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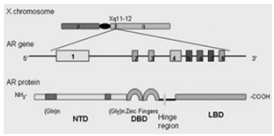
- I have no actual or potential conflict of interest in relation to this program/presentation.

- What is complete androgen insensitivity (CAIS)
- Review specific case presentation of CAIS
- Additional considerations in CAIS
- Questions/Discussion

- Disorder of sex development (DSD)
  - Genetically male (46, XY)
  - Unable to respond to androgens → develop female sex characteristics
  - Formerly called testicular feminization
- Prevalence: 2 to 5 per 100,000 people who are genetically male
- Complete or partial

- **Complete:** body cannot use androgens at all
  - External sex characteristics of females
    - Short blind pouch vagina, no uterus, fallopian tubes, or ovaries
  - Internal male sex organs (undescended testes in abdomen or pelvis)
  - Sparse or no pubic hair, axillary hair, or body odor
- **Partial:** body partially sensitive to androgens
  - Appearance of external genitalia may vary

- AR gene provides instructions for making a protein called an androgen receptor
  - Androgen receptors allow cells to respond to androgens, which direct male sexual development
- Mutations in the AR gene prevent androgen receptors from working properly
- Inherited in an X-linked recessive pattern



- **Complete AIS**
  - May be picked up at birth if:
    - Baby develops an inguinal hernia
    - Female newborns w/ prenatal 46, XY karyotype
  - Usually not identified until child reaches puberty
    - Amenorrhea, lack of pubic hair and axillary hair
- **Partial AIS**
  - Usually identified after birth due to atypical genital appearance

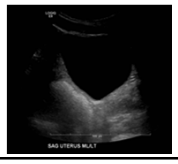
- L.C. was referred to adolescent medicine in February 2017, at age 16 years 7 months for evaluation of primary amenorrhea
  - Primary amenorrhea
    - The absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics
  - Differential for primary amenorrhea:

Turner syndrome	PCOS	Anorexia nervosa	Pituitary tumor	Cushing's
MRKH syndrome	GnRH deficiency	CAIS	CAH	Other
Constitutional delay	Transverse vaginal septum	Hyperprolactinemia	Hypothyroidism	

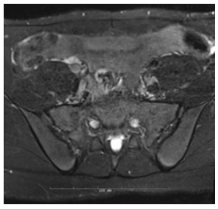
- Elevated testosterone (319 ng/dL)
  - Tanner 5 Female range: 20-38
- Elevated DHEA(S) (462 ug/dL)
  - Tanner 5 Female range: 44 - 248
- LH/FSH not elevated
  - No evidence of gonadal failure
- 17OHP and Androstenedione WNL
  - Can rule out CAH
- Estradiol WNL
- TFTs WNL
- Prolactin not elevated

Component *Lateral Ref Rng & Units*	1/9/2017	2/21/2017
Testosterone, Serum (Total) *ng/dL*		319
% Free Testosterone *%*		1.1
Free Testosterone, S *pg/mL*		35
Sex Hormone Bind Glob (SHBG) *nmol/L*		63.5
FSH *mIU/mL*	5.0	
Luteinizing Hormone (LH) ECL *mIU/mL*	18	
Prolactin *4.8 - 23.3 ng/mL*	11.6	
TSH *0.450 - 4.500 uIU/mL*	3.070	
T4, Free(Direct) *0.93 - 1.60 ng/dL*	1.05	
17 Alpha-Hydroxyprogesterone *ng/dL*		57
Androstenedione, Ser *ng/dL*		141
Follicle Stimulating Horm *mIU/mL*		4.4
Luteinizing Hormone *mIU/mL*		14.9
Estradiol *pg/mL*		22.0
DHEA-Sulfate, LCMS *ug/dL*		462

- The uterus is not well visualized. On the sagittal images, there is a small, linear, hypoechoic structure which measures 1.4 mm in AP dimension x 1.8 cm in length. There is soft tissue in the region of the cervix which measures 4.7 mm in AP dimension. A normal vaginal stripe is noted. The ovaries are not visualized.
  - Impression: Findings suggestive of a hypoplastic uterus. The ovaries are not visualized which may be related to morphology.



