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Clinical and hormonal status of infants with nonmosaic XXY karyotype

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Abstract

Aim—To compare our recent findings in a cohort of 77 nonmosaic XXY infants <2 years of age with clinical and biological features already reported.

Results—The majority of reported XXY neonates had normal external genitalia. Only undescended testes and/or micropenis were identified reasons for referral. Delayed ambulation and speech skills were also indications for postnatally karyotyping. All subjects from our cohort (73 prenatally detected subjects, five postnatal diagnoses) had height and weight within the normal range, and were not dysmorphic. Insulin-like-peptide-3 and testosterone secretion by Leydig cells appeared normally sensitive to luteinizing hormone. In reported studies, inhibin B levels were within normal range, anti-Mullerian hormone levels were normal or high and follicle-stimulating hormone (FSH) levels were significantly higher than control values, data consistent with a relative resistance to FSH.

Conclusion—Early detection of Klinefelter syndrome is desirable for prospectively monitoring the apparition of developmental problems and the progressive decline in the tubular function of the testis, with the hope of designing future conservative interventions before germ cell degeneration is completed.

Keywords

Infant; Inhibin B; Insulin-like peptide 3; Klinefelter; Sertoli

INTRODUCTION

Klinefelter syndrome (KS) is the most common sex chromosome disorder characterized by one or more extra X chromosomes and is one of the main causes of male infertility. According to the studies in the early 1990s (1) as well as more recent ones (2,3), KS affects about one in 600 males at birth. However, the disease is very much underdiagnosed before adulthood, because the main clinical features, tall stature, hypogonadism and gynecomastia are clinically evident only at or after puberty.

As regards infants, the disorder hardly deserves the name KS as the main clinical features of the disease described by Klinefelter in 1942 are lacking in infancy. Diagnosis is generally ascertained postnatally only in the course of careful investigations, including karyotyping, because of various nonspecific clinical abnormalities.

On the other hand, the practise of prenatal screening by cytogenetic studies in amniotic fluid from pregnancies at risk for Down syndrome, set up in the 80s–90s in some countries, has allowed prenatal diagnosis of a significant number of XXY foetuses. Although the majority of these pregnancies were legally interrupted (2), important cohorts of infants with XXY karyotype can now be investigated and monitored. Indeed early detection of the disorder is highly desirable because it may permit early identification of speech and educational problems and also may ensure prospective monitoring of gonadal function development with the hope to compensating for possible gonadal insufficiency.

The aim of this study was to present the main clinical and biological features reported in infants with nonmosaic XXY karyotype, including our recent cohort of 77 infants.

PRENATAL DIAGNOSIS: <10% OF XXY FOETUSES MIGHT BE DETECTED

In some countries, prenatal cytogenetic examination of amniotic fluid from pregnancies at risk for Down syndrome can be performed. When indicated by maternal age >38 years, it permits detecting <1% of XXY foetuses, given the percentage of pregnant women above 38 years of age relative to the number of pregnancies (4). In countries where routine prenatal screening for Down syndrome by means of the measurement of Down syndrome serum markers in the first or second trimester of pregnancy was set up, about 80% of pregnant women undergo prenatal screening. About 7% of them are found at risk for Down syndrome, and cytogenetic examination of amniotic fluid is performed (4). That would allow prenatal diagnosis of <10% of all foetuses with the XXY karyotype (5). Our recent experience is consistent with this assumption: one in 594 examined male foetuses is found with the XXY karyotype (M Roger and C Hamberger, personal unpublished data), which represents only one of 14 actual XXY foetuses, given that 594 male foetuses correspond to 1188 amniocenteses, which are 7% of all screened pregnancies. Although this is far from our wish to diagnose before puberty a maximum of number of cases, it provides an opportunity to carefully study a significant number of infants with XXY karyotype (6). In our recent cohort of infants with nonmosaic XXY karyotype originating from New York, Philadelphia and Paris (7), 68 of 73 infants were prenatally diagnosed.

