Heterozygous Aromatase Deficiency Discovered in Young Male with a Slipped Capital Femoral Epiphyses

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Introduction

Aromatase, or CYP19A1, is a type II cytochrome P450 enzyme which plays a critical role in the conversion of androgens to estrogens. Specifically, aromatase catalyzes the conversion of testosterone, androstestenedione, and 16alpha-hyroxytestosterone to estradiol (E2), estrone (E1), and estriol, respectively. Aromatase deficiency, also known as estrogen synthase deficiency, is an exceedingly rare, phenotypically variable disease of mutational CYP19A1 by where deficient aromatase results in inability to appropriately convert androgens to estrogens throughout life.

Females with aromatase are typically discovered as neonates due to 46, XX pseudohermaphroditism with subsequent lack of pubertal development. In contrast, aromatase deficient males have more subtle phenotypic features and are normal at birth with expected pubertal development however with clinical features related to a lack of estrogen development at bone. As a result, males are often diagnosed in adulthood with findings of elevated testosterone, metabolic syndrome, and tall stature wit eunuchoid proportions due to excessive growth of long bone and unfused epiphyses, genu valgum, low bone density and increased fracture.

Here we describe a new case of a young adult male patient with aromatase deficiency and a heterozygous mutation in CYPA19A1 t discovered following urgent evaluation of slipped capital femoral epiphyses.

Case Presentation

A historically healthy 20-year-old African American male is initially evaluated for evaluation of ongoing left hip pain following fall from standing height that was unresponsive to conservative management; workup revealed ipsilateral slipped capital femoral epiphysis requiring percutaneous pinning. He had denied prior trauma or injury but interestingly, did endorse progressive vertical growth continuing throughout his sophomore year of college with a current height of 6'4".

In investigation, bone age radiographs were obtained of the left hand which was notable for a delayed bone age consistent with that of a 14-year-old (Fig 1.).

- Personal history was notable only for premature delivery; no intrapartum maternal virilization was reported. Family history NC
- Physical development had been normal aside from mild genu varum. He had normal pubertal development, hair pattern and secondary sexual characteristics and function.
- Throughout his teen years, the patient continued to grow in height far beyond that of his father (5'7"), mother (5'2") and family members with particularly notable lengthening of his legs, fingers, and wingspan.
- Social history NC; plays contact sports without history of injury.

Investigation

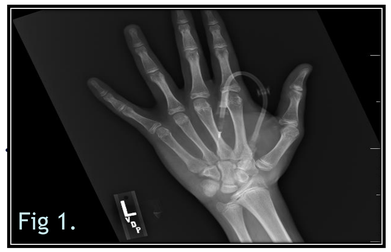


Fig 1.

Lumbar Spine	0.870 gm/cm 2	-3.6STD
Femoral Neck	1.048 gm/cm2	-1.5 STD

Fig 2.

On physical exam, the patient appeared tall with significant lengthening of limbs and fingers consistent with arachnodactyly and with focal centralized obesity. He was also noted to have acanthosis nigricans as well as non-violaceous striae of the shoulders and central abdomen. Genital exam revealed micro-phallus, normal-appearing testicles with a volume of approximately 15ml and normal pubic hair distribution. VS: 1.93m (76"0), 133kg (BMI 35.8), BP 146/82 mm/HG,

The patient was referred for evaluation of bone density with **a DXA scan significant for osteoporosis based on Z scores** (Fig 2).

