Klinefelter - An Evolving Syndrome

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Characteristics

- Gynecomastia
- Small testes
- Absent spermatogenesis
- Normal to moderately reduced Leydig cell function
- Increased secretion of FSH.
Original patients
Current patients
Evolving paradigm for fertility preservation in adolescents with Klinefelter Syndrome (KS)

• KS is the most common sex chromosome disorder in azoospermic men.

• Testicular sperm extraction success decreases with age and after testosterone therapy.

• Consider sperm retrieval in KS males at the onset of puberty and before testosterone therapy.

47 XXY
Normal meiosis

Meiosis I
- Telophase & cytokinesis

Meiosis II
- Prophase II
- Metaphase II
- Anaphase II
- Telophase II

Cleavage furrow

Two haploid cells form; chromosomes are still double

During another round of cell division, the sister chromatids finally separate; four haploid daughter cells result, containing single chromosomes
Nondysjunction

Failure of chromosomes to separate: anaphase meiosis I, meiosis II, mitosis

http://www.youtube.com/watch?v=Huf1-il_p84
Hypotheses of spermatogenesis in KS

M Maiburg et al, The genetic origin of Klinefelter syndrome and its effect on spermatogenesis, Fertility and Sterility, 98(2), 253, 2012
Mechanisms leading to aneuploidy

- **Nondisjunction** – failure to separate at meiosis I, meiosis II or mitosis
  - “Classical” (“true nondisjunction”) – failure to resolve chiasmata in meiosis I, failure to establish chiasmata or premature resolution of chiasmata
  - “Nonclassical” – premature separation of sister chromatids in meiosis II
- **Anaphase lagging** – failure of chromosome or chromatid to be incorporated into the daughter cell
- **Origin of aneuploidy** – almost 50% are paternal
- **Risk factors** – maternal age is the only known one
- **Mosaics** develop from early postzygotic nondisjunction or from loss of one of the X chromosomes (“trisomy rescue”)

Effect of Additional X Chromosome

Manifestations

- Azospermia Infertility
  - Mediastinal tumor
  - Breast cancer
- Systemic lupus erythematosus
- Heart disease
- Epilepsy
- Diseases of the respiratory system
- Type 1 diabetes
- Type 2 diabetes

Mechanisms

- Hyalinization of seminiferous tubules
- Insulin resistance
- Fasting glucose
- Fat Mass
- Lean Body Mass
- Estrogen
- Androgens
- Gynecomastia

Increased gene dosage of X-chromosome material
- SHOX (BNP, FGFR3)
- Other genes?
- Altered methylation profile?
- Skewed X-inactivation?

- Increased psychiatric morbidity
  - Anxiety disorders
  - Autism spectrum diseases
  - ADHD
  - Schizotypal traits
- Cognitive deficits
  - Verbal problems
  - IQ in the low range
  - Memory problems
- Sexual dysfunction
- Increased
  - Final height
  - Armspan
- Fracture Risk
- Osteoporosis
- Physical fitness
- Muscle strength

- BMD

Congenital abnormalities
- Maldescended testes
- Heart?
Hypergonadotropin Hypogonadism
Basics

✧ Classic KS patients have an extra X-chromosome, resulting in 47,XXY karyotype (80 - 90% of cases)
✧ Mosaic KS 10% - 20%
✧ Other genetic variants exist
✧ 1:500-1:1000 live male births
✧ 3% of infertile males and 10% of patients with non-obstructive azoospermia exhibit KS (Mau-Holzmann, 2005).
✧ Most frequent genetic cause of azoospermia (67%)
✧ Unfortunately, only 10% of XXY males are diagnosed before 14 years (Bojesen et al., 2003; Tuttelmann et al., 2010)
Medical issues in KS patients

✧ Motor, cognitive and behavioral dysfunction
  • Reduction in gross and fine motor skills, coordination, dexterity, running ability, poor muscle tone, tremor
  • Difficulties with language and language-based learning
  • Increased rate of executive dysfunction
  • Judgmental problems and impaired decision making

✧ Mediastinal germ cell tumors (MGCT): ~60 times more common in KS than general population
  • Usually present with precocious puberty and thorax-associated symptoms

✧ Breast cancer – 3.7-7.5% of men

✧ No documented relationship between testicular cancer and KS
Medical issues in KS patients (cont.)

