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CfDNA testing for Klinefelter syndrome

Matalliotaki Ch, Matalliotakis M, Papoulidis I, Patelarou E, Dimosthenous E, Nikoletakis G, Petra G, Ganelli A, Goulielmos G
Obstetric and Gynecology department of Venizeleio General Hospital, Crete, Greece, Heraklion, Greece

Objective

Klinefelter syndrome (XXY) represents the most common sex-chromosome disorder and affects 1/500 men. The prenatal prevalence is 0. 15% to 0. 17%. The pathophysiology of the syndrome is due to a nondisjunction event during paternal or maternal meiosis I and is usually random. Increased maternal age is slightly associated with this syndrome. In 5–10% of cases, there may be mild hypospadias or ambiguous genitalia; however, compared with other autosomal aneuploidies, fetuses with 47 XXY syndrome have relatively few sonographicaly serious structural abnormalities making diagnosis a challenge. Thus, most men with Klinefelter syndrome will not be diagnosed. Prenatal diagnosis of sex chromosomal abnormalities (SCAs) will benefit new-borns by offering early medical interventions and potentially beneficial therapies. cfDNA testing to determine fetal sex and detect XXY syndrome poses unique challenges.

Methods

We present a case of a multiparous 38 years old patient with no previous abnormal medical or family history. First trimester combined screening test at 12 5/7 days had shown low risk for trisomies 21, 18 and 13. The couple decided to perform a non-invasive prenatal testing (NIPT) due to the maternal age.

Results

CfDNA results indicated extremely low risk for trisomies 21, 18 and 13, but an increased risk for Klinefelter syndrome (Fetal fraction 14%). Fetal DNA was analysed with QF-PCR and thereafter by conventional Karyotyping by G banding standard techniques and the diagnosis of Kleinefelter syndrome was confirmed. The parents were offered Prenatal Genetic Counselling, however, eventually opted for termination of pregnancy that was performed at 18 weeks of gestation by 3 tabs of mifepristone in combination with misoprostol to induce a vaginal delivery.

Conclusion

Many individuals with XXY syndrome are undiagnosed until adulthood. Affected men usually experience azoospermia and infertility. Early diagnosis and management with preventive testosterone replacement treatment, along with a multidisciplinary approach for physical, behavioural, and occupational therapy, promotes satisfactory developmental, social, and intellectual progress. Testosterone supplementation at puberty promotes male phenotype development, increases penile size, eliminates gynecomastia, and improves cognition and social integration. A cohort study observed that prenatal compared to postnatal diagnosis carried out better cognitive function to individuals and less likelihood of autistic development. The sensitivity of cfDNA to detect XXY syndrome can be affected by various parameters including the type of the chromosomal imbalance (i. e. structural or numeral), placental mosaicism and the mother being a carrier of sex chromosome abnormality (e. g. mos 46, XX/45, X). A minor deletion, interruption or translocation of genes in a sex chromosome may not be found by cfDNA screening, but could account for the unconformity of the phenotype with the prediction of fetal sex. Interestingly, NIPT is between 95-99% accurate for the prediction of fetal sex. Low concentration of fetal cfDNA in the maternal circulation (fetal fraction) and the difficulty in distinguishing fetal from maternal chromosomes restrict the clinical use of the test. PPV is of critical importance for a screening test as it defines the probability of a positive test to be true positive. NIPT tests shows relatively low PPV, even for Down syndrome (~80-90%), though much higher than combined testing (~5%). Kleinefelter and other sex chromosome abnormalities have a similar PPV (~80-90%). According to the literature, Bianchi et al. reported a low frequency (0. 26–1. 05%) of false positive results for SCA. Additionally, a meta-analysis showed that the detection rate was 90. 3% for monosomy X and 93. 0% for SCAs other than monosomy X. Another report showed that the analysis of maternal plasma cfDNA using a targeted assay could detect fetal SCA with a reasonably high sensitivity (92. 6%) with a combined false-positive rate of less than 1%. If cfDNA test has

indicated a high chance for XXY syndrome, a diagnostic confirmation should be performed by CVS or amniocentesis to rule out a false positive result. We believe that the test should be offered to all women in order to identify fetal SCAs by using Next Generation Sequencing and continue to strive to improve its accuracy. In the case of a definitive diagnosis, information should be provided to the parents in order to aid them to reach a decision appropriate to their circumstances and beliefs.