Endocrine Issues Related to X and Y Chromosome Variations

And a few Rocky mountain wildflowers

Philip S. Zeitler MD, PhD
Division of Endocrinology
Children’s Hospital Colorado
Aurora, Colorado

Topics
- Hypogonadism (testosterone deficiency)
  - Physiology and cause
  - Benefits and disadvantages of testosterone therapy
  - Timing
  - Treatment options
- Small penis
- Gynecomastia
- Other hormonal abnormalities in KS
- Whatever else you want to talk about

Pituitary Hormones
Gonadal axis

Pituitary – gonadal axis

Testosterone secretion
Normal Puberty

Withdrawal of CNS inhibition
Pulsatile GnRH secretion
Pulsatile LH, FSH secretion
Stimulation of testes
Increased sex steroids
Development of secondary sexual characteristics
Production of sperm

Pituitary–gonadal axis

• Axis is functional at birth
  • LH, FSH, and testosterone levels similar to young adults
• Axis is quiet during childhood – latency
  • Mechanism unknown
  • LH, FSH and testosterone very low
• Axis slowly activates at puberty
  • LH rises at night initially
  • Pulses of LH become larger and more frequent
  • Mechanism unknown

LH pulsatility during pubertal onset
Signs of Puberty (Boys)

- Testicular enlargement (>3 ml) 11.8 years
- Pubic hair 12 years
- Penile enlargement 13 years
- Growth acceleration 14 years (peaks in latter half of puberty)

Adrenarche

- Increase in adrenal androgen production (DHEA, DHEA-s, androstenedione)
- Usually at same time of puberty but not always
- Manifest with acne, oily skin, axillary hair, pubic hair
- No testicular enlargement
  - May be difficult in KS, though most boys will have some testicular enlargement at puberty

Tanner Staging (Pubic Hair)

- 2
- 3
- 4
- 5
Pubertal Onset (Boys)
- Testicular enlargement >3 ml
- Age range 9-14 years

Hypogonadism in KS
- Primary testicular failure
  - Central hormones responsible for onset of puberty are normal
  - The testis itself is abnormal and unable to respond appropriately to LH and FSH
Normal Testis

Klinefelter testis
Hypogonadism in KS

- Once “pituitary puberty” starts
  - Pituitary attempts to drive response from the testis
    - Sperm cell production abnormal – FSH rises
    - Testosterone production abnormal – LH rises
- Hypergonadotropic hypogonadism
- LH and FSH won’t be elevated prior to puberty
  - Bone age

Bone age

- A means to determine degree of development
- Puberty generally starts at a bone age of 12 in boys
- Bone age is a better predictor of puberty than chronological age
- LH and FSH are expected to rise only after bone age (biological age) has reached an appropriate development
- Bone age delay does not diagnose anything
- Bone age indicates the remaining growth potential
Timing of testosterone therapy

- Early or late childhood?
  - Small penis
  - Behavioral benefits?
  - Physical benefits of low doses?
    - Theoretical based on low doses present in typical boys

- Age driven
  - Normal time of puberty in boys – 12 to 12.5 years

- LH driven
  - Start testosterone when LH begins to rise
  - Indicates that the pituitary is trying and failing

- Gynecomastia – breast development in males

Small penis

- Normal penis – wide range
  - > 2.5 cm in length and 1 cm in diameter
- The penis may be small due to inadequate testosterone production in utero or in early childhood
- Short courses of low-dose testosterone may be used to promote penile enlargement
- Therapy is not required except for cosmetic purposes
  - No evidence of effect on adult penis size
  - May need to get repeated due to regression
- Depot testosterone 25 mg injection once a month for 3 months
Sex Steroids and Breast Development

- Hormonal effects on breast development
  - Estrogens stimulate breast development
  - Androgens inhibit breast development
  - Breast development thought to reflect increases in E/T ratio
    - decreased T
    - increased E
    - change in conversion rate

Gynecomastia – causes of abnormal E/T ratio

- Slow rise in testosterone fails to keep up with early estrogen in boys with gonadal abnormalities
- Increased LH promotes estrogen secretion preferentially
- Adrenal androstenedione production a precursor for estrogen
  - Decreased testosterone production early doesn’t balance

Consequences of Testosterone Deficiency

- Reduced body hair
- Decreased muscle mass and strength
- Increased fat mass & altered fat distribution
- Unfavourable cholesterol changes (increased LDL and reduced HDL)
- Decreased hemoglobin
- Decreased libido, erectile dysfunction
- Osteoporosis
- Depressed mood
Benefits of testosterone

- Virilization
  - Outward signs of pubertal development
  - Promotion of normal sexual function and development
- Maintain similarly with peers
- Self-esteem
- Muscle development/fat distribution
- Body proportions – reduction in excess limb length
  - Testosterone promotes bone maturation
  - Testosterone promotes spine growth
  - Bone maturation and mineral accumulation
  - Prevention/treatment of gynecomastia
- Behavior?

