Prader Willi Syndrome and Hypogonadism

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No Conflict of Interest to Disclose

Objectives

- Identify the clinical features of hypogonadism and incomplete / delayed puberty in a male with Prader Willi syndrome (PWS)
- Understand the role of hCG in evaluation and treatment of hypogonadism in PWS
- Discuss expert recommendations for the treatment of hypogonadism in males with PWS
Introduction

• PWS is a multisystem genetic disorder (15q11.2-q13)

• Complex phenotype likely caused by hypothalamic dysfunction leading to hormonal dysfunction and the absence of satiety

• Hypotonia and hypogonadism are the first manifestations of a primitive hypothalamic alteration, which many believe is the basis of PWS

Introduction

• Hypogonadism is a common clinical feature of PWS which confirms the importance of hypogonadism as a major diagnostic criterion of PWS

• Patients with PWS commonly fail to spontaneously initiate or complete puberty

• However, many have premature adrenarche

• Precocious puberty is more rare

Case Study Hypogonadism in PWS
Currently 19 year old male

History:
• Diagnosed clinically at age 2 years, and at 6 years based on methylation studies; Consistent with imprinting abnormality*
• Hypotonia and poor feeding in the newborn period
• Developmental delay and hyperphagia in the early childhood years
• Seen at outside institution, on GH for 6 months, but therapy stopped due to hyperglycemia
• Lost to follow up until age 14 years, when referred by PCP regarding micropenis and crypto-orchidism
Case Study Hypogonadism in PWS

**Stature**

- Restarted GH at ~18 years of age

**Weight**

- Hospitalized at Pittsburgh for medical weight loss program at ~16 years of age

**Concurrent Health Issues**

- Obesity
- Sleep apnea - on CPAP
- A lot of daytime tiredness and fell asleep easily
- History of strabismus (wears corrective lenses)
- History of behavioral problems
- Vitamin D insufficiency 21 ng/mL, improved to 29 ng/mL after taking 2000 units daily from April-November 2013
- Normal Ca, Phos, Alk Phos
- Diabetes T2
Case Study Hypogonadism in PWS
Initial Evaluation in Endocrine Clinic

- Age 14 years; clinic visit after lost to follow up
- Acanthosis nigricans
- BMI: 41 kg/m²
- Tanner 2 PH, large suprapubic fat pad, stretched penile length difficult to measure but was ~ 3.5 cm, testicles not palpable
- Plan to obtain gonadotropin and testosterone blood work, bone age, refer to urology and PWS clinic

Case Study Hypogonadism in PWS
Results
Pre-pubertal Testosterone, LH, FSH

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FOLLICLE STIMULAT.</td>
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<tr>
<td>TESTOSTERONE, TOTAL</td>
<td>15 *</td>
<td></td>
</tr>
<tr>
<td>LH BICMA</td>
<td>0.021 *</td>
<td></td>
</tr>
<tr>
<td>FREE TESTOSTERONE</td>
<td>1.8 *</td>
<td></td>
</tr>
<tr>
<td>FREE TESTOSTERONE (%)</td>
<td>1.2 *</td>
<td></td>
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<tr>
<td>SEX HORMONE BINDING</td>
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Ranges
- FSH: Tanner 1, 0.26 – 3
- T: Tanner 1, <3 - 10
- LH: Tanner 1, 0.02 - 0.3
- Free T: Adult Males: 52 - 280
- Free T %: Adult Males: 1.5 - 3.2
- SHBG: Pubertal Males: 16 - 100

Case Study Hypogonadism in PWS
Results
Bone Age Reading

- Chronological age 14 years 1 month
- Bone age 16 years
- Previously on GH therapy at outside institution, was stopped due to hyperglycemia
Case Study Hypogonadism in PWS

- 15 years
- Very prominent suprapubic fat pad which completely engulfed his penis; circumcised but fairly small in size
- Scattered thin pubic hair
- Testicles were difficult to feel. Possibly palpated right testicle higher up above the scrotum; could not palpate left testicle
- Referred to Urology

Case Study Hypogonadism in PWS
Scrotal Ultrasound

Testes not identified

Case Study Hypogonadism in PWS
Urology Plan

“Because this is a much older child and he is morbidly obese, I think that it may be helpful to obtain a scrotal ultrasound to locate the testicles and assess their size