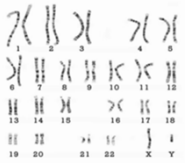
- Impression: No uterus or ovaries identified. Testes identified in the bilateral inguinal canals, compatible with androgen insensitivity syndrome. Normal kidneys.



- NP and Attending Endocrinologist met with parents only (no patient)
- Karyotype not yet performed
- Referred to:
  - Counselor in the Gender and Sexuality Development Clinic
  - Genetics
  - Urology

- Mother and patient met counselor in the Gender and Sexuality Development Clinic
- L.C. was informed that there is more information to be gained but we know that she does not have uterus or ovaries, so will be unable to have a period
  - Became upset once she realized this meant that she would not be able to give birth to her own children
  - Also upset with the idea that her parents knew this for a lot longer than she did

- 46, XY
  - Cytogenetic analysis of PHA stimulated cultures revealed an apparently normal MALE karyotype in all cells examined.



- First time for NP and attending actually meeting and examining the patient
- Physical Exam: Breast Tanner IV, PH Tanner 2-3, axillary hair few. Left gonad palpable in inguinal canal. Right gonad non palpable (but patient reports that she has been able to feel it)
- At this time, no need for hormone replacement
  - Gonads intact; aromatization of testosterone → estrogen
- Referred to Genetics and Urology

- In office physical exam: Normal appearing clitoris, normal vaginal introitus, normal urethra
- Recommended exam under anesthesia to evaluate vaginal length/depth
- Also discussed monitoring of gonads versus gonadectomy as they present an increased cancer risk
  - Urologist recommends laparoscopic gonadectomy

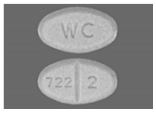
- Germ cell tumors may develop in the cryptorchid testes
- Girls with CAIS have a normal pubertal growth spurt and feminize at the time of expected puberty secondary to aromatization of androgen to estrogen
  - Prophylactic gonadectomy is not recommended at this time because testicular tumors do not usually develop until after puberty
- Gonadectomy in women with CAIS is now typically delayed until sexual maturation is complete
  - This approach also respects patient autonomy
- Clinical guidelines have not yet been developed on the optimal screening and timing of gonadectomy for patients with gonads in situ

- Vaginal exam under anesthesia performed
  - Shallow vagina measured at approximately 3 cm
  - Vagina was noted to be blind ending without any additional channels and no cervix
- Vaginal dilation begins few weeks after EUA
  - Patient able to insert dilator about 2-3 cm with some mild discomfort

- One pathogenic change was identified in the AR gene (c.1771A>T, p.Lys591*)
  - Reported to be pathogenic for Androgen Insensitivity Syndrome.
- Functional studies to determine the level of residual activity of L.C.'s AR could be available to investigate further whether the activity is consistent with complete or partial
  - Determining the level of function could help better clarify options regarding whether surgery is needed
- Discussed that there is a chance that Mom is a carrier
  - Whether mom is a carrier impacts whether L.C.'s sister may be a carrier herself, which could have implications for her family planning

- Appointment was scheduled for 4/24/18 to discuss timing of gonadectomy and hormone replacement
  - Two days prior to appointment received message from L.C.'s mother:
    - "I need to postpone our Tuesday appointment. After some discussion on our end we're holding off for now on surgery so it probably makes sense to wait a bit to discuss hormone replacement and do it when L.C. is ready/available."

- Hormone treatment is indicated when gonadectomy is performed after puberty or at the time of expected puberty if gonadectomy was performed prepubertally
- Low doses of estrogen should be begun to promote feminization and gradually increased to full adult doses, similar to induction of puberty protocols
- Adult women can be given full estrogen replacement immediately



- Three ethical principals that apply to the management of DSD:
  - To foster the well-being of the child and the future adult
  - To uphold the rights of children and adolescents to participate in and/or self-determine decisions that affect them now or later
  - To respect the family and parent-child relationships

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