✧ Vascular and cardiac disease
  • DVT, PE, thrombophlebitis
  • CAD

✧ Endocrine and metabolic diseases
  • Osteoporosis, DM, MetS, obesity, hypothyroidism

✧ Rheumatologic diseases
  • SLE, RA, Sjogren syndrome
Evolving Concepts of Testicular Function

Testicular Function

- Sperm production
- Age dependence

- Testosterone production
- Factors controlling production
Are Adolescent Boys with KS Androgen Deficient?

- 14 non-mosaic 47,XXY boys, aged 10–13.9 y, were followed up for 4–37 mo with staging of puberty and frequent reproductive hormone measurements
- In KS boys after 13 years of age testosterone was normal but LH and FSH increased
- Changes of androgen action (decreases in serum SHBG, leptin and PSA increase) occurred normally
- Decrease of testis size in pubertal testis due to a decrease in number of seminiferous tubules

As described by Wikstrom AM, Dunkel L, Wickman S et al. in their study titled "Are adolescent boys with Klinefelter syndrome androgen deficient? A longitudinal study of Finnish 47, XXY boys. Pediatric Research 2006b; 59: 854–859." the graphs illustrate the development of pubic hair and genitalia by age in boys with Klinefelter syndrome (KS). The gray rectangles represent the mean age ± 2 SD for healthy Finnish boys.
Testicular Volume by Age in Boys with KS

Shaded rectangles = mean age ± 2 SD for healthy Finnish boys. Gray area = range of the volume of the right testis in healthy pubertal Swiss boys.
So why are KS patients started on Testosterone at the start of puberty?

- Prevent osteoporosis
- Prevent obesity
- Prevent metabolic syndrome
- Prevent diabetes

However these thoughts are not evidence based. There are limited studies supporting these.
Studies that demonstrated a decrease in testosterone in KS boys

- Lahlou N, Fennoy I, Carel JC, Roger M 2004 Inhibin B and anti-Mullerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. J Clin Endocrinol Metab 89:1864–1868

Concentration by age of INSL3, LH and T in KS as Compared to Healthy Boys

Mean (±SD) plasma insulin-like factor 3 (INSL3), LH, and testosterone (T) concentrations by age in boys with Klinefelter syndrome compared to healthy boys

Questions

• Should we be treating with testosterone for elevated gonadotropins when a normal serum testosterone is present?

• Should we be treating for symptoms of low T (not including signs) when a normal serum testosterone is present?

• What are the risks v benefits?
What does this mean for spermatogenesis?

1. Are sperm present in KS patients?
2. Is there a ‘window of opportunity’ for retrieving any sperm that might be present?
3. How can these sperm be used for conception?
4. Are these sperm functional?
5. Are there concerns regarding use of sperm from KS patients?
There is no treatment for the sterility. The gynecomastia should be treated by excision of the tissue with preservation of the nipple. This should be done not only for cosmetic reasons but because cancer of the breast is about 20 times as frequent in this condition as in normal men. If hypogonadism is present, treatment with injected testosterone is effective. There is some evidence to suggest that treatment with testosterone in adolescence helps to correct some of the personality abnormalities that these patients show.

Harry F. Klinefelter Jr, M.D.
Are Sperm present in KS Patients?

Recovery rate of 66% (which is euploid in the vast majority), and 45% of these achieved a live birth of a child.