Performing orchidopexy in this young man would be extremely difficult because of his age and size in addition to the anesthetic risks because of his obesity

There is no guarantee that the testicles would function properly, even after surgery

Discuss the situation with endocrinology”
Case Study Hypogonadism in PWS

- Plan to do hCG stimulation testing, monitor for rise in testosterone indicating presence of testes, then repeat scrotal ultrasound with anticipated enlargement of testes*
- Administer hCG, 1500 units/m2 (3000 units) twice per week
- Draw total testosterone 3 days after every other hCG injection
- For example, hCG Monday, hCG on Friday, then hCG injection and testosterone level on Monday
- Continue for up to 6 weeks. Stop test if testosterone level reaches 300 ng/dl

Case Study Hypogonadism in PWS

Results

hCG Stimulation Test Results

Rise in testosterone, but overall below reference range 100-500 ng/dL

<table>
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<tr>
<th></th>
<th>5/10/2012</th>
<th>5/24/2012</th>
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<td>023</td>
<td>1610</td>
<td>1603</td>
<td>1608</td>
</tr>
<tr>
<td>TESTOSTERONE</td>
<td>24*</td>
<td>50*</td>
<td>90*</td>
<td>92*</td>
</tr>
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</table>
Case Study Hypogonadism in PWS

Scrotal Ultrasound Report

- On US he had small, ovoid hypoechoic structures in inguinal canals bilaterally
- No vascularity on doppler
- Essentially, testes were present, but small and atropic

Case Study Hypogonadism in PWS

Case Management

Laparotomy

- Diagnostic laparotomy performed February 2013 with potential for orchidopexy, age 17 years
- Orchiectomy was performed
- Pathology report showed infantile, atrophic changes with no evidence of spermatogenesis

Case Study Hypogonadism in PWS

Case Management

Testosterone Dosing IM (Q month)

- Testosterone 50 mg started in April 2013
- Increased to 100 mg in November 2013
- Increased to 150 mg in June 2014
- Increased to 200 mg in February 2015
Case Study Hypogonadism in PWS

Case Management
Response to Testosterone

• At testosterone dose of 100 mg monthly:
  Penis increased to 6 cm x 2 cm
  Tanner stage 4 pubic hair
  Axillary hair present

• At testosterone dose of 150 mg monthly:
  Noted voice change
  Noted increased assertiveness
  No noted aggression or anger

Case Study Conclusion

Hypogonadism in Males with PWS

• Cryptorchidism in ~ 80-100%
• Small testes ~76%
• Scrotal hypoplasia 69%
• Incomplete, delayed, or disordered pubertal development
• Premature adrenarche common ~14%
• Premature puberty can occur ~3%
• No reports of paternity from PWS men
• Testosterone levels often subnormal but lower SHBG can raise free testosterone

(Goldstone AP et al, 2008)
Hypogonadism in Males with PWS

Prevalence of genital abnormalities and pubertal findings in PWS subjects

<table>
<thead>
<tr>
<th></th>
<th>Male: n = 42 (14.2% of 301)</th>
<th>Female: n = 4 (1.3% of 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptorchidia</td>
<td>13 (31%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Microphallus</td>
<td>10 (24%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Phimosis</td>
<td>3 (7%)</td>
<td>0 (0%)</td>
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</table>

(Crino et al., 2003)

Hypogonadism in Males with PWS

What about hCG?

TREAT

NOT TO TREAT

Role of Hcg in Treatment of Males with PWS

Diagnostic Management of Cryptorchidism

American Urological Association : Guideline Statement 3

- Refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by six months *
- Testes that remain undescended by six months are unlikely to descend spontaneously
- The rationale for referral for orchidopexy by six months is the low probability of spontaneous descent and the probable continued damage to testes that remain in a non-scrotal location.

