3- & 12-Year-Old Sisters with Li-Fraumeni Syndrome

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ENDORAMA
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Sisters referred by Peds Oncology to Endo clinic for adrenocortical carcinoma screening

TP53 mutation confirmed in 2010 when mother was found to have mutation during breast cancer evaluation

Followed by Heme/Onc since 2010

New screening recommendations for LPS available in 2011

Both currently cancer-free
Li-Fraumeni Syndrome

- Germline inactivating mutation in tumor suppressor gene p53
- Autosomal dominant inheritance
- Predisposition to early onset cancers
  - Soft tissue sarcomas, osteosarcomas, adrenal cortical carcinoma, Wilms tumor, leukemia, brain tumors
  - Lifetime risk: 73% in males, 93% in females
- Diagnostic criteria
  - Proband with sarcoma dx < age 45 with
    - 1st-degree relative with any cancer < age 45 or
    - 1st-degree relative with sarcoma at any age
  - 70-83% of pts who meet criteria have TP53 mutations
  - 29-35% meet criteria for Li-Fraumeni-like syndrome (Chompret criteria)
PMH & SH

- **12-YO (KK)**
  - Obesity, h/o OSA, chronic constipation, TP53 mutation, HbAS
  - Born via c-section, normal weight and development
  - PSH: T & A at age 9
- **3-YO (KW)**
  - Born via repeat c-section, normal weight and development
  - Screened for p53 mutation in 2010, pelvic U/S at age 2 months revealed multiple ovarian cysts
  - Endo-eval consistent with normal infant ovarian activation
- **Social History**
  - Both live with mother and mother’s husband (KW’s father). Relocated from IL to NY 2 years ago due, father is in the military. Mother and sisters regularly follow with oncologists at the U of C.
HPI: 12-Year-Old (KK)

- Increased appetite and weight gain of ~ 50 lbs in past 6 months, increased anxiety
- Pertinent +
  - Acne x 2 years, H/A with menstruation
- Pertinent -
  - No excessive hair growth, voice change, polyuria/polydipsia, hypertension, pain, normal menstruation since age 12
- Meds: none
PE: KK

- HR 63  BP 105/59 Wt: 86.3 kg (>>97th %ile) Ht: 163.7 cm (90th %ile) BMI: 32.2 kg/m² (+5 SD)
- Pertinent +
  - Acanthosis nigricans
  - Dark brown, raised striae on breasts and abdomen
  - Tanner V breasts
  - Mild facial acne
  - < 1 cm Left cervical node
- Pertinent –
  - No clitoromegaly
  - No hirsutism (mild hypertrichosis, score 6)
Evaluation: KK

- Initial 14:13 → F/U 5 months later 16:30
  - Aldosterone < 4
  - Renin < 0.6 ng/mL/h (12-17y: 1.2-2.4)
  - 17-OHprogesterone < 40 → 201 (pubertal < 285)
  - Androstenedione 158 → 252 (Tanner V: 80-240)
  - DHEA-S 64 → 70
  - Total testosterone 26 → 42 (15-60)
  - Calc free testosterone 10 → 15 (3-9)
  - 24-hour urinary free cortisol 240 µg/24hrs (58-403) (urine creatinine was not obtained, urine vol ~0.8 ml/kg/h)
  - HbA1c 5.2% → 5.4%
  - Tot chol 141 HDL 41 LDL 63 TG 186
  - Brain MRI & abdominal U/S: unremarkable
1 Month Later: KK

- **Dexamethasone Androgen Suppression Test**
  - Tot Te 42 → 30
  - Calc free Te 15 → 11
  - 17-OHP 201 → 142
  - Androstenedione 252 → 129
  - Cortisol < 4
  - DHEAS 70 → 18
  - Dex level 203

- **Diagnosis: Mild ovarian hyperandrogenism**
  - Began metformin 500 mg → 1000 mg daily
3-Month Follow-Up: KK

