4 year-old boy with micropenis and hypospadias

Endorama
April 30, 2015
Carmen Mironovici, M.D.
Chief Complaint

- Ambiguous genitalia
- Patient was referred to pediatric endocrinology by Pediatric Urology for evaluation and management of “Perineal hypospadias and extreme penoscrotal transposition with bifid scrotum”
HPI

- 4 y 5 mo boy adopted from China on 11/20/14, with a known history of DSD
- He was abandoned as a newborn and has been raised as a male at an orphanage in China
- **Chinese medical records:**
  - Karyotype (3/2013): 46, XY
  - Pelvic US (3/2013): No presence of uterus, ovaries or vagina
  - Head CT (7/2013): Right cerebral hemisphere, corpus callosum and septum pellucidum are not well developed. Gray matter heterotopia is observed beside the R ventricle. Mild hydrocephalus.
Past Medical History

- **Birth Hx:** Unknown
- **Medical Hx:**
  - Hydrocephalus
  - UTI
  - Malnutrition
  - Micropenis, hypospadias
- **Family Hx:** Unknown
- **Social Hx**
  - LAHW adoptive parents
  - He is their first child
  - Knows a few English words
  - Did not start school yet
- **Allergies:** NKDA
Important Info from Family History

• Any infertile/amenorrheic females or partially virilized men

• Current and any previous pregnancies: maternal virilization; exposure to androgens

• Exposure of either parent to endocrine disruptors such as phenytoin or aminoglutethimide

• Any siblings with ambiguous genitalia

• Any unexplained infant deaths (especially neonatal)

• History of consanguinity in biological parents
ROS

- **Constitutional**: Negative for fever, fatigue
- **Endo**: Ambiguous genitalia. Negative for polyuria, polydipsia, polyphagia, cold intolerance
- **HENT**: Negative - no neck swelling. Unsure sense of smell.
- **Eyes**: Negative for redness
- **Respiratory**: No wheezing / stridor
- **Cardiovascular**: Negative for chest pain, leg swelling
- **Gastrointestinal**: Negative for abdominal pain and distention
- **Genitourinary**: Positive for hypospadias, micropenis, bifid scrotum. Positive for dysuria, foul smelling and turbid urine. Negative for difficulty urinating.
- **Musculoskeletal**: Negative for joint swelling
- **Skin**: Positive for diaper rash. Negative for color changes, pallor
- **Neurological**: Positive for headaches. Negative for weakness, dizziness
Physical Exam

- **Vitals:** T 98.4 F, HR 103, RR 21, BP 97/62, SpO2 98% on RA
- **Height 97cm (3%ile), Wt 15.3 kg (16 %ile), BMI 16.2 kg/m2 (73%ile), BSA 0.64 m2**

- **Constitutional:** WN, WD, interactive by gestures
- **HENT:** Oral mucous membranes are moist. **Dolicocephaly. No midline defects**
- **Neck:** Neck supple. **Non palpable thyroid.** No cervical LAD
- **Chest:** No gynecomastia. No breast discharge. No AH
- **GU:** Tanner I external genitalia/pubic hair
  Penile urethra. Severe perineal hypospadias associated with separation of the scrotal sacs. Stretch penile length: 2.5 cm. Penile width: 1 cm. Severe ventral curvature (chordee) Gonads palpable in the labioscrotal folds bilateral. No PH. Patent, normal appearing anus. **No penoscrotal transposition**
- **Musculoskeletal:** **No limb abnormalities**
- **Neurological:** Awake, alert. Normal DTRs. Normal tone
- **Skin:** Warm, cap refill < 2 secs. **Mild erythematous rash** in the diaper area, spares inguinal folds. No satellite lesions, no denuded skin. No hyperpigmentation.
External genitalia appearance
Initial thoughts?