Disadvantages of testosterone

- Acne
- Increased sexual activity
- Increased strength
- Short stature if started too early or titrated too fast

Options for testosterone therapy
Oral Testosterone

- Not used extensively in the US
- Concern for liver pathology
- May be less of a concern with more modern agents, but pediatric endocrinologists are cautious

Injected testosterone

- Testosterone enanthate or cypionate in oil
- Given every 2-4 weeks

Benefits
- Supervised injections
- Inexpensive
- Don’t have to fuss with it

Disadvantages
- Effect may be inconsistent over the month
- Requires an injection
Injected testosterone

- Starting dose
  - Prepubertal – 75 mg once a month
  - Pubertal 150-200 mg once a month
- Titration
  - Adult dose is 200 mg every 2-4 weeks
  - Titrate to adult dose over 3-4 years (every 12 months or so)
- Adult dose determination
  - Serum testosterone levels – peak or trough?
  - subjective

Transdermal testosterone

- Patch
  - 2.5 or 5 gram patches –
    - Adult dose 2.5 – 10 grams a day
  - Changed daily
  - More consistent than injections
  - Doses fixed
  - Have not been well received in general
    - Itchy
    - Fall off
    - visible
Transdermal testosterone

- Gel
  - Fixed dose pack or pump
  - Applied daily
  - More consistent than injections
- Disadvantages
  - Daily application
  - Messy for some boys
  - May require parental assistance
  - Concern over transfer of testosterone to others

Other

- Buccal
  - Applied to the lining of the mouth
- Implants
  - Placed every 3-4 months by minor surgical insertion
  - Dosing remains uncertain
- Depot testosterone
  - Injected every 3-4 months
  - Delivery designed to be more consistent than monthly injections

Fig. 2. Serum T levels (mean ± SD) during the whole study period (up to 30 months of therapy). After 30 wk of therapy, all patients switched to TU injected every 12 wk.

Monitoring of therapy

- Serum testosterone
  - Injections – trough or peak
  - Subjective
- Gel
  - Morning testosterone 1 month after a dose change
  - Twice a year when on stable dose

Does testosterone help with behavioral difficulties, mood, speech, learning, or motor skills in XXY?

Psychological Effects of Testosterone therapy in XXY

  - Results: Improvements in mood, attention, and social relationships following testosterone treatment
  - Treated group (n=5) had increased verbal fluency scores and increased temporal lobe gray matter compared to untreated group (n=5)
  - Conclusions: Improvements in aggressive behavior and mood after initiation of testosterone in XXY
Current studies:
- Dr. Judith Ross at Thomas Jefferson University
  - NIH funded study on low-dose oral androgen replacement in young males (age 4-13) with XXY
  - Double-blinded
  - Study is no longer enrolling and results will be published in 2012.

Pilot study at Children’s Hospital Colorado
- Inclusion Criteria:
  - 12-21 year old males with XXY, XXYY, XXXY
  - Starting on testosterone replacement therapy
- Recruitment from:
  - Children’s Hospital Colorado, Denver
    - eXtraordinary Kids Clinic
  - National Advocacy Organizations
    - Klinefelter syndrome & Associates (KS&A)
    - The XXXY Project

AIMS / HYPOTHESES

Specific Aim: To identify psychological, behavioral, and motor changes in males with KS/XXY, XXYY and XXXY before and after 12 months of testosterone treatment.
NEXT STEPS:

- Placebo-controlled trial of testosterone gel started in early puberty in adolescents with XXY
- Children’s Hospital Colorado, eXtraordinarY Kids Clinic
- Principal Investigator: Nicole Tartaglia, MD
  - Co-investigators: Phil Zeitler, MD, PhD
  - Bruce Bender, PhD (psychologist)
  - Richard Boada, PhD (psychologist)

Study Protocol:

- Included: Males with XXY just starting puberty (approximately 10-14 years of age)
- 3 research visits in Denver
  - Travel costs and testosterone gel included as part of study participation
- Study visit will include:
  - Physical Examination
  - Neuropsychological testing (Cognitive skills/IQ and executive functioning)
  - Motor Skills (strength, balance, coordination)
  - Behavioral questionnaires

- Contact Susan Howell or Dr. Tartaglia for more information about the study at the eXtraordinarY Kids Clinic table in the lobby

Other hormonal abnormalities in KS

- Hypothyroidism
Thyroid axis

Hypothyroidism
- Primary thyroid failure
- Cause unknown
- Analogy to gonadal failure
  - Thyroid fails
  - Low T4
  - TSH rises
- Treatment easy
- Levothyroxine (T4) replacement
  - No need to replace T3 – body converts naturally
  - Titrate to normal TSH

Other hormonal abnormalities in KS
- Diabetes
  - Generally related to excess body fat
- Low bone density
  - Vitamin D deficiency
  - Hypotonia, low muscle mass
  - Delayed testosterone replacement or testosterone deficiency
  - Overt osteoporosis (fracturing) is uncommon
Questions?