Klinefelter Syndrome: A Near Miss in a Child with Congenital Hypothyroidism

Mandi Cafasso, RN, DNP, CPNP
Cincinnati Children's Hospital Medical Center
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Objectives

- Present case of patient with congenital hypothyroidism
- Review signs of Klinefelter syndrome
- Discuss when to consider evaluation for Klinefelter syndrome

Disclosures

- I have no disclosures to report.

The Patient

- B.M. was seen in Endocrine outpatient clinic at 11 DOL.
- Uncomplicated birth history.
- NBS: TSH- > 100mcIU/mL and Free T4-0.8ng/dL
- Repeat venous sample: TSH- >100mcIU/mL.
- Levothyroxine was started at 50mcg daily.

- Child now 16 years of age…

The Patient

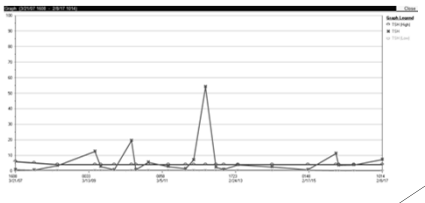
- Problem list:
  - Hearing loss, unspecified sensory neural
  - Poor school performance
  - Obesity
  - Constipation
  - Hyperlipidemia
  - NASH
  - Acne

The Patient

- FMHX:
  - Mom treated for Grave's disease with RAI prior to pregnancy.
  - Mother died of MI at age 32years
  - PGM Rheumatoid Arthritis

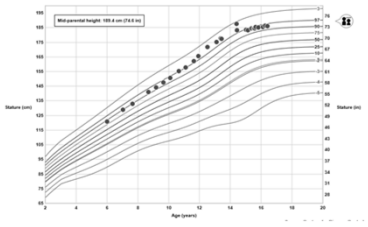
Congenital Hypothyroidism

- Child was seen in Endocrinology clinic irregularly for the first 10 years.
- Poorly controlled with levothyroxine (adherence issues)



The Patient

- Growth



- Normal puberty growth spurt
- Testes documented at 8-10ml at 11-12 years of age
- Achieved MPH
- Bone age normal

The Patient

- Development
  - At age 11y 7mo grandmother expressed concerns about his behavior
    - Not normal for his age, seems behind
    - Concern for depression (dysthymia)
  - At age 12y 6mo
    - Failing all of his classes and refusal to participate in activity
    - "Bad attitude", doesn't listen, lazy
    - Started on Ritalin
  - At 13y 5 mo (seen by behavioral pediatrics)
    - Stopped Ritalin
    - Struggling in school- no IEP

The Patient

- At age 15y 1m continue behavioral problems (11/2015)
  - Eats until he vomits
  - Diagnosed with ADHD and ASD
    - "he doesn't understand and doesn't get it"
  - Seeing psychiatry
    - Suicide attempt

Differential?

- Uncontrolled hypothyroidism
- Hearing Problems
- ADD/ ADHD
- Fragile X
- Learning disability/low IQ (73)
- Klinefelter Syndrome

Biochemical Evaluation

November 2015

- Thyroid function
  - TSH- 11.2 mcIU/mL (nl. 0.43-4mciu/mL)
  - Free T4- 1.8ng/dL (nl. 1-2.8ng/dL)
- Obesity
  - Insulin- 31mcIU/mL
  - Glucose- 87mg/dL
  - ALT- 81 units/L
  - Hgb A1c- 5.1%
  - HDL- 29mg/dL

Biochemical Evaluation

November 2015

- Development
  - Fragile X- negative
  - Chromosomes- 47, XXY

Why did I screen for Klinefelter Syndrome?

Klinefelter Syndrome

- Discovered in 1942
  - Nine men with similar symptoms
- Chromosomes were not identified until 1956
- Extra X chromosome was identified in 1959
- Only 30% of males with Klinefelter syndrome are diagnosed during life
  - Neonatal
  - Delayed Puberty
  - Infertility

https://genetic.org/variations/about-47xxy/

Klinefelter Syndrome

- Most common abnormality of the sex chromosome (1 in 500 to 1000)
- 47, XXY most common (80-90%)
  - 48, XXXY; 48XXYY and 49, XXXYY
- Mild phenotypic characteristics
  - Tall stature
  - Curved little finger
  - Small testes
  - Radio-ulner synostenosis
  - Flat feet
  - Small chest depression
  - Hidden Phenotype

https://genetic.org/variations/about-47xxy/Salzano, et al. (2016)

Klinefelter Syndrome

- More X = more phenotypic characteristics
  - Long bone abnormality (long limbs)
  - Small, firm testes, low sperm count, infertility, decreased virilization
    - Hi FSH, and LH, low testosterone
    - Cryptorchidism is more common
- Other phenotypic features
  - Narrow shoulders and wider hips
  - Less facial body hair
  - Low energy
  - Low muscle tone
  - Gynecomastia

Klinefelter Syndrome

- Symptoms
  - Impaired Sexual function/desire
  - Learning disabilities
  - Expressive language disorder
  - "lack of insight, poor judgement, and impaired ability to learn from experience"
  - ADHD
  - ASD like behaviors

Klinefelter Syndrome

- Risks
  - Advanced maternal age >40 years
  - ? Advanced paternal age

The Patient

47, XXY Phenotype

- ✓ Tall stature
- ✓ Curved little finger
- ✓ Narrow shoulders and wider hips
- ✓ Less facial body hair
- ✓ Low energy
- - Low muscle tone
- ✓ Gynecomastia
- ✓ Small testes
- - Radio-ulner synostenosis
- - Flat feet
- - Small chest depression

The Patient

- ✓ Learning disabilities
- ✓ Expressive language disorder
- ✓ Lack of insight
- - Poor judgement
- ✓ Impaired ability to learn from experience
- ✓ ADHD like behaviors
- ✓ ASD like behaviors

Where to go from here?

- ▶ Genetics referral
- ▶ Fertility specialist
  - ▶ Semen or testicular tissue cryopreservation
- ▶ Behavioral Medicine
- ▶ Psychology
  - ▶ Family counseling
- ▶ Academic support if desired

Where to go from here?

- Testosterone replacement
  - Use LH and FSH, not necessarily testosterone
- Increased risk of
  - Diabetes
  - Metabolic Syndrome
  - Cardiovascular Disease

Summary of Lessons Learned

- Pubertal entry does not mean pubertal progression
- Be suspicious of tall stature with average mid-parental height
- Consider learning difficulties in all patients
- Even with reasonable explanation, if the shoe fits- test.
  - Phenotype, look closely at your patients!
- If you get a positive Klinefelter test refer and screen.
  - Genetics, fertility, behavioral medicine, psychology/counseling
  - Biochemical markers for cardiovascular disease, diabetes, ? DEXA

References/ Resources

- https://genetic.org/variations/about-47xxy/
- Salzano, et al. (2016). Klinefleter syndrome, cardiovascular system and thromboembolic disease. A review of the literature and clinical perspectives. European Journal of Endocrinology, 175, R27-R40.
- Lifshitz, F. Pediatric Endocrinology (5th ed.)
- Andrology. 2016 Nov;4(6):1178-1186. doi: 10.1111/andr.12249. Epub 2016 Sep 9.