• One in 4,500 live births have “ambiguous genitalia”

• Gonads palpable below the inguinal ligament (in the labioscrotal folds) are usually testes

• Work up for ambiguous genitalia is usually initiated at birth
Mean and calculated -2.5 SD values for stretched penile length

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean</th>
<th>Mean -2.5 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm newborns (30 weeks)</td>
<td>2.5±0.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Preterm newborns (34 weeks)</td>
<td>3.0±0.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Term newborns</td>
<td>3.5±0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Infants and children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5 months</td>
<td>3.9±0.8</td>
<td>1.9</td>
</tr>
<tr>
<td>6-12 months</td>
<td>4.3±0.8</td>
<td>2.3</td>
</tr>
<tr>
<td>1-2 years</td>
<td>4.7±0.8</td>
<td>2.6</td>
</tr>
<tr>
<td>2-3 years</td>
<td>5.1±0.9</td>
<td>2.9</td>
</tr>
<tr>
<td>3-4 years</td>
<td>5.5±0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>4-5 years</td>
<td>5.7±0.9</td>
<td>3.5</td>
</tr>
<tr>
<td>5-6 years</td>
<td>6.0±0.9</td>
<td>3.8</td>
</tr>
<tr>
<td>6-7 years</td>
<td>6.1±0.9</td>
<td>3.9</td>
</tr>
<tr>
<td>7-8 years</td>
<td>6.2±1.0</td>
<td>3.7</td>
</tr>
<tr>
<td>8-9 years</td>
<td>6.3±1.0</td>
<td>3.8</td>
</tr>
<tr>
<td>9-10 years</td>
<td>6.3±1.0</td>
<td>3.8</td>
</tr>
<tr>
<td>10-11 years</td>
<td>6.4±1.1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Hatipoglu N et al.  
J Clin Res Pediatr Endocrinol 2013
Etiology of micropenis

I. Deficient testosterone secretion
   A. Hypogonadotropic hypogonadism
      1. Isolated, including Kallmann’s syndrome
      2. Associated with other pituitary hormone deficiencies
      3. Prader-Willi syndrome
      4. Laurence-Moon syndrome
      5. Bardet-Biedl syndrome
      6. Rud’s syndrome
   B. Primary hypogonadism
      1. Anorchia
      2. Klinefelter’s and Poly X syndromes
      3. Gonadal dysgenesis (incomplete form)
      4. Luteinizing hormone receptor defects (incomplete forms)
      5. Genetic defects in testosterone steroidogenesis (incomplete forms)
      6. Noonan’s syndrome
      7. Trisomy 21
      8. Robinow’s syndrome
      9. Bardet-Biedl syndrome
     10. Laurence-Moon syndrome

II. Defects in testosterone action
   A. Growth hormone/insulin-like growth factor-I deficiency
   B. Androgen receptor defects (incomplete forms)
   C. 5α-reductase deficiency (incomplete forms)
   D. Fetal hydantoin syndrome

III. Developmental anomalies
   A. Aphallia
   B. Cloacal extrophy

IV. Idiopathic

V. Associated with other congenital malformations
### 46,XY DSD DUE TO TESTOSTERONE SYNTHESIS DEFECTS

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Leydig cell differentiation (LHCGR defects)</td>
<td>Complete and partial forms</td>
</tr>
<tr>
<td>Enzymatic defects in testosterone synthesis</td>
<td></td>
</tr>
<tr>
<td><strong>Defects in adrenal and testicular steroidogenesis</strong></td>
<td></td>
</tr>
<tr>
<td>STAR deficiency</td>
<td></td>
</tr>
<tr>
<td>P450scc deficiency</td>
<td></td>
</tr>
<tr>
<td>3-β-hydroxysteroid dehydrogenase type II deficiency</td>
<td></td>
</tr>
<tr>
<td>17α-hydroxylase and 17,20 lyase deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Altered steroidogenesis due to disrupted electron transfer</strong></td>
<td></td>
</tr>
<tr>
<td>P450 oxidoreductase defect</td>
<td></td>
</tr>
<tr>
<td>Cytochrome b5 defect</td>
<td></td>
</tr>
<tr>
<td><strong>Defects in testicular steroidogenesis</strong></td>
<td></td>
</tr>
<tr>
<td>Isolated 17,20-lyase deficiency</td>
<td></td>
</tr>
<tr>
<td>17β-hydroxysteroid dehydrogenase III deficiency</td>
<td></td>
</tr>
</tbody>
</table>

