Endocrine Features of Fibrous Dysplasia/McCune-Albright Syndrome

Alison Boyce, MD
Section on Skeletal Disorders and Mineral Homeostasis, NIDCR, NIH
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Fibrous Dysplasia/McCune-Albright syndrome: A complex bone and endocrine disorder

Bone, pituitary, gonads, thyroid, adrenal, other

fibrous dysplasia
rickets
GH excess
precocious puberty
hyperthyroidism
Onset of manifestations of affected tissues

- Fibrous dysplasia
- Café-au-lait
- Precocious Pub.
- Thyroid
- Phosphate
- Growth hormone
- Cushing’s

Most affected and unaffected tissues can be identified in childhood.

Legend:
- Subclinical
- Clinically evident
- Spontaneous resolution possible
Precocious Puberty in MAS

- Recurrent ovarian cysts
- Breast development, growth acceleration
- Vaginal bleeding when cysts resolve
Precocious Puberty in MAS

Estrogen causes early closure of growth plates

Treatment is needed to:
• Prevent disabling short stature in adulthood
• Prevent psychosocial consequences of early sexual maturation

AVOID SURGERY
Current Treatment Options

Tamoxifen (Eugster et al, 2003)
- Alters estrogen receptor activity
- 12 month prospective trial, 25 girls with MAS
  - Decreased: linear growth, bone age advancement and vaginal bleeding
  - Increased: uterine volume

Letrozole (Feuillan et al, 2007)
- Prevent estrogen production
- 36 month pilot study, 9 girls with MAS
  - Decrease: growth rate, bone age advancement and vaginal bleeding
  - One case of ovarian torsion
Extended efficacy of letrozole in NIH cohort

Length of treatment

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<th>Years</th>
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n = 22
mean Tx = 4.3y

Bone age advancement

p < 0.0001

Estrada et al, EJE 2016
MAS Testicular Disease

- Testicular lesions in ~85%
- Precocious puberty in ~15%
- Treatment: Spironolactone + letrozole
  - NO SURGERY!
- Cancer has been rarely reported
  - Ongoing monitoring
Thyroid Disease in MAS

- US abnormalities in ~66%; hyperthyroidism in ~30%
- T3 overproduction; increased T3/T4 ratio (>20)
- Kids with US abnormalities may develop hyperthyroidism later

Collins JCEM 2003, Celi JCEM 2008
Thyroid Disease in MAS

Management

• Short-term: methimazole

• Long-term:
  ▪ Surgery
    ▪ prefer high-volume center
    ▪ May regrow
  ▪ Radioactive iodine
  ▪ cancer reported
Growth Hormone Excess

- ~15% of patients
- Growth acceleration may be subtle, confounded by FD & endocrinopathies
GH excess: deformity and vision loss

Prophylactic optic nerve decompression is not indicated
Lee, NEJM, 2002 (n=38)

Watchful waiting is superior to surgery (meta-analysis)
Amit, PLoS ONE 2011

GH excess is a risk factors for vision loss
Cutler, Neurosurgery, 2006

Early GH excess treatment prevents morbidity
Boyce…Collins, JCEM 2013 (n=129)
GH excess management issues: macrocephaly, vision & hearing loss

Treatment:
• medication (octreotide, lanreotide, pegvisomant)
• surgery (hypophosectomy, always difficult)
• radiation (cancer risk)
Cushing’s syndrome

- Presents age <1 year
- Early recognition is essential!
- Adrenalectomy if possible
- Caveat: spontaneous resolution in ~1/3
- Neurodevelopmental sequelae

Brown et al, JCEM, 2010
Fibrous Dysplasia/McCune-Albright Syndrome
Alison M Boyce, MD  Michael T Collins, MD

Fibrous Dysplasia Evaluation
- History and physical to identify limp, bone pain, fractures, limb length discrepancy, facial asymmetry.
- Skeletal survey - VHR and/or TRP
- MRI or MMR brain scan

Age < 5 years
- High clinical suspicion for significant FD
  - Skeletal survey - VHR and/or TRP
  - MRI or MMR brain scan
- Low clinical suspicion for significant FD
  - Monitor clinically - HR and/or TRP
  - MRI or MMR brain scan at age 5 years

Age ≥ 5 years
- Abnormal HR and/or TRP
  - Significant FD
    - Baseline skeletal survey
    - Baseline head CT for craniofacial deformity
    - Serial phos, TRP
- Normal HR and/or TRP
  - Low likelihood for significant FD
  - Monitor clinically

Gonadal Evaluation in Girls
1. History of breast development, vaginal bleeding and/or signs of estrogenization below age 6-7 years
2. No history of breast development, vaginal bleeding and/or signs of estrogenization below age 6-7 years

Bone age advanced ≥ 2 years
- High sensitivity LH, FSH and estradiol
- Pelvic US
- Likely MAS-associated PP
- Surgical oophorectomy is contraindicated
- MAS-associated PP unlikely
- Consider subclinical PP
- Consider hyperthyroidism and/or GH excess

Bone age advancement < 2 years
- No bone age advancement
- No history of breast development, vaginal bleeding and/or signs of estrogenization below age 6-7 years

Bone age advanced ≥ 2 years
- Monitoring
- Bone age, growth velocity, PE q 6 mo
- No routine labs or imaging

Bone age advancement < 2 years
- Treatment
- Letrozole 2.5 mg daily
- If ineffective - add or replace with tamoxifen 5 mg daily
- Monitor for central precocious puberty (bone age ~11 years); treat with monthly leuprolide
Questions?