</td>
<td>–0.17</td>
<td>0.63</td>
<td>1.36</td>
<td>4</td>
<td>–0.96</td>
<td>2</td>
<td>0.86</td>
<td>–1.519</td>
<td>–0.173</td>
</tr>
</tbody>
</table>
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).

**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 SDSs 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**


Ross/Samango-Sprouse/Lahlou/Kowal/Elder/Zinn
Androgen Deficiency in Klinefelter Syndrome

Horm Res 2005;64:39–45


