Chapter 37
What is Klinefelter Syndrome and how best to care for these patients

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In 1942, Harry F. Klinefelter and colleagues published "Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone" in The Journal of Clinical Endocrinology & Metabolism, first describing what would later become known as Klinefelter's syndrome (KS). Klinefelter's Syndrome is the most common sex-chromosomal aneuploidy in males, characterized by a supernumerary X-chromosome, which affects 1:500 males. Phenotypic characteristics include but are not limited to cryptorchidism, hypospadias, small testes, intellectual disability, delayed or incomplete pubertal development with normal or low serum testosterone, and infertility. The predominant form of KS, which is present in 80–90% of cases, is defined by a 47, XXY karyotype whereas higher-grade aneuploidies (e.g. 48, XXXY or 48, XXYY), or mosaicisms (e.g. 47, XXY/46, XY) make up approximately 10–20 % of cases. Phenotype varies with severity of genotypic abnormality, which contributes to Klinefelter syndrome being under-diagnosed.

Laboratory examination of KS cases resembles that of primary testicular failure, and is typically characterized by non-obstructive azoospermia, low serum testosterone, and high serum LH and FSH levels. Importantly, men with KS, have higher rates of diabetes, epilepsy, cerebrovascular disease, breast cancer, and non-Hodgkin lymphoma, compared to euploid males. Lifespan for KS men is generally similar to that for euploid, men; however, life expectancy is 1-2.5 years less than the general population.

Early identification of individuals with KS is key for managing their underlying hormonal derangements. Management typically focuses on three major facets: gynecomastia, hypogonadism (and indirectly, fertility), and the psychosocial aspects of the disease which are often the most trying aspect of the disease for patients.

While treatment such as testosterone replacement therapy is an important aspect of care delivery, a multidisciplinary approach is recommended, given the fact that this disease affects multiple organ systems.

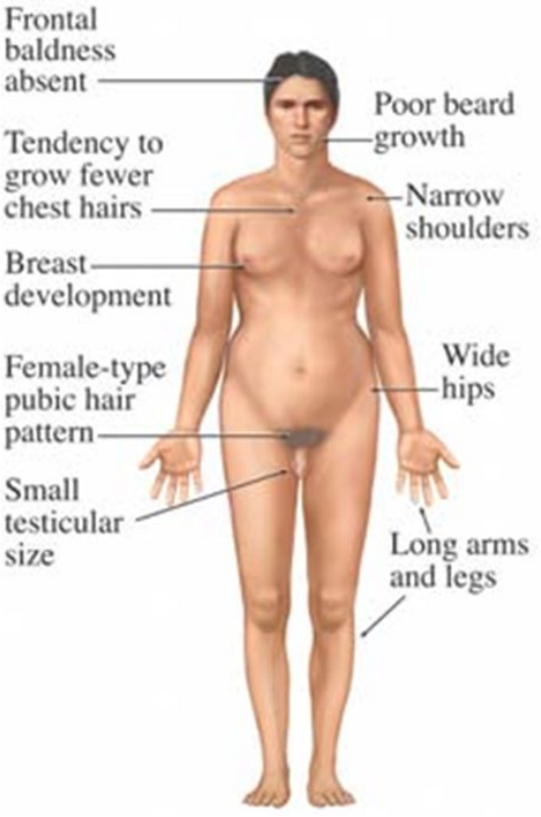

Figure 1. Klinefelter's syndrome.jpg. (2020, September 27). Wikimedia Commons, the free media repository. Retrieved 13:34, June 20, 2022 from https://commons.wikimedia.org/w/index.php?title=File:Klinefelter%27s_syndrome.jpg&oldid=473127011

Childhood Therapy and Prenatal Diagnostics

Only 25% of patients with KS are diagnosed with the disease in the pediatric age group. However, pre-natal diagnosis is becoming more common as an incidental finding on pre-natal testing such as amniocentesis and chorionic villi sampling, performed for other indications. In the post-natal period, karyotype analysis of a peripheral blood sample remains the primary diagnostic test for Klinefelter syndrome.

During mini-puberty, the sex-specific activation of the hypothalamic-pituitary-gonadal axis begins between 2-6 months of age. During this time, patients with micropenis or hypospadias can be treated with topical or intramuscular testosterone to promote maturation. Although this therapy has been utilized for the purpose of penile growth and development in infants with KS, data on long-term benefit are limited.

