“Testotoxi-WHAT?”
Overview of Diagnosis and treatment of testotoxicosis

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Objectives
Increase knowledge of diagnostic criteria for testotoxicosis
2 case studies
Differentiate diagnosis from central precocious puberty and adrenal issues
Discuss treatment and monitoring of therapy
(In)experienced Nurse Practitioner scenario

PCP calls office to ask about …
NP sees patient
Presents to MD
Is it “testotoxicosis?”

Testotoxicosis: Definition

Precocious puberty
- Peripheral source of origination
- Occurs ONLY in males
- Caused by mutation of LH receptor

Testotoxicosis-WHAT?
Testotoxicosis: Clinical criteria

Secondary sexual maturation begins early (ages 1-4)
Rapid growth acceleration
Skeletal development advancement
Genital maturation
  Testicular/genital enlargement
  No adrenarche

Testotoxicosis: Clinical criteria

Laboratory testing
  Testosterone level significantly elevated
  LH/FSH suppressed
    No LH response to GnRH

Testotoxicosis: Clinical criteria

Histological examination
  Leydig cell maturation
  Potential for spermatogenesis
Testotoxicosis: Causes

Mutation of LHCG receptor
  Luteinizing hormone
  Human chorionic gonadotropin
  Familial - male limited

Case studies

21 month old male presents with
  enlarged genitalia
  testicular enlargement
  rapid growth
  very "strong"
  ? pubic hair development

Case study

Picky eater
  Active child
  Sleeps 10 hours/night (though recently has been sleeping less)
  General health "good"
Case study

Birth history

Full term, uncomplicated pregnancy
8 lb 4 oz - 21.5 inches

Case studies

Past medical history
Unremarkable
Normal developmental milestones except delayed speech
Immunizations UTD
No medications
No hospitalizations
No head trauma/loss of consciousness
No exposure to androgens

Case studies

Family history
Unremarkable for endocrine diseases EXCEPT “similar problem with other males in family”
Mom 5'3” - 170 lbs (pregnant) - 22 years old
Dad 5'10”, 168 lbs - 24 years old
2 siblings “normal”
Maternal grandfather
- “developed early” - pubic hair at 19 months
- 4'11” as adult
Great uncle with early puberty
- “short”
Case studies

Review of systems
Endo
Polydipsia "loves to drink"
Rapid growth
Pulmonary
Occasional wheezing
Remainder of ROS normal

Case studies

Physical examination
Height: 92.5 cm >95th%
Weight: 15.7 kg >95th/4ile
General: large/tall for age
HEENT: Normal
EOMs intact
Fundi benign
Neck: No thyromegaly

Case studies

Chest: Symmetrical
Lungs: CTA bilaterally
Cardio: No murmur, RRR
Abdomen: Soft, non distended
Extremities: Full ROM, reflexes intact
Neuro: grossly intact
Skin: normal, no rash, birthmark
Case studies

GU
Normal male external genitalia with significant pubertal development
Genitalia: Tanner III, stretched length 10 cm, 3 cm diameter, testes 5 ml bilaterally
Pubic hair: Tanner very early III
Axillary hair: Tanner I

Case studies

Labs
LH <0.1 uIU/ml
FSH <0.2 mIU/ml
Testosterone 22.2 (?)
Additional labs ordered by endo
LH, FSH, T, Estradiol
DHEA-S, DHEA, androstenedione, CAH profile
Genetic testing for LHCGR mutation
Bone age X-ray

Endo labs back
LH 0.1 uIU/ml
FSH <0.3 mIU/ml
TE 294 ng/dl
Estrogen <12 pg/ml
Adrenal androgens all low and CAH profile normal except T 392 ng/dl
Bone age
CA 1 9/12 - Bone age 2 9/12 (wrist), 2 0/12 (carpals), 4 6/12 (phalanges)
Genetic testing (Athena Diagnostic)
Pathologic mutation in LHCGR gene
Treatment

Anti-androgen
Casodex (Biclutamide) *50 mg po daily
Aldactone (Spironolactone)
Other anti-androgenic effects in anti fungal Ketoconazole
Aromatase inhibitor
Arimidex (Anastrazole) * 1 mg po daily
Teslac (Testolactone)
Unresponsive to GnRH agonists
(at least early in treatment)

Treatment:
antiandrogens

Biclutamide
Typical use in prostate cancer
Dosing: 50 mg once daily

Treatment:
anti-androgens

Biclutamide mechanism of action
Nonsteroidal antiandrogen binding to androgen receptors
Inhibitor for binding of DHT and T
Treatment: antiandrogns

Biclutamide side effects
- Gynecomastia/breast pain
- Anemia
- Hepatotoxicity
- Cardiovascular issues
- Decreased bone mineral density

Treatment: aromatase inhibitors

Anastrazole
- Typical use in breast cancer
- Dosing 1 mg po daily

Anastrazole mechanism of action
- By inhibiting aromatase, conversion of androstenedione to estrone AND testosterone to estradiol prevented
Treatment: aromatase inhibitors

Anastrazole monitoring
Decreased bone mineral density
Hypercholesterolemia
Hepatotoxicity

Long term follow up

LH, FSH, T, estradiol serially
Bone age serially
CMP (liver functions)
Monitor growth and development every 3 months
Watch closely for signs of central precocious pubertal development

Long term follow up

Patient now ___ years old
Recent labs
Recent BA
Ht
Wt
Growth velocity
Tanner staging
Case study #2

5 years, 6/12 year old male diagnosed with testotoxicosis and on treatment with Casodex and Arimidex

Ht 131.1 cm - >97th %ile
Wt 30.3 kg - >97th %ile

Exam WNL except:
- Chest: Breast development bilaterally
- Tender
- GU: Genitalia: Tanner III, testes 8 ml bilaterally
- Pubic hair: Tanner II
- Axillary hair: Tanner I

Case study #2

Routine labs
- LH 2.2 uIU/ml
- FSH 2.1 mIU/ml
- T 628 ng/dl
- Estradiol <12 pg/ml

Bone age
- CA 5 6/12 years - BA 8 0/12 - 9 0/12

Case study #2

Lupron challenge
- Premed labs
  - LH 0.5 mIU/ml
  - FSH 1.4 mIU/ml
  - T 333 mg/dl
- Depot-Lupron Peds 11.25 mg IM x1
- LH 17.8 mIU/ml

Dx: Central precocious puberty, secondary to testotoxicosis
Case study #2

Treatment

Continue patient on present Casodex and Arimidex
Add Depot-Lupron 11.25 mg IM every 28 days (awaiting Supprelin approval)

Treatment

Depot-Lupron Peds (1 or 3 month)
Supprelin (Histrelin) implant annually

Testotoxicosis vs. Central puberty

<table>
<thead>
<tr>
<th>Testotoxicosis</th>
<th>Central puberty</th>
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<tbody>
<tr>
<td>LH, FSH low</td>
<td>LH, FSH elevated</td>
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<tr>
<td>TE elevated</td>
<td>TE elevated</td>
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<tr>
<td>Genitalia/testicular enlargement</td>
<td>Genitalia/testicular enlargement</td>
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<tr>
<td>Typically no hair</td>
<td>Hair</td>
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</tbody>
</table>
Genetics

Parents and siblings of affected child should be tested

Case study #2: Mom and sisters both carriers of gene for testotoxicosis

Could have affected male children (50% chance)

Genetics

Autosomal recessive

Girls are unaffected because activation of both LH and FSH receptors required for estrogen biosynthesis

similar to HcG secreting germ tumor

References
Questions?