A Rare Case of Disorders of Male Sex Development

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October-19-2010
Sexual Development During Embryogenesis

- Establishment of chromosomal sex at fertilization (XX vs XY)
- Determination of gonadal sex (week 8)
  SRY (sex determining region of the Y chromosome)
- Development of sexual phenotype (completed by week 12 in male and somewhat later in female)
Gonadal sex is translated into male phenotypic sex by hormonal secretions of the fetal testis.

**Mullerian inhibitory hormone (MIH)**

**Testosterone (T)**
- Wolffian duct differentiation

**Dihydrotestosterone (DHT)**
- Male external genitalia development

In females, the Müllerian ducts give rise to the fallopian tubes, uterus, and upper vagina, and the Wolffian ducts persist in vestigial form. In males, the Wolffian ducts give rise to the epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts, and the Müllerian ducts regress.
Gonadal sex is translated into male phenotypic sex by hormonal secretions of the fetal testis.

Mullerian inhibitory hormone (MIH)

Testosterone (T)
Wolffian duct differentiation

Dihydrotestosterone (DHT)
Male external genitalia development

In females, the genital tubercle becomes the clitoris, the genital swellings become the labia majora, and the genital folds become the labia minora. In males, the genital tubercle becomes the glans penis, the genital swellings fuse to become the scrotum, the genital folds elongate and fuse to form the shaft of the penis and the penile urethra, and the prostate forms in the wall of the urogenital sinus.
Androgen Action
Androgen Receptor Defects (common):
- Androgen insensitivity syndrome
  - Complete: female with high LH and T
  - Incomplete: ambiguous genitalia
- Partial androgen insensitivity: Male Infertility
- MIH gene/receptor defect: persistent Mullerian ducts, normal external genitalia and variable testis descent
- Testicular Atrophy
  - Gonadal dysgenesis
  - Testis Regression Syndrome
  - Vanishing Testis
- Endocrine disruptors
  - Compounds with anti-androgen action e.g. DDE, vincozolin
46 XY Disorders of Sexual Development

- Androgen Biosynthesis Defect (testis, hCG stimulation test)
  - 5 alpha reductase deficiency
  - 17 beta hydroxysteroid dehydrogenase 3 defect
  - LH receptor defect

- Congenital Adrenal Hyperplasia (adrenal and testis, ACTH stimulation test)
  - StAR protein deficiency – adrenal insufficiency
  - Side chain cleavage deficiency – adrenal insufficiency
  - 3 beta hydroxysteroid dehydrogenase deficiency – adrenal insufficiency
  - 17 alpha hydroxylase deficiency- hypertension, hypokalemia
Testosterone Biosynthesis Pathway

Adrenal and testis
- Cholesterol → Pregnenolone
  - CYP11A1 (cholesterol side chain cleavage enzyme)
- Pregnenolone → Progesterone
  - 3-beta-HSD (3-beta-hydroxysteroid dehydrogenase/isomerase)
  - CYP17 (17-alpha-hydroxylase)
- Progesterone → 17-OH-Progesterone
  - CYP17 (17,20-lyase)
- 17-OH-Progesterone → Androstenedione
  - CYP17 (17-beta-hydroxysteroid dehydrogenase)

Testis
- Androstenedione → Testosterone
  - 5-alpha-reductase
- Testosterone → Dihydrotestosterone
  - CYP19 (aromatase)
- Testosterone → Estradiol
  - CYP19 (aromatase)
17 β hydroxysteroid dehydrogenase 3 in testis/ovary converts Androstenedione to Testosterone and Estrone to Estradiol.
AIS: androgen insensitivity syndrome; MIS: Müllerian inhibiting substance; p450scc: P450 side chain cleavage.
History

- 50 y/o female born in Vietnam with Chinese parents.
- CC: bilateral inguinal mass
- The groin masses were present since childhood but they start growing since 1998 and progressively the left side enlarged since 6 years ago and now is painful.
- No constitutional symptom.
Past Medical History

- Primary amenorrhea
- Never been sexually active
- Bilateral breast implant in 2004
- Medication: none       Allergy: none

Family History:

- Has 4 sisters and 2 adopted brothers.
- All sisters are healthy and have kids.
Exam
Exam

