Primary Amenorrhea, age 16: Recent Reflections

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February 1, 2017
Primary Amenorrhea

- No menses by age 13-14
  - WITHOUT BREAST DEVELOPMENT

- No menses by age 15-16
  - WITH BREAST DEVELOPMENT
OUR CLINICAL CASE

• 16 Year old presents with a history of absent menses. She denies any pelvic/abdominal pain. Her development has followed usual milestones, and she has Tanner IV breast development on PE. She does note a paucity of pubic hair compared to her peers

– WHAT IS YOUR DIFFERENTIAL DIAGNOSIS, EVALUATION, AND MANAGEMENT?
HOW DOES THE PRESENCE OF BREAST DEVELOPMENT CHANGE YOUR DIFFERENTIAL DIAGNOSIS?

- Eliminates TWO LARGE CATEGORIES
  - Women who cannot MAKE estrogen (complete gonadal dysgenesis, eg Turners Syndrome) **HIGH FSH**
  - Women who are not sending a SIGNAL to make estrogen (Hypothalamic amenorrhea, constitutional delay) **LOW FSH**
Hypothalamic Amenorrhea

• Space-occupying lesions of CNS
  – Hamartoma, craniopharyngioma
• Functional lesions of the CNS
  – Prolactinoma
• Kallmann syndrome
• Female Athlete Triad/Overexercisce
• Eating disorders
• “Stress”
Today, Breast Development +

- Does NOT eliminate
  - Mosaicism (like Turners mosaic)
  - Outflow tract obstruction
  - Anovulation
  - MRKH/AIS

- NEXT STEPS?
Physical Exam

• Growth
• Tanner stages (Breast/Pubic hair)
• Genital exam
  – External – pubic hair amount
  – Digital exam for vaginal patency/presence of cervix
  – Ultrasound (Abdominal)
Our Patient

• Growth – normal
• Breast Development – Tanner IV
• Genital exam
  – Sparse pubic hair
  – Blind ending vagina – 2 cm
  
  – NEW DIFFERENTIAL DIAGNOSIS?
Our Patient

• Blind ending vagina
  – ? Imperforate hymen – bulging, bluish, distal
  – Transverse vaginal septum – 1/3 – 2/3
  – Vaginal agenesis (alone, cervix and uterus present)
    – rare
  – WNT4 mutation (MA and hyperandrogenism)
  – MRKH Syndrome (Mullerian Agenesis)
  – Androgen Insensitivity Syndrome (AIS)
Mullerian Agenesis vs AIS

• SHARE these findings:
  – Primary amenorrhea
  – Normal secondary sexual development
  – Blind ending vagina
  – Sexual dysfunction
  – Infertility

  – How do you differentiate??
MA – normal female  
AIS – normal male
Mullerian agenesis
• Normal female testosterone
• 46XX
• Normal ovaries
• Non-functional vagina

Androgen Insensitivity
• Normal male testosterone
• 46XY
• Normal testes – intra-abdominal or in inguinal canal
• Non-functional vagina
Management

Mullerian agenesis

- Create functional vagina – when she wants to be sexually active
  - Surgical
  - Dilators
- Gonads – normal ovaries, no treatment needed
- HRT – none needed
- Fertility – need gestational carrier

Androgen insensitivity

- Create functional vagina when she wants to be sexually active
  - Surgical
  - Dilators
- Gonads – normal testes – require surgical removal after puberty completed to reduce risk of cancer
- HRT – estrogen replacement
- Fertility - adoption
### Table 2  Treatment options for the creation of neovagina

<table>
<thead>
<tr>
<th>Non-surgical treatment</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank method</td>
<td>Traction-based methods</td>
</tr>
<tr>
<td>Vaginal dilators with</td>
<td>- Vechietti (laparotomic or laparoscopic)</td>
</tr>
<tr>
<td>progressive caliber</td>
<td></td>
</tr>
<tr>
<td>Ingram method</td>
<td>Graft-based methods</td>
</tr>
<tr>
<td>Vaginal dilators</td>
<td>- Abbe-McIndoe (vaginal approach, various tissues used, skin graft most common)</td>
</tr>
<tr>
<td>attached to a seat</td>
<td>- Intestinal (combined vaginal and laparotomic or laparoscopic approach)</td>
</tr>
<tr>
<td></td>
<td>- Davydov (combined vaginal and laparoscopic approach using peritoneum)</td>
</tr>
</tbody>
</table>

**Note:** Most surgical methods require the continued use of non-surgical methods or frequent intercourse to maintain results.
Using Vaginal Dilators

• 15-20 minutes twice a day
• Lie on back, lithotomy position, legs relaxed to side
• Lubricate dilator, place in vaginal dimple
• Using pressure, push dilator toward lower back/tailbone (15 degrees)
• Hold in place for 15-20 minutes – should feel pressure but not pain
• Rinse dilator with soap and water
• Progressively
Androgen receptor mutations

- Over 400 AR mutations have been reported
- 30% of the time, the AR mutation is a spontaneous
- **X-linked recessive**
### SUMMARY

<table>
<thead>
<tr>
<th>Characteristic findings</th>
<th>MRKH/ MURCS</th>
<th>Isolated vaginal atresia</th>
<th>WNT4 syndrome</th>
<th>Androgen insensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper vagina</td>
<td>Absent</td>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Uterus</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Gonads</td>
<td>Ovary</td>
<td>Ovary</td>
<td>Masculinized ovary</td>
<td>Testis</td>
</tr>
<tr>
<td>Breast development</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pubic-hair development</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Sparse</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Karyotype</td>
<td>46, XX</td>
<td>46, XX</td>
<td>46, XX</td>
<td>46, XY</td>
</tr>
</tbody>
</table>


MURCS – rare; short stature, fused cervical spine bones, hearing loss
Kennedy disease is a neurological condition that is also due to a mutation of the androgen receptor gene. Affected individuals are phenotypically normal males who are fertile, although after puberty they may develop enlarged breasts, consistent with very mild androgen insensitivity. The disorder causes progressive weakness over several decades, along with tremor, difficulty swallowing, and some sensory problems. The mutation that causes Kennedy disease is an expanded "triplet repeat" of CAG nucleotides, making this condition one of the family of triplet repeat diseases that includes Huntington's disease.