K Groth et al, Klinefelter Syndrome—A Clinical Update, J Clin Endocrinol Metab, January 2013, 98(1)
Presence of testicular sperm in Klinefelter’s Syndrome and disappearance with age

  - 4 of 9 (44%) non-mosaic patients had testicular sperm retrieved
- Schiff et al, J Clin Endo Metab, 90(11):6263, 2005
  - 39 of 54 (72%) patients had sperm retrieved with TESE
  - Progressive deterioration of spermatogenesis with age
What we know

- **Regular TESE** can retrieve sperm in 44% of men while **microTESE** can detect residual foci of active spermatogenesis in 55% of azoospermic adult XXY males (Fullerton et al., 2010).
- 78% of patients age 14-22 had testicular sperm retrieved with **microTESE**. (Meta et al, 2013)
What we know….

- Parameters such as testicular volume, FSH, LH and inhibin B plasmatic levels are very poor predictive factors for TESE outcome in KS patients
- The potential for successful sperm retrieval decreases with age in XXY patients (range 30.5 – 35 years) (Okada et al., 2005; Emre Bakircioglu et al., 2006; Ferhi et al., 2009; Bakircioglu et al., 2011; Wikstroëm and Dunkel, 2011)
- The argument has been made that KS patients would benefit from fertility preservation at the onset or just after the onset of puberty and before testosterone therapy

Is there a ‘window of opportunity’ for retrieving any sperm that might be present?
Histological sections from testicular biopsies from boys of various ages with normal testicular function (left panel) and from boys with nonmosaic Klinefelter syndrome (right panel).

Aksglaede L, and Juul A Eur J Endocrinol 2013;168:R67-R76
Testicular biopsies from patients with KS at various ages.

Aksglæde L, and Juul A Eur J Endocrinol 2013;168:R67-R76
Testicular biopsies of adolescent boys with Klinefelter syndrome
Case: DG

- 17 yo with Classic Klinefelter’s
- Low libido, Normal erections, Nocturnal emissions
- T 421, FSH 84, LH 19, E2 19.4, Prl 15.1
- PE: Testes 1 cc bilateral and soft, bilateral varicoceles present
- Azoospermia on 3 spun specimens given 2 months apart
- Had been placed on testosterone for 5 years
LEFT TESIS BIOPSY
How can these sperm be used for conception?
Are these sperm functional?

- In KS, the fertilization potential and the live-birth rate are close to that obtained from nonspecific causes of sperm defects. D Garza, P Patrizio. *Current Opinion in Obstetrics and Gynecology*, 25(3), 2013
Are there concerns regarding use of sperm from KS patients?

- Staessen et al, Human Repro, 11(8) :1650, 1996
  - PGD: All 5 embryos biopsied had normal sex chromosome pattern
  - FISH: 3.9% sex chromosome disomy
- Sciurano et Al, Human Reproduction, 24(9),2353, 2009
  - 11 men, non-mosaic KS had TESE
    - 92 meiotic spermatocytes with FISH were euploid
    - Sertoli cells were 47,XXY
  - 15 KS men w/ sperm retrieved in 26 ICSI cycles
  - 16 children born with normal karyotype (amniocentesis)
Spermatogenesis in KS

- Testicular biopsies of prepubertal KS boys have shown preservation of seminiferous tubules with reduced numbers of germ cells, but Sertoli and Leydig cells have appeared normal.
- The testes in the adult KS male are characterized by extensive fibrosis and hyalinization of the seminiferous tubules, and hyperplasia of the interstitium. However, the tubules may show residual foci of spermatogenesis.
Closing Thoughts for Preserving Fertility in the Adolescent KS Patient

✧ 3 - 8% of adolescent KS patients have sperm in the ejaculate*
✧ Few spontaneous pregnancies have been reported
✧ With TESE sperm can be retrieved in about half of adult KS patients (42% with regular TESE, 55% with microdissection TESE)
✧ Cryopreservation should be offered to adolescent boys having even very few sperm in the ejaculate
✧ Surgical sperm retrieval should be considered for adolescents with azoospermia (50-70% success rate in nonmosaic patients)

* RG Fine, DA Paduch, J Urol, 179(4), 2008 1/30 (3%) KS with sperm in ejaculate
Questions?

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