5-2021

Klinefelter's Syndrome: A fortuitously diagnosed by non-invasive prenatal testing

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Klinefelter's Syndrome: A case fortuitously diagnosed by non-invasive prenatal test

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Abstract

Klinefelter Syndrome is a genetic disorder caused by the presence of supernumerary sex chromosomes. An additional X chromosome(s) and hypogonadism are the two defining features of Klinefelter syndrome (Groth, 2013). The excess of genes from the additional X chromosome drives the pathogenesis of the disease and distinguishing features of the affected individuals. Genotypic variants exist within the affected population, leading to differences in phenotype and severity of symptoms (Bonomi, 2017). The increase in the prevalence of prenatal testing has led to the earlier recognition of fetal chromosomal abnormalities. Early detection of Klinefelter syndrome through noninvasive prenatal testing is an extraordinary medical tool, giving the family much need information and allowing for early intervention, ensuring the best outcome for the child (Groth, 2013). This case report shows a patient that will greatly benefit from the early diagnosis of a genetic syndrome to implement early and timely interventions upon delivery and then later on in the child's developing years.

Case Report

A male infant was born at 37 weeks gestation. His mother was a 29-year-old, gravida 4 para 3 woman. During her pregnancy she was curious as to the gender of the fetus and requested a non-invasive prenatal test (NIPT) rather than fetal ultrasound. The NIPT returned with a karyotype of XXY. The male infant was born vaginally with a birth weight of 2670 grams. Apgar scores were 8 and 9 at one and five minutes respectively. He was admitted to the newborn intensive care unit secondary to respiratory distress. He had no obvious dysmorphic features. He had normal appearing male genitalia with testes descended bilaterally. Fluorescent in situ hybridization and blood chromosomes confirmed an XXY karyotype. He was discharged from the newborn intensive care unit with follow up by genetic counselors and close monitoring for developmental delays.

Genetics

Supernumerary X chromosomal aneuploidy leads to the majority (80%) of Klinefelter individuals possessing the karyotypic pattern 47XXY (Bonomi, 2017). This arises due to nondisjunction occurring in gametogenesis. Nondisjunction arises equally from paternal and maternal origins. The remaining minority of genotypes includes, but is not limited to, 47,XXY/46,XY mosaicism, 48,XXXY/47,XXY, and 48,XXXY. arises due to the non-disjunction event of the X chromosome occurring in the early mitotic stages of the developing 46,XY zygote or through a X chromosome being lost due to anaphase lag in the mitotic development of a 47,XXY zygote (Bonomi, 2017).

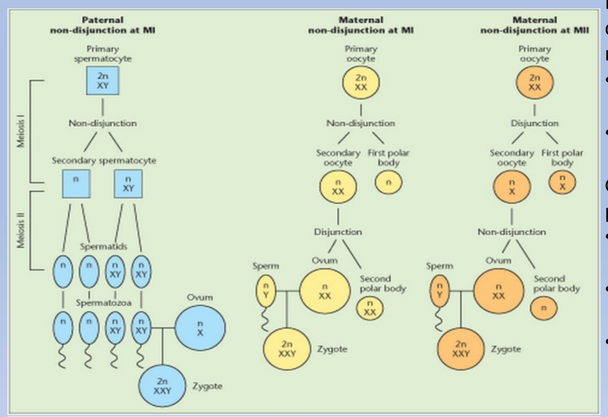

Figure 1, Non-disjuntional of Klinefelter producing gametogenesis. (Kanakis, 2018)

Nondisjunction occurs during meiosis of the respective gametes:

- Meiosis I or II of maternal Oocyte
- Meiosis I of paternal Spermatocyte

Genotypic factors driving phenotype and variance:

- Gene dosage by additional X
- CAG repeat polymorphisms
- Pseudo autosomal regions (PARs) expressed
- Gene's copy number variants (CNVs)

Table 1. Klinefelter Syndrome's Manifestations - Modified table from Groth et al., 2013 publication on Clinical Features of KS	
Feature	Tentative Frequency
Infertility	> 95%
Increased Gonadotrophin Hormones	> 95%
Decreased Testicular Volume	> 95%
Azoospermia	> 95%
Learning Disability	> 75%
Testosterone Deficiency	60-85%
Decreased Distribution of Male Body Hair	30-80%
Gynecomastia	40-75%
Speech Delays	40%
Increased Height	30%
Elevated BMI	~50%
Metabolic Syndrome	46%
Decreased Bone Density	5-40%
Type II Diabetes Mellitus	10-40%
Cryptorchidism	37%
Decreased Penile Size	10-25%
Psychiatric Conditions	25%
Congenital Malf. (i.e. Cleft lip, Inguinal Hernia)	18%
Cardiovascular Abnormalities	0-55%

Table 1, KS Manifestations and general frequency of presentation in confirmed cases (Groth, 2013).