Upon endocrine consultation and further inquiry, subsequent investigation aimed at evaluation of possible disorders of sex steroid deficiency or resistance. **This revealed undetectable estradiol and low total estrogens with normal/high testosterone (as below):**

Biochemical Analysis	07/08/2019
Total testosterone	**584 ng/dL**
Free testosterone	**34.3 pg/dL** (9.3 - 26.5 pg/mL)
DHEA-S	**840.9 ug/dL** (164-530.5 ug/dL)
Androstenedione	**167ng/dL** (27 - 152 ng/dL)
Total estrogens	**38 pg/ml** (40 - 115 pg/mL)
Estradiol	**<5.0 pg/m** (24 - 61 pg/mL)
SHBG	12.6 nmol/L
FSH	10.9 mIU/mL
LH	6.2 mIU/mL
17-Hydroxyprogesterone	118 ng/dL
Prolactin	8.8 ng/mL
IGF-1	209 ng/mL
TSH	0.86 uIU/mL

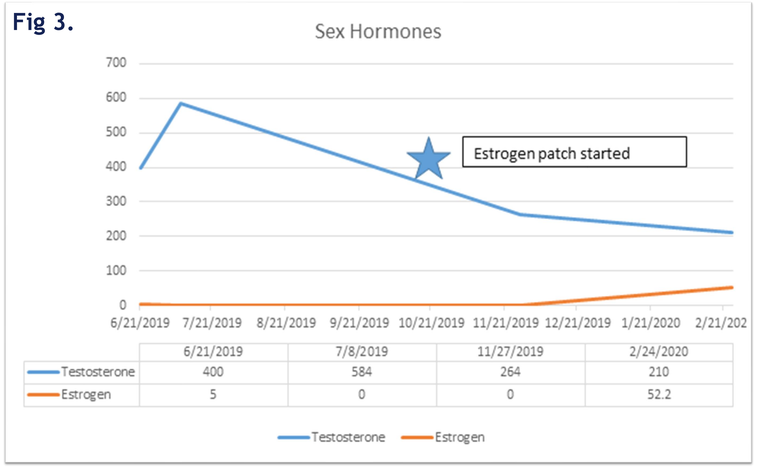
Chemistry	
Creatinine	1.1mg/dL
Glucose	88mg/dL
Albumin	4.6g/dL
Alkaline Phosphatase	170 IU/L
Bone specific ALP	82%
AST	28 IU/L
ALT	52 IU/L
Calcium	10.2 mg/dL
25-Hyroxyvitamin D	12.6 ng/mL
HgbA1c	5.5%
Total Cholesterol	152 mg/dL
HDL	29 mg/dL
LDL	103 mg/dL
Triglycerides	107 mg/dL

Management

The patient was confirmed to have **heterozygous mutation of CYP19A1** (6.28+2 in intron 6) consistent with a pathogenic variant of aromatase deficiency.

In addition to genetics referral, therapy with estrogen replacement and Vitamin D was initiated. Initial estrogen replacement was delivered by way of transdermal estradiol patch with an initial dose of 0.025mg daily. After six months of estrogen therapy, and interestingly without need for dose titration, gradual normalization of estradiol (52.2pg/mL) and testosterone levels (total testosterone 210 ng/dL, free testosterone 17.5 pg/mL) were achieved (Figure 3.). . Maintained on this dose, the patient has also achieved cessation of vertical height growth and awaits repeat bone density studies.

Fig 3.



	6/21/2019	7/8/2019	11/27/2019	2/24/2020
Testosterone	400	584	264	210
Estrogen	5	0	0	52.2

Discussion:

- Located on chromosome 15q21.2, the CYP19A1 gene encodes an approximately 500AA protein expressed diffusely throughout various organs, encoding for transcription of the aromatase enzyme required for conversion of androgens to estrogens.
- Aromatase deficiency is an autosomal recessive condition whereby deficient or insufficent aromatase results in the permanent inabilityo appropriately convert androgens to estrogens with various clinical sequelae; most profound detrimental effects are seen at the gonadal and bone level.
- While the prevalence of aromatase deficiency remains unknown, less than a total of 40 cases are reported in current literature.
- Thought to be a likelihood of underdiagnosis of this rare condition given its genetic and phenotypic variability, particularly in male patients with more obscure manifestations developing in adulthood.
- Management of aromatase deficiency in both male and female patients involves replacement with estrogens targeting physiologic doses and normalization supraphysiologic androgens and/or gonadotropes.