- **Abdomen** soft non-tender, no masses
- **GU**
  - Bilateral inguinal masses: Left 6x5x7cm inguinal mass lateral to left labia majora, tender to palpation
  - Right 2x1cm lateral to right labia majora, nontender to palpation
- **Pelvic**
  - Clitoromegaly
  - Blind ending vagina (depth 2 cm)
  - No cervix
  - Urethral meatus normal
- **Tanner stage** unclear (pubic hair shaved and breast implants)
Laboratory

- Karyotype 46 XY
- Testosterone 114 ng/dl
- DHT 20 ng/dl
- FSH 38 mIU/ml
- LH 32 mIU/ml
- Estrone 154 pg/ml
- Estradiol 16 pg/ml
- Prolactin 10.5 (3-29) ng/ml
- 17-OH Pregnenolone 33 ng/dl
- DHEA 331 mcg/dl
- Androstenedione 451 ng/dl

U/A nl
LDH 348 (98-192) U/L
β-hCG 54.4 (<2.9) mIU/ml
AFP 1.2 (0-9) ng/ml
Summary

- Karyotype XY
- High LH & FSH
- Normal pregnenolone, progesterone and 17 α pregnenolone and 17 α progesterone, DHEA
- Normal cortisol and ACTH
- Normal T to DHT ratio 114: 20 ng/dl
- **High Androstenedione to Testosterone ratio 451: 114 ng/dl**
- **High Estrone : Estradiol ratio 154:16 pg/ml**
- HCG stimulation tests required for diagnosis in pre-pubertal subjects, baseline levels are adequate for diagnosis in adults
Imaging
CT scan of chest didn’t show any evidence of pulmonary metastasis or mediastinal lymphadenopathy.
Operation

- Bilateral Inguinal Exploration
- Excision of Bilateral Inguinal Masses
Pathology

Gross, left testicle
- 270 grams
- 10 x 8 x 6 cm
- Entire testicle replaced with tumor

Slides from: Tauseef Haider, M.D.
Histology, Left testicle

- Sheets of uniform tumor cells
- Foci of necrosis

Slides from: Tauseef Haider, M.D
Histology, Left testicle

- Large round cells
- Clear cytoplasm
- Large central nucleus
- Delicate fibrous septa
- Lymphocytic infiltrate

Slides from: Tauseef Haider, M.D
Gross, right inguinal mass

- 3.5 x 1.5 x 2 cm

Slides from: Tauseef Haider, M.D.
Histology, right inguinal mass

- Scattered nodules

Slides from: Tauseef Haider, M.D
Histology, right inguinal mass

- Leydig cell nodules
- Extensive tubular atrophy

Slides from: Tauseef Haider, M.D
Histology, right inguinal mass

- No evidence of spermatogenesis

Slides from: Tauseef Haider, M.D
Left Testicle

- Seminoma with necrosis (10 cm)
- Lymphovascular invasion not identified
- No invasion of epididymis noted, and tumor limited to testis
- Margins free of tumor
- PT1NXMX
Right Inguinal Mass

- Testis showing advanced tubular atrophy, no evidence of spermatogenesis and nodular hyperplasia of Leydig cells.
Clinical Course

- XRT: covering pelvic and inguinal nodes and para-aortic chain (2500 cGy in 15 sessions in 3 weeks).
- Osteopenic base on bone mineral density.
- Low density lesion in left thyroid bed.
- Tender mass 2X 2.5 cm on exam on left lateral side below knee for last 6-7 years, c/w peripheral nerve sheet tumor.
Discussion
17β Hydroxysteroid Dehydrogenase 3 Deficiency

- Rare autosomal recessive male underandrogenization with variable phenotype (female no phenotype)
- External genitalia female at birth
- Hypoplastic Wolffian duct structures
- Testes in inguinal canal
- Pubertal surge in LH and FSH may cause some virilization (due to extra-gonadal 17β HSD activity)
- Gynecomastia may be present
- Testes: atrophic seminiferous tubules with Sertoli cells and Leydig cell hyperplasia
17β Hydroxysteroid Dehydrogenase 3 Deficiency

- High Androstenedione to Testosterone ratio
- High estrone to estradiol ratio
- Encoded by the HSD 17B3 gene exclusively in the testes
- Located on chromosome 9q22
- More than 20 mutations were reported (homozygous or compound heterozygous)
Treatment

- Most patients are raised as female and undergo virilization during adolescence.
- Partial virilization or early post-natal diagnosis → androgen treatment → male sex assignment and normal male phenotype in adulthood
- Gonadectomy
- Hormone replacement therapy → female characteristics
Acknowledgment
- Christina Wang, M.D.

Thank You