CLINICAL STATUS

A very small number of XXY subjects are diagnosed during infancy. Kleczkowska et al. (8) reported 12 infants below 3 years of age, representing only 2.1% from a cohort of 569 subjects with X-chromosome polysomy. In the more recent report by Bojesen et al. (2), only 2.6 KS subjects in 100 000 males were diagnosed before the age of 5 years (to be compared with the actual prevalence of one in 600). In our recent cohort (7), only five in 77 infants (about 7% of the cohort) were postnatally diagnosed because of a clinical abnormality. This very low prevalence of early diagnosis results from the lack of very specific clinical symptoms before puberty. However, some abnormalities summarized below should draw attention and prompt physicians to look for chromosomal abnormalities. On the other hand, the selection of patients that actually become known may result in overestimation of the phenotypical features.

Somatic abnormalities: almost all XXY subjects are clinically normal at birth

Neonates with the XXY karyotype generally have height and weight within the normal range, and do not have any dysmorphic feature. In our series of 77 infants, including 73 prenatal diagnoses, mean length and weight $\pm$ SD were 50.5 ± 1.9 cm (SD score = 0.02) and 3.39 ± 0.44 kg (SD score = 0.6), respectively. None were dysmorphic (7).

At examination during infancy and childhood, height, weight and body mass index were normal (SD score = 0.6, 0.5, and 0.5, respectively) in a cohort of 35 subjects including 14 infants <3 years of age and 20 boys aged 4–15 years (9).

Dysmorphic features were the reason for referral in some reports: 9.8% of 569 males including seven of 12 infants <3 years of age, in the report by Kleczkowska et al. (8). In addition, coincidental disorders like Prader–Willi syndrome (review in Ref. 10) or Down syndrome (review in Ref. 11) have been reported which may lead to early detection of the XXY karyotype.

Genital anomalies may be a reason for referral, but are absent from the majority of XXY neonates

Most of the subjects with nonmosaic KS have male genitalia without ambiguity. Consequently, the male gender is regularly assigned to newborns and no cytogenetic investigations are performed.

Ambiguous genitalia—An abnormal development of the external genitalia has been reported in some subjects with X polysomy. Complete androgen insensitivity was reported in a few subjects with nonmosaic XXY karyotype. Cases of true hermaphrodites have also been reported including two cases with nonmosaic XXY karyotype. However, most of subjects with ambiguous genitalia had the mosaic karyotype 46XX/47XXY (review in Ref. 12).

Undescended testes—The most frequently reported abnormality of external genitalia is undescended testes: five of seven cases of abnormal genitalia reported by Lee et al. (12), eight cases of KS of 600 subjects with cryptorchidism in the study by Ferlin et al. (13), two

cases of two infants diagnosed before 2 years of age in the report by Bastida et al. (14), three cases of cryptorchidism of five infants diagnosed in infancy in our recent cohort (7).

Testis volume—Small testis volume is a well-known symptom of KS in adults. Unfortunately, data are very scarce regarding testis volume in infants. Zinn et al. (9) found a reduced volume in a cohort of 35 subjects aged 0.1–39 years, including 12 infants <2 years of age: SD score -1.1 ± 1.5 .

Penile length—Micropenis and cryptorchidism are features which may lead to cytogenetic analysis. In our cohort, two of the five infants diagnosed postnatally had micropenis. Two infants from the series of seven reported by Lee et al. (12) had a micropenis, including one case of ambiguous genitalia.

Penile length was found slightly reduced in the series reported by Zinn et al. (9), which included 12 infants: SD score -1.4 ± 1.1 . Interestingly the authors found a negative correlation between penile length and androgen receptor CAGn repeat length.

Cognitive and language deficit can be an indication for karyotyping in infancy

Developmental delays are regarded as a common feature of KS in adulthood. In fact, this is an important reason for referral in some studies dealing with young males including boys under 1 year of age (8,15,16). Studies in infants with the XXY karyotype indicated delayed ambulation skills (mean age 18 months) and delayed speech at 24 months of age (review in Ref. 17). However, a recent study by Ross et al. (18) showed no discrepancy between verbal and non-verbal reasoning skills in older young patients (>4 years of age). The described defects in young boys with XXY karyotype are under investigation by means of structural and functional neuroimaging (review in Ref. 19).

Germ cell tumours in XXY subjects are rarely encountered before the age of 4 years

A number of germ cell tumours have been reported in prepubertal children with XXY karyotype. Mediastinal germ cell tumours associated with precocious puberty because of hCG secretion (20) have not been reported in boys under 4 years of age (review in Ref. 21). A retroperitoneal germ cell tumour has been shown as the event leading to the diagnosis of KS before the age of 1 year in two different reports (22,23).

