Management of Pediatric Fibrous Dysplasia/McCune-Albright Syndrome

Alison Boyce, MD

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Fibrous Dysplasia/McCune-Albright syndrome: A complex bone and endocrine disorder

Bone, pituitary, gonads, thyroid, adrenal, other

Images:
- Fibrous dysplasia
- Rickets
- GH excess
- Precocious puberty
- Hyperthyroidism

Images of individuals with symptoms related to the syndrome.
Onset of manifestations of affected tissues

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

**Age**

Subclinical

Clinically evident

Spontaneous resolution possible

Most affected and unaffected tissues can be identified in childhood.
Precocious Puberty in MAS

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

Treatment is needed to:

• Prevent disabling short stature in adulthood
• Prevent psychosocial consequences of early sexual maturation

AVOID SURGERY

Estrogen causes early closure of growth plates
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

n = 22
mean Tx = 4.3y

bone age advancement

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
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
Prophylactic optic nerve decompression is not indicated

Watchful waiting is superior to surgery (meta-analysis)

GH excess is a risk factors for vision loss

Early GH excess treatment prevents morbidity
GH excess management issues: macrocephaly, vision & hearing loss

**Treatment:**
- medication (octreotide, lanreotide, pegvisomant)
- surgery (hypophossectomy, 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
Phosphate Wasting in FD

Low Blood Phosphorus

FD + rickets

Osteomalacia, Bone Pain

o = osteoid  b = bone
FGF23 is made by FD cells

FGF23 is a Hormone that Causes Phosphate Wasting in FD

May show up during times of rapid growth (ex: infancy, puberty)
May resolve in adulthood
Hypophosphatemia Increases Fractures

Fracture rate (fractures/patient/year)

Age (years)

- hypophosphatemia
- normal phosphorus

(Leet, JBMR, 2004)
Hypophosphatemia: Treatment

1. Phosphorus Supplements
   - Pills, powder, or liquid
   - Short-acting, must give 3-5 times a day
   - Diarrhea, GI discomfort

2. Calcitriol
   - Prevents hyperparathyroidism (major side effect of Phosphorus supplements)
   - May increase urine calcium
     • Monitor urines and kidney ultrasounds
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.
- Age < 5 years:
  - High clinical suspicion for significant FD
    - Skeletal survey
    - Vision and hearing evaluation
    - Serum phos., TRP
    - 99mTc-MDP bone scan at age 5
- Low clinical suspicion for significant FD
  - Monitor clinically
    - 99mTc-MDP bone scan at age 5

- Age ≥ 5 years:
  - Abnormal 99mTc-MDP bone scan
    - Significant FD
      - Monitor clinically
        - Baseline skeletal survey
        - Baseline head CT for craniofacial FD
        - Serum phos., TRP
      - Trivial FD
        - Consider baseline XR of affected area(s)
  - Normal 99mTc-MDP bone scan
    - Low likelihood for significant FD
      - Monitor clinically

Fibrous Dysplasia Management

- Craniofacial FD
  - Vision and hearing assessment annually
  - Baseline and periodic head CT
  - Avoid surgery in absence of pain and healing defects
- Axial and Appendicular FD
  - Encourage low impact cardiovascular activity
  - Shoe inserts for correction of leg length discrepancy
  - Monitor for scoliosis
  - Sural nerve biopsy if Cobb angle > 50 degrees
  - Consult with orthopedic surgeon experienced in FD as needed for fracture, severe deformity
- Bone pain
  - Osteoid osteoma/pain
    - Evaluate for acute or impending fracture
  - Fibrous dysplasia pain
    - Monitor for hypercalcemia
    - Bisphosphonates for persistent, moderate to severe pain
    - Pamidronate: children 0.3 mg/kg, adults 60-90 mg
    - Zoledronic acid: children 0.05 mg/kg, adults 4.5 mg
    - Repeat dosing intervals determined by symptoms

Gonadal Evaluation in Girls

1. Targeted H&P
2. Review growth curve
3. Bone age

- History of breast development, vaginal bleeding and/or signs of estrogenization below age 6-7 years
  - High sensitivity LH, FSH, estradiol
  - Pelvic US
  - Ovarian cyst
    - Abnormal labs
      - Likely MAS-associated PP
        - Surgical cyst removal is contraindicated
  - Normal US +/- abnormal labs
    - Possible MAS-associated PP

- No history of breast development, vaginal bleeding and/or signs of estrogenization below age 6-7 years
  - Bone age advancement ≥ 2 years
    - Bone age advancement ≥ 2 years
      - Consider subclinical PP
        - Consider hyperthyroidism and/or GH excess
  - No bone age advancement
    - Consider MAS-associated PP

Precocious Puberty Management in Girls

- 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
  - Bone age advancement < 2 years
  - Monitoring
    - Bone age, growth velocity, PE q 6 mo
      - No routine labs or imaging
Questions?