- Increased physical activity and dietary modifications
- Weight loss of 8 lbs.
- Labs
  - Tot Te 42 → 15
  - Calc free Te 15 → 5
  - 17-OHP 201 → < 40
  - Androstenedione 252 → 62
  - DHEAS 70 → 78
- Abdominal and pelvic ultrasound: unremarkable, ovarian volumes right 8.75 mL, left 5.76 mL
Presentation: 3-Year-Old (KW)

- **HPI**
  - Tall stature, negative ROS
  - Meds: None

- **PE**
  - Vitals: HR 115 BP 104/55  Wt: 97th %  Ht: 99th  Wt-for-Ht: 76.8th %  Ht age: 5 y  Growth velocity: 1.7cm/yr over 5 months (< 3rd%)
  - **Pertinent +**: Few strands of intra-labial Tanner II hair
  - **Pertinent -**: no thyromegaly or nodules, prepubertal genitalia, nl clitoris, Tanner 1 breasts, mild hypertrichosis, no hirsutism
Evaluation: KW

- **Time 14:22**
  - Aldosterone 21 (< = 124)
  - Renin 3.8 ng/mL/h (3-5 y: 1.5-3.5)
  - 17-OHprogesterone 54 (prepubertal < 100)
  - Androstenedione < 15 (Tanner I: < 51)
  - DHEA-S 18 (age 1-5 y: < 5-57)
  - Total testosterone < 7 (< 20)
  - Calc free testosterone < 1 (prepubertal < 3)
  - 24-hour urinary free cortisol 60 ug/24hrs (58-403) (urine creatinine was not obtained, urine vol ~1.3 ml/kg/h)

- Brain MRI & abdominal U/S: unremarkable
- Bone age 5 years 3 months at chronological age 3 years 5 months
Adrenocortical Carcinoma

- **Age of presentation**
  - Large case study had ~80% of pts from southern Brazil known to carry TP53 mutation
  - 60% age < 4, 14% age > 13 y
  - Higher female:male ratio at < 4 yrs (1.7:1) and > 13 yrs (6.2:1)

- **Presentation**
  - In adults 60% are hormone-secreting, children 84-90%
  - > 50% children present with virilization alone, 84% presented with virilization + other hormones, 6% with Cushing syndrome, 43% with HTN

- **Screening**
  - ENSAT recommends fasting glucose, serum K, ACTH, cortisol, 24-hr urinary cortisol, overnight dex suppression, adrenal androgens

- **50-100% of children with ACC have TP53 mutation**
Surveillance in Li-Fraumeni Syndrome

- Challenges
  - Diverse range of tumors
  - Variable age of onset
  - Weak genotype-phenotype correlation
  - Little evidence for effectiveness of screening

- Case reports
  - ACC detected in asymptomatic child using U/S and adrenal hormone testing
  - $^{18}$F-FDG PET and CT scan—controversial due to increased risk of tumors from radiation exposure in LFS pts
Surveillance in Li-Fraumeni Syndrome

- **Case report**
- **Villani & Malkin et al 2011**
  - 8 families, 48 *TP53* mutation carriers
  - 33 genotyped-18 chose surveillance, 16 opted out
  - All compliant, no losses
Increased Survival with Surveillance

- 10 tumors in 7 asymptomatic pts found in surveillance group
  - All survived
- 10/16 followed prospectively developed cancers, all were symptomatic
  - 2/10 survived
Take Home Points & Plan

- **Plan**
  - 17-OHP, AD, DHEAS, total & free Te, abdominal U/S, BP q4 mo
  - urinary free cortisol, aldo and renin, yearly or if high suspicion
  - AFP and b-hCG not recommended

- LFS predisposes pts to early cancers including ACC, usually presenting in early childhood

- Surveillance in these pts in the past has been challenging

- New protocol gives hope that cancer survival may be increased

- Larger studies and cost-effectiveness analysis are needed to assess long-term effectiveness of current protocol