HORMONAL STATUS AND TESTIS FUNCTION

Leydig cell function

Leydig cells are normally sensitive to the LH-stimulating effect—The partial defect in testosterone secretion in adult subjects with KS is well documented, although it has also been reported as normal in a recent study (24). In infants, either low normal (6,25) or high normal testosterone levels (26) have been reported. In the latter study, the authors reported testosterone values from 2.2 to 12.2 nmol/L at age 1.8–3.8 months (54–114 days). The mean value, 5 nmol/L, was significantly higher than the healthy control mean value. It should be noted however that the XXY group includes only 10 patients and that the range in the control group was lower than our own data (Table 1). We recently assessed testosterone

serum levels in a cohort of 77 infants with XXY karyotype by means of tandem mass spectrometry, compared with control values obtained using the same assay. In 20% of samples collected between 2 and 180 days of age, testosterone levels were below the 5th percentile of controls, and in only five of 38 infants aged 17–152 days, was the testosterone level above the median of controls (Fig. 1). As a consequence, testosterone levels in this age class were lower than in the corresponding age class of controls (Mann–Whitney $p = 0.01$), although when taken individually, most of infants are within normal range. In our XXY cohort, testosterone levels increased in the first 3 months of life, a change typical of the so-called minipuberty and were positively correlated with luteinizing hormone (LH) levels: Spearman $r = 0.72$ ($p < 0.0001$).

Insulin-like peptide 3 (INSL3) is a dimeric protein originating, like insulin, from a single-chain precursor. In the male, it is secreted by Leydig cells under LH control and is involved in testicular descent during foetal development (review in Ref. 27). The postnatal role of INSL3 is not fully understood. However, it is generally considered that reduced INSL3 levels can contribute to symptoms of hypogonadism, such as reduced bone mineral density as recently evidenced (28). In XXY subjects, INSL3 levels increased at puberty but rapidly levelled off despite high LH levels (29). However, INSL3 levels in nontestosterone-treated adult Klinefelter subjects were within normal range (30). In XXY infants, INSL3 levels did not differ from controls (7) and like testosterone levels are significantly higher at 1–5 months of age than in older infants (Table 2). INSL3 levels were positively correlated with testosterone and with LH levels: Spearman $r = 0.72$ ($p < 0.0001$) and 0.666 ($p < 0.0001$), respectively.

These data give evidence that in the infant with XXY karyotype, the Leydig cells are quite sensitive to the proliferating effect of LH.

Sertoli cell function

Sertoli cell secretions are normal, although a partial resistance to FSH can be suspected in some subjects—Inhibin B levels are markedly suppressed in adolescent and adult Klinefelter subjects (31,32), and this decline in inhibin B secretion occurs early during pubertal development (33). In contrast, inhibin B levels in XXY infants did not differ from controls (6,26). However, in our recent cohort completing the large series of Cabrol et al. (7), 13 of 77 subjects have inhibin B levels below the 5th percentile of controls despite follicle-stimulating hormone (FSH) values within normal range (Table 1). On the other hand, 25% of subjects from the same cohort have FSH levels above the 95th percentile of controls despite inhibin B levels within normal range (Fig. 1), and FSH levels are higher than in controls in the age class 17–152 days (Mann–Whitney $p = 0.0002$). They did not differ in the older infants. Aksglaede et al. (26) also found significantly higher FSH levels in their group of XXY infants relative to controls (Mann–Whitney $p = 0.007$). It should be noted that in our study, inhibin B and FSH levels were positively correlated: Spearman $r = 0.49$ ($p = 0.0002$), a relationship not evidenced in the report by Aksglaede et al. (26).

Taken together, these findings support the assumption that early in infancy, the Sertoli cells from XXY boys are, at least in some subjects, partially resistant to FSH.

Anti-Mullerian hormone (AMH) levels are normal or high in infants with XXY karyotype (6,34). In our recent cohort, AMH levels were significantly higher in XXY infants than in controls only in the age class 153–750 days (Mann–Whitney $p = 0.021$). There is no correlation ($r = 0$) between AMH levels and testosterone levels or FSH levels (7). The lack of any suppressive effect of testosterone on AMH secretion is consistent with the recent findings that Sertoli cells from infants do not express the androgen receptor (35,36). AMH secretion is also independent from FSH although Sertoli cells are sensitive to the proliferating effect of FSH as shown by the simultaneous increase in FSH and inhibin B levels during the minipuberty.