### DEFECTS IN TESTOSTERONE METABOLISM

- 5α-reductase type 2 deficiency

### DEFECTS IN ANDROGEN ACTION

- Androgen insensitivity syndrome
  - Complete and partial forms

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Wisniewski AB et al.  
J Clin Endocrinol Metab, 2011
Algorithm for evaluation of 46,XY DSD

Walter KN et al. Horm Res Paediatr 2010
Window of opportunity to test the function of hypothalamic-pituitary-testicular axis

Rey RA et al. Andrology, 2013
# Initial Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>&lt; 52 pg/mL</td>
<td>13.5</td>
</tr>
<tr>
<td>Cortisol</td>
<td>6.8-26 ncg/mL</td>
<td>4.6</td>
</tr>
<tr>
<td>DHEAS</td>
<td>&lt; 45 ng/dL</td>
<td>&lt; 15</td>
</tr>
<tr>
<td>11-deoxycortisol</td>
<td>&lt; 344 ng/dL</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>0.9-1.7 ng/dL</td>
<td>1.19</td>
</tr>
<tr>
<td>TSH</td>
<td>0.3-4.0 mcU/mL</td>
<td>1.62</td>
</tr>
<tr>
<td>IGF-1</td>
<td>49-283 ng/mL</td>
<td>110</td>
</tr>
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</table>
## Initial labs (Cont’d)

<table>
<thead>
<tr>
<th></th>
<th>range</th>
<th>1/12/15 1102</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>&lt; 3.0 mIU/mL</td>
<td>2.5</td>
</tr>
<tr>
<td>LH</td>
<td>&lt; 0.15 mIU/mL</td>
<td>0.1</td>
</tr>
<tr>
<td>TeBG</td>
<td>72-220 nmol/L</td>
<td>111</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>&lt; 3 pg/mL</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>&lt; 20 ng/dL</td>
<td>&lt; 7</td>
</tr>
<tr>
<td>DHT</td>
<td>&lt; 50 pg/mL</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>PRL</td>
<td>4.0-15.2 ug/mL</td>
<td>10.93</td>
</tr>
</tbody>
</table>
46,XY DSD work up (Cont’d)

Bone age (1/12/15): 3 y 6 mo (1 SD = 8.4 mo)

Height age: 3 y 6 mo

Pelvic US (3/6/15):
Both testes have homogeneous echostructure and normal vascularity:
  • R testis: 2.1 x 1.5 x 0.8 cm
  • L testis (located in the L inguinal canal): 1.9 x 1.1 x 0.8 cm
Both epididymis have normal echostructure:
  • R epididymis: 0.8 x 0.4 x 0.4 cm
  • L epididymis: 0.6 x 0.5 x 0.4 cm
  • No hydrocele is present. No Mullerian remnants are identified.
| Test                          | Range          | Value  
|-------------------------------|----------------|--------
| FSH                           | < 3.0 mIU/mL   | 3.6    
| LH                            | < 0.15 mIU/mL  | 0.3    
| Total Testosterone            | < 3 pg/mL      | < 7    
| Free Testosterone             | < 20 ng/dL     | < 7    
| DHT                           | < 50 pg/mL     | < 50   
| Androstenedione               | < 51 ng/dL     | < 50   
| 17-OH pregnenalone            | < 209 ng/dL    | 20     

Labs (Cont’d)
hCG stimulation test

- hCG stimulates Leydig cells, as does LH, with which it shares a structural subunit, and stimulates testicular production of testosterone

- Dynamic and reliable test to assess the presence and secretory ability of testicular tissue and to test the adequacy of penile response to testosterone

- 3,000 IU hCG/m2/day Q 3-4 days for total of 14 days

- Serum Testosterone, DHT, DHEAS, androstenedione, LH, FSH are measured at baseline and then 48 hrs. after the 14th day
## hCG stim test results