Clinical Consideration

Klinefelter Syndrome can present with any number of symptoms as indicated by table 1. It's understood that these symptoms are attributed to several factors.

- Number of genetic abnormalities (# of X, CAG repeats, PARs, & CNVs)
- Androgen dependent, Supernumerary X, or combined factors
- Age of presenting individual (symptoms worsen with age)

These features can be grouped by age of onset, androgen-dependence, supernumerary X-dependence, or combined etiology (Bonomi, 2017).

The neonate in question presents with no distinct, characteristic signs of Klinefelter Syndrome, which is common in many individuals. Due to the underwhelming and subtle nature of many Klinefelter phenotypes, a majority of patients go undiagnosed. Only two findings, other then the NIPT results, weakly suggest a possible abnormality.

- Respiratory distress seen in 9.2% of KS births as opposed to 1.2% in normal neonates (Dotters-Katz, 2016).
- Lower than normal birth weights for gestational age have been reported in KS neonates (Dotters-Katz, 2016), but as of this time, low birth weight alone does not give reason to suspect Klinefelter Syndrome.

The underwhelming clinical presentation of the neonate shows that if NIPT wasn't conducted, neither our patient nor his family would have known he was 47,XXY, until much later in life. Timely hormonal intervention is possible for our patient because of NIPT. This demonstrates a need of a standard KS screen.

Non-Invasive Prenatal Testing

Non-invasive prenatal testing (NIPT), also known as cell-free DNA testing, is a prenatal screening tool used in the assessment of fetal chromosomal abnormalities. Cell-free DNA can be found in all individuals as a result of the natural turnover of cells. Small DNA fragments from this cellular turnover is found briefly in circulating blood plasma prior to being cleared. In pregnant mothers, a fraction of the small DNA fragments found in circulating plasma is from the outer trophoblastic cell layer of the placenta. These trophoblasts DNA fragments usually match the genotype of the developing fetus. A blood sample is drawn from the mother, then plasma concentrations of cell free DNA are divided into maternal and fetal fractions. This fetal fraction is compared to normal standards for the corresponding gestational age of the fetus. Individual chromosomes appear at known standard ratios within the fetal fraction. Ratios that deviate from the norm indicate an abnormality in that particular chromosome (Harraway, 2017). WHO's criteria for use of the test in listed in table 2.

World Health Organization's Criteria for NIPT
The condition should be an important health problem
The natural history of the condition should be adequately
Facilities for diagnosis and treatment should be available
The overall benefit of screening should outweigh the harm
There should be scientific evidence regarding screening program effectiveness
The screening program should respond to a recognized need
The objectives of screening should be defined at the outset

Table 2, WHO's criteria for non-invasive prenatal testing (Suciu, 2019)

Discussion

Klinefelter's Syndrome carries with it a significant number of manageable symptoms and considerable comorbidities. With a larger number of men, up to 70-75%, going undiagnosed throughout their lifetime (Bojesen, 2003). Screening is needed to help in the diagnoses of the vast majority of these patients. With the technology of NIPT advancing and improving in its ability to detect a variety of other conditions outside of the traditional autosomal aneuploidy, it should be considered a technique for screening for clinically silent conditions, such as mild Klinefelter syndrome phonotypes. When a majority of patients are going undiagnosed and untreated the benefit of adding sex chromosomal aneuploidy to the test is two-fold. One if it allows for use to detect patients that would otherwise go undiagnosed until later in life, resulting in late introduction of testosterone replacement therapies, missing the critical stage of puberty. Second it allows us to improve our understanding of Klinefelter patients' development during early childhood and the use of NIPT in prenatal diagnostics overall.

References

Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab*. 2003;88(2):622-626. doi:10.1210/jc.2002-021491

Bonomi M, Rochira V, Pasquali D, et al. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. *J Endocrinol Invest*. 2017;40(2):123-134. doi:10.1007/s40618-016-0541-6

Dotters-Katz SK, Humphrey WM, Senz KL, Lee VR, Shaffer BL, Caughey AB. The impact of prenatally diagnosed Klinefelter Syndrome on obstetric and neonatal outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:173-176. doi:10.1016/j.ejogrb.2016.05.006

Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. *J Clin Endocrinol Metab*. 2013;98(1):20-30. doi:10.1210/jc.2012-2382

Harraway J. Non-invasive prenatal testing. *Aust Fam Physician*. 2017;46(10):735-739.

Kanakis GA, Nieschlag E. Klinefelter syndrome: more than hypogonadism. *Metabolism*. 2018;86:135-144. doi:10.1016/j.metabol.2017.09.017

Suciu, I. D., Toader, O. D., Galeva, S., & Pop, L. (2019). Non-Invasive Prenatal Testing beyond Trisomies. *Journal of medicine and life*, *12*(3), 221–224. https://doi.org/10.25122/jml-2019-0053