Germ cells

Germ cells have been reported reduced in number as early as in infancy—In the KS foetal testis, it has been shown that germ cell number is significantly reduced as early as mid gestation although the testicular tubules appear normal in density and number. By contrast, Leydig cell appeared morphologically normal (review in Ref. 37).

In the neonatal period, the seminiferous tubules showed no sign of degeneration in a 1-month infant from the study by Muller et al. (38), but no germ cells were observed in boys aged 2 years. In three infants with XXY karyotype aged 90 days, 120 days and 12 months, Mikamo et al. (39) found a reduced number of spermatogonia in otherwise normal testicular tissues. In a boy of 9 months of age, histological examination revealed interstitial fibrosis and a decreased number of germ cells (40).

Finally, it appears from these reports that the germ cell depletion characteristic of the status of adult subjects with XXY karyotype (36) can be evidenced as early as infancy.

CONCLUSION

A very small number, <10%, of subjects with XXY karyotype, are prenatally detected. Even fewer subjects are diagnosed postnatally during infancy because of somatic abnormality or delayed ambulation or verbal reasoning skills. This is unfortunate because a defect in Sertoli cell sensitivity to FSH and a reduced number of germ cell may be evidenced early in infancy. Early detection of KS is desirable for making it easier the management of developmental problems and for prospectively monitoring the progressive decline in testicular tubules with the hope of designing future conservative interventions before total germ cell degeneration is completed.

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Abbreviations

AMH	anti-Mullerian hormone
FSH	follicle-stimulating hormone

INSL3	insulin-like peptide 3
KS	Klinefelter syndrome
LH	luteinizing hormone

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Figure 1.

Testosterone, anti-Mullerian hormone (AMH) and follicle-stimulating hormone values in 77 infants with nonmosaic XXY karyotype. The limits of the shaded areas are the smoothed 5th and 95th percentiles of control levels.

Table 1

Gonadotropin and testis hormone levels in XXY infants (median and range), compared to median, 5th–95th percentiles of controls

Age	2–16 days	17–152 days	153–750 days
Testosterone (nmol/L)			
XXY	n = 5 1.3 (0.07–2.4)	n = 38 4.15 (<0.06–12.3)	n = 34 0.09 (<0.06–2.1)
Controls	n = 35 1.6 [0.36–5.0]	n = 68 7.3 [1.9–15.4]	n = 65 0.17 [<0.06–1.9]
Inhibin B (pg/mL)			
XXY	n = 5 101 (50–186)	n = 38 199 (91–411)	n = 34 102 (48–281)
Controls	n = 31 167 [75–540]	n = 45 188 [105–575]	n = 37 105 [97–318]
AMH (pmol/L)			
XXY	n = 5 467 (206–1210)	n = 38 777 (359–2393)	n = 34 793 (242–1972)
Controls	n = 33 575 [180–1100]	n = 52 630 [240–1200]	n = 40 589 [295–1200]
FSH (IU/L)			
XXY	n = 5 0.34 (0.03–1.7)	n = 38 1.95 (0.14–6.0)	n = 34 0.49 (0.01–3.4)
Controls	n = 30 0.41 [0.2–2.0]	n = 57 1.1 [0.29–3.6]	n = 55 0.30 [0.13–1.32]
LH (IU/L)			
XXY	n = 50.23 (0.03–2.7)	n = 38 1.98 (0.13–7.7)	n = 34 0.65 (0.01–2.34)
Controls	n = 30 0.20 [0.01–1.5]	n = 66 2.2 [0.6–5.4]	n = 55 0.70 [0.01–3.7]

AMH, anti-Mullerian hormone.

Table 2

Insulin-like peptide 3 levels (median and range) in XXY infants and controls

<u>Age</u>	<u>16–152 days</u>	<u>153–750 days</u>
<u>n</u>	<u>32</u>	<u>18</u>
XXY infants	92 (26–222)	39 (<11–110)
Controls	88 (<11–180)	32 (<11–80)