Many children with KS will present with cognitive and developmental abnormalities, including, but not limited to, hyperactivity, decreased ability to cope with labile emotional states, attention, and poor verbal comprehension. Patients exhibiting these symptoms should be referred to developmental psychologists and therapists with expertise in this area.

Puberty for KS patients tends to begin within the normal age ranges; however, some patients with KS do suffer from delayed puberty (Chapters 28, 35). In the majority of cases, once initiated, puberty does not progress in a timely fashion. As such, assessment of tanner stages, measurements of testosterone and gonadotropins, and body proportion measurements should be trended during pubertal years to determine the need for testosterone supplementation. In cases of delayed puberty and or symptoms of hypogonadism with corresponding lab values, testosterone supplementation may be considered. Testosterone replacement therapy is indicated to help patients progress through puberty if they are struggling with cognitive function or secondary sex characteristics. Suppression of spermatogenesis is a risk of testosterone supplementation and should be discussed with the patient. Long term impact of testosterone supplementation on fertility outcomes is unknown. Sperm banking should be offered to all patients prior to initiating testosterone supplementation.

During puberty, while spermatogenesis cannot be observed in the majority of seminiferous tubules, a minority will begin spermatogenesis and few spermatozoa can be found on microscopic

examination. In one 2016 study, adolescents with KS aged 13-14 years had spermatozoa collected in only 10% of the TESE (testicular sperm extraction) attempts, while in adolescents of 15-19 years, spermatozoa were found in 45%. Serum testosterone level does tend to correlate with prognosis of TESE success in identifying sperm. In the same 2016 retrospective study, Klinefelter's syndrome patients with spermatozoa in their ejaculate had similar mean T levels (10.2 ± 2.7; range 7.1–15.3 nmol/L) and similar mean LH levels (15.5 ± 7.1 U/L; range: 7.1–18.1), compared to those of patients with azoospermia (T: 12.3 ± 5.5 nmol/L; range: 2.3–31; LH: 19.3 ± 12.3 U/L; range: 1–62). However, in all nine spermatozoa-positive patients with KS, T levels were ≥7.0 nmol/L[i]. [I wonder if the authors would considered adding the values of testosterone in ng/dL for the US readership]

Infertility Management

Most men with KS will be azoospermic or severely oligospermic. According to the 2020 AUA/ASRM Guidelines, these men should be evaluated with karyotype and y chromosome microdeletion test to consider all possible underlying causes. Once KS is confirmed, these patients should be counseled about associated health risks, including an increased risk of breast cancer, osteopenia/osteoporosis, type 2 diabetes, and increased risk of thrombosis. An EKG should be done at least once during their lifetime to check for elongated QTc and risk of Torsades-de-pointes. Patients with or without gynecomastia should receive imaging with ultrasound or mammogram as well as a clinical breast exam at least every two years.

Sperm banking should be offered to every patient wishing to have children who carry a diagnosis of KS as well as any patient being considered for testosterone replacement therapy (TRT). In a study published in 2006, it was identified that KS patients' sperm counts can decline as they age with increased testicular atrophy and decreased spermatogenesis. Furthermore, all patients with KS and confirmed azoospermia as well as a current or future wish for paternity should undergo a testicular biopsy for TESE and be educated about possible benefits of microdissection-TESE (mTESE). Patients falling into this category should also be counseled on alternatives including use of donor sperm, adoption, or donor embryo utilization. While sperm retrieval rates in KS patients is lower than that of the population of non-obstructive azospermic patients, retrieval rates may be as high as 50% and have been used

via intracytoplasmic sperm injection (ICSI) and *in vitro* fertilization (IVF) to produce offspring.

Adult Hormonal Management

For adult KS patients testosterone supplementation is recommended in several patient groups. In the KS patient whose fertility issues have all been addressed, testosterone supplementation should be recommended if the patient has hypogonadism on laboratory results as this helps prevent certain aspects of the disease, namely those concerned with decreased bone mineral density. These patients should be monitored as every other hypogonadal patients on testosterone supplementation, with interval monitoring of hemoglobin and hematocrit levels and liver function studies every 6-12 months when on supplemental testosterone. Dose titration is recommended in accordance with response to therapy. In patients not receiving supplemental testosterone, it is still recommended that they receive an endocrine evaluation every 12 months. As with all patients with low testosterone, prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. PSA should also be measured in men over 40 years of age prior to the initiation of testosterone.

Suggested reading

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