“Testotoxi-WHAT?”

Overview of
Diagnosis and treatment
of testotoxicosis

Janet L. Moore, MSN, RN, PNP-BC
University of Toledo College of Medicine

Financial Disclosure

I have no financial disclosures

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?”

Testotoxi-WHAT?

Testotoxicosis: Definition

Precocious puberty

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

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 sisters "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%ile
- 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 II
  - 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

Case studies

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 8/12 (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
- Hepatotoxitity
- Cardiovascular issues
- Decreased bone mineral density

Treatment: aromatase inhibitors

Anastrazole

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

Treatment: aromatase inhibitors

Anastrazole mechanism of action

- By inhibiting aromatase, coversion 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 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

Testotoxicosis	Central puberty
LH, FSH low	LH, FSH elevated
TE elevated	TE elevated
Genitalia/testicular enlargement	Genitalia/testicular enlargement
Typically no hair	Hair

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?