(American Urological Association, 2014)
Role of hCG in Treatment of Males with PWS

Treatment Management of Cryptorchidism
American Urological Association: Guideline Statement 10

- Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy
- Studies show a significant risk of recurrence. An individual study may show a reasonable effect in inducing testicular descent, the overall review of all available studies fails to document long-term efficacy

(American Urological Association, 2014)

Role of hCG in Treatment of Males with PWS

Dr. Jennifer Miller, "Approach to the child with Prader-Willi syndrome"

- Treatment with hCG is recommended for infant males with undescended testes because it may help with testicular descent, "more than in typical males with cryptorchidism"
- And it improves the size of the scrotal sac if orchiopexy is needed

(Crino et al., 2003; Goldstone et al., 2008; Miller, 2012)

Hypogonadism in Males with PWS

hCG may be beneficial to assess function of the testes, but may not be beneficial for treatment of undescended testes
Experts on Hypogonadism in PWS

- Cryptorchidism: Address during the first or the second year, particularly because there is evidence of both primary and central hypogonadism

- Rare cases of testicular cancer have been reported in PWS

- Scrotal hypoplasia and obesity can make surgery difficult if delayed until a later age and could require repeated surgical interventions


Experts on Hypogonadism in PWS

- Rare cases of testicular cancer have been reported in PWS

(Pediatric Research, 1999)

Hypogonadism in Males with PWS

- Children with PWS display a specific form of combined

- Hypothalamic (low LH) and peripheral (low inhibin B and high FSH)

- Hypogonadism, suggesting a primary defect in Sertoli and / or germ cell

- Maturation or an early germ cell loss. hCG therapy stimulates testosterone production and virilization

(J Clinical Endocrinology Metabolism, 2006)
Hypogonadism in Males with PWS

Testicular Failure After Puberty Onset
• Boys have normal inhibin B levels until age 10 yrs, but after puberty onset inhibin B levels declined to < 5% tile and FSH increased to > 95% tile
• Testosterone increased with puberty but remained < 5% tile
• LH increased but not above 95% tile
• Major cause is primary hypogonadism

( Siemensma EP et al, 2012)

Normal Puberty

(Myer, date unknown)

Effects of Hypogonadism in PWS Males

• Likely contributes to decrease in bone and muscle mass and increase in body fat
• Severe obesity in PWS contributes to mortality and decreased quality of life
What about Testosterone Replacement?

Japanese Study with PWS Males

Japanese study of 22 PWS male patients age 16 and 48 years; serum Testosterone < 300
Patients with existing modified overt aggression scale > 4 excluded

Example:

- Threatens violence toward self or other; repeatedly or deliberately
- Sets fires; throws objects dangerously
- Inflicts major injury on self or makes a suicide attempt
- Attacks others, causing serious injury (fracture, loss of teeth, deep cuts, loss of consciousness, etc.)

(Kido et al, 2013)
Japanese Study with PWS Males

• Measurements prior to testosterone replacement and 1 month after last injection
• Testosterone 125 mg IM monthly
• Measurements: pubertal stage, body hair, T, LH, FSH, HGB/HCT, HDL, AST/ALT, Chol, Trigs, LDL, BG, A1C
• Measured erectile dysfunction, ejaculation, spermatogenesis
• Measured DEXA, BMI, % body fat
• MOAS- aggression scale

(Kido et al, 2013)

Japanese Study with PWS Males After Two Years

• Increased pubic hair 16/22 patients
• Emergence of erectile function 8/22 patients
• Ejaculation 3/22 patients
  – No sperm in samples
• 1 month post-injection Testosterone levels all <300
• Improvement in DEXA and body composition
• No change in aggression
• Non-significant increase in HGB/HCT
• Non-significant decrease in HDL

(Kido et al, 2013)

Treatment for Hypogonadism in PWS

Recommendations: Expert care meeting on PWS 2008

• No standardized protocols for sex hormone treatment nor prevention of osteoporosis
• Benefits of treatment include prevention of osteoporosis and fracture
Expert Treatment of Hypogonadism in PWS

Hormone replacement:

- Low dose testosterone (injections, transdermal patch or gel) using escalating doses every 3-6 months to allow testosterone to get to normal level or HCG injections


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Expert Treatment of Hypogonadism in PWS

- Monitor androgen status annually during adolescence and adulthood
- DEXA as clinically indicated
- Consider gonadal hormone replacement


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Body Image and Sexual Interests in PWS

PWS FYI:

- Half of patients reported having been on a date and kissing romantically
- All males and 64% females wished to marry
- 77% of males wanted hormonal treatment to increase phallic size
- 43% of females wanted hormonal treatment to achieve regular menstruation
- No correlation between hormonal levels and sexual interests

(Gross-Tsur et al, 2011)
“We don’t know a millionth of one percent about anything.”

A Special Thanks

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Endocrine Fellow

References

References