Genetics Corner: Prenatal Diagnosis of Klinefelter Syndrome

Robin Clark, MD

Case Summary:

A one-day-old 39-week 1-day gestation male was referred for a genetics consultation because he had been prenatally diagnosed with Klinefelter syndrome, initially by NIPT and then confirmed by amniocentesis. His mother, a 26-year old G3P1SAb1TAb1 female, delivered him vaginally by spontaneous vertex delivery. Apgar scores were 81 and 95. Growth parameters were normal: BW 3.27 kg, BL 52 cm, HC 34 cm. The baby had had no complications and was rooming in with his mother.

During her pregnancy, the mother had a normal sequential (1st and 2nd trimester) maternal serum screening test. A noninvasive prenatal test (NIPT) that utilized cell-free fetal DNA techniques was abnormal with an increased risk for a sex chromosome aneuploidy. An amniocentesis, performed for this indication, confirmed 47,XXY, in each of 15 metaphases. The fetal US at 26w 3d showed no major anomalies but abnormal toes on both feet, suggesting syndactyly.

Genetics evaluation:

On physical exam, the baby cried but calmed with sucking. He was nondysmorphic and normocephalic. He had a single transverse palmar crease on the right palm. His fingers were long as were his feet. His 4th and 5th toes were overlapping, but there was no syndactyly. He had dermal melanocytosis on his lower back. His genitalia were unremarkable with a normal, deeply pigmented, rugated scrotum bilaterally descended testes and an uncircumcised phallus of normal length (2 cm) and caliber. His neuro exam was normal with good tone, symmetric movements, a strong grasp and a lusty cry.

The family history was significant for a 25-year old maternal uncle with 21-hydroxylase deficiency and a 33-year old maternal aunt, who was hirsute and short with polycystic ovaries, but who had not been formally diagnosed with congenital adrenal hyperplasia (CAH). The mother was tested for CAH carrier status in this pregnancy, with positive results, confirming a heterozygous pathogenic sequence change in CYP21A2: p.V282L, a known, mild (non-classical) variant. The father of the baby, a healthy 31-year old, had not yet been tested for CAH carrier status. Consanguinity was denied. The parents had two previous pregnancies together that ended in a miscarriage and a therapeutic abortion. There was no other history of congenital anomalies or chromosome abnormalities.

Conclusions and Counseling:

Klinefelter syndrome (KS) occurs in males with an extra X chromosome. In 90% of affected males, the chromosome complement is 47,XXY. Mosaicism with a normal cell line is present in 7%: 46,XY/47, XXY. Rare and more severe variants are found in 3%: 48,XXXY, 48,XXYY, 49, XXXXY. The extra X chromosome is maternally derived in 50%.

Although KS is relatively common, occurring in 1/600 male births, it is not commonly diagnosed in the newborn period. Less than 10% of affected males are diagnosed before puberty. Another 25% of males with KS are diagnosed in adulthood. The majority, approximately 65%, are never diagnosed throughout their lifespans.

The widespread acceptance of NIPT as a screening tool has increased the prenatal diagnosis of Klinefelter syndrome. NIPT, which is offered as early as ten weeks gestation, utilizes cell-free fetal DNA circulating in the maternal bloodstream. Although it is highly accurate (91% sensitivity, 99.6% specificity), NIPT is not a diagnostic test. A positive NIPT test should be confirmed with chromosome analysis, either prenatally, with invasive testing by amniocentesis or chorionic villous sampling, or postnatally, with a blood sample. Although prenatal diagnosis with amniocentesis is considered reliable, confirming the prenatal diagnosis of a chromosome anomaly in a blood sample settles any doubts that parents may have, which would be understandable when the phenotype is normal as it usually is in KS.

Babies with KS are usually healthy and nondysmorphic. This infant had few if any signs that would have suggested a chromosome abnormality. His condition would have certainly gone undetected without NIPT screening and prenatal diagnosis.

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The classic features of KS are more evident near puberty when hypergonadotrophic hypogonadism and/or tall stature may become apparent, or even later, in adulthood, because of azoospermia and infertility. Intelligence is usually normal though it may be 9-10 points lower than unaffected siblings. Behavioral (shyness, anxiety, depression, low self-esteem) & learning problems (reading/language disability, memory), ADHD, executive dysfunction, and motor delays are common. In a study of 43 boys with KS, aged 8-18, among those diagnosed postnatally, developmental delay (11.6%) was the most common reason for ordering the karyotype (Close 2015).

Speech delay and language disabilities are common in KS. In general, boys with prenatally diagnosed Klinefelter syndrome do better than those who are postnatally diagnosed. However, feeding difficulties, which may be the earliest evidence of oral motor dyspraxia in KS, have been seen in almost half of a cohort of prenatally diagnosed infants with 47,XXY.

Early diagnosis of KS raises questions about which, if any, interventions may be beneficial in infancy and childhood. Androgens, specifically testosterone, affect typical brain development in males and an early androgen deficit in KS may impact motor, language, cognitive and social function in KS. Although there are no guidelines for hormone replacement therapy in Klinefelter syndrome, testosterone therapy has typically been offered near puberty. However, recent studies have reported positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. Early therapy with androgens, which reinforces a naturally occurring testosterone peak at 2-4 months of life, has improved neurodevelopmental performance related to cognitive functioning, visual and motor skills, and language development in treated boys compared to untreated controls with Klinefelter syndrome. Samango-

Sprouse et al. (2015) treated 29 prenatally diagnosed boys with KS with three monthly injections of testosterone enanthate (from 4-15 months) and compared them with 57 controls with 47,XXY, who did not receive hormone therapy. They found significant differences in social communication and social cognition scores and on measures of initiation, externalizing, affective and aggressive behaviors. Ross et al. (2017) conducted a randomized, double-blind, placebo-controlled clinical trial in which 84 boys with Klinefelter syndrome, aged 4-12 years, were treated with daily Oxandrolone or placebo for 24 months. Their study showed benefits in visual-motor function and improvement in anxiety/depression and social problems scales in the treated group. Flannigan et al. (2018), in their meta-analysis on the behavioral effects of early androgen supplementation in KS, reviewed three retrospective studies and two randomized controlled trials and concluded that these studies showed an improvement in several aspects of social and cognitive functioning, with benefits that were "very encouraging."

Finally, it is intriguing to speculate that this baby boy may have benefitted from his mother's carrier status for 21-hydroxylase deficiency because even a mild, non-classical allele could have modestly increased maternal adrenal androgen production during his intrauterine life. It is also possible that, if he were also a CAH carrier, his own excess adrenal androgen production might ameliorate his Klinefelter syndrome-associated hypogonadism.

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Practical Applications:

1. Klinefelter syndrome is underdiagnosed. Expect more boys with Klinefelter syndrome to be prenatally diagnosed as NIPT becomes a routine screening test in pregnancy.
2. Order chromosome analysis (not a microarray) to confirm a prenatally diagnosed sex chromosome abnormalities or a positive NIPT test. NIPT is considered a screening test, not a diagnostic test.
3. Half of the babies with Klinefelter syndrome may have feeding problems, which are early manifestations of the oral-motor dyspraxia of this condition.
4. Early androgen hormone therapy during infancy may offer behavioral, social, language, and cognitive benefits to boys with Klinefelter syndrome.

References:

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The authors have no relevant disclosures.

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Corresponding Author

Robin Clark, MD
Professor, Pediatrics
Loma Linda University School of Medicine
Division of Genetics
Department of Pediatrics
rclark@llu.edu