<table>
<thead>
<tr>
<th></th>
<th>range</th>
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<th>3/25/15 0851</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>&lt; 3.0 mIU/mL</td>
<td>3.6</td>
<td>0.2</td>
</tr>
<tr>
<td>LH</td>
<td>&lt; 0.3 mIU/mL</td>
<td>0.3</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>TeBG</td>
<td>72-220 nmol/L</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td><strong>Total Testosterone</strong></td>
<td>&lt; 3 pg/mL</td>
<td><strong>&lt; 7</strong></td>
<td><strong>192</strong></td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>&lt; 20 ng/dL</td>
<td></td>
<td><strong>32</strong></td>
</tr>
<tr>
<td>DHT</td>
<td>&lt; 50 pg/mL</td>
<td><strong>&lt; 50</strong></td>
<td><strong>185</strong></td>
</tr>
<tr>
<td>17-OH pregnenalone</td>
<td>&lt; 209 ng/dL</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td>&lt; 51 ng/dL</td>
<td><strong>&lt; 15</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>
Interpretation of hCG stim test

- 2 to 20 times rise in testosterone:
  1) adequate rise indicates functioning testes
  2) blunted rise:
     - Low T/DHT and Elevated LH/FSH: primary gonadal failure, LH receptor mutation
     - Low T/DHT and elevated precursor steroid: testosterone biosynthesis defect

3) T:DHT > 20:1 → 5 alpha reductase deficiency
Response of external genitalia to hCG stim test

Physical Exam:
- Penile length: 5 cm (stretched)
- Penile width: 1 cm
- Severe hypospadias
- Bifid scrotum
Clinical Questions

1) Which are the factors involved in sexual differentiation of the male?
Molecular events in sex differentiation

Mendonca B et al. Clinical Endocrinology, 2009
Clinical Questions

2) What factors affect the psychosexual development of 46,XY DSD patients?
Psychosexual development

- Recent knowledge about prenatal cerebral exposure to critical sex chromosome genes and hormones that influence fetal brain predisposition for later psychosexual development
- Socialization and learning in the absence of early androgen exposure exert major influences on the establishment of gender
- For some types of 46, XY DSD, psychosexual development is condition specific and perhaps more strongly influenced by genes and hormones; for other types of 46, XY DSD factors such as sex of rearing, are paramount
Back to our patient

- By proving he can make T, DHT and documenting phallic growth post hCG indicates response to testosterone, we demonstrated the level of dysfunction is most likely at the hypothalamic/pituitary level
- Scheduled tests: brain MRI with anesthesia
- **Rx:** testosterone enanthate 50 mg Q 4 wk x 3 to induce phallic growth
- Urology plan: complex 2 or 3 stage reconstruction surgery for external genitalia
- Follow growth velocity
- **Monitor for panhypopituitarism**
- At pubertal BA, after verifying LH/FSH deficiency or insufficiency: testosterone replacement therapy to induce phallic growth, normal secondary male sexual characteristics and maximum growth potential
- **Adult:** testosterone replacement regimen
- Either gonadotropin therapy or pulsatile GnRH stimulation can induce spermatogenesis
Reconstructive Surgery

- Urethroplasty and correction of chorddee - perineoscrotal hypospadias repair in a multistage procedure, at 6-18 mo. of age
- Bifid scrotum repair
- Orchiopexy— if needed
Conclusions

• We concur with continued child rearing as a male

• We will monitor for hypopituitarism

• Molecular mechanisms that underlie hypogonadotropic hypogonadism may involve his brain anomaly or genes that regulate development and/or GnRH secretion or action

• DSD guidelines:
  - Multidisciplinary team to include PCP, pediatric endocrinologist, urologist, psychologist specialized in gender identity, geneticist, social worker who must act as soon as the diagnosis is suspected
  - Implement long-term follow-up of patient and his family to evaluate outcome, to ensure quality care and to advance team learning
  - Provide consistency, in order to avoid ambiguous sex of rearing
References

• Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology, 2013, 1, 3-16
• Wisniewski AB. Gender Development in 46,XY DSD: Influences of Chromosomes, hormones and Interactions with parents and Healthcare Professionals. Scientificia; Vol 2012, Article ID 834967
• Byne W. Developmental Endocrine influences on Gender Identity: Implications for Management of Disorders of Sex Development. The Mount Sinai Journal of Medicine, vol.3, no. 7, November 2006