Insights into McCune Albright Syndrome: A Complex, Rare Disease with Individual Presentations

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Conflict of Interest Disclosure

- Conflicts of Interest
  - None
    - Lori Guthrie
    - Beth Brillante

The National Institutes of Health (NIH) is the nation's largest hospital devoted entirely to clinical research.

We are located in Bethesda, Maryland, just a few miles north of Washington, DC.
We are Research Nurse Specialists who coordinate research studies for children and adults with rare bone and endocrine conditions, one of which is McCune Albright Syndrome.

We work on a team that is comprised of:
- Adult and Pediatric Endocrinologists
- Endocrine Fellows
- Dental/Craniofacial Surgeon
- Lab Technician
- Research Nurses

McCune Albright Syndrome Research Study at NIH
- Prospective Cohort Study – investigate cause of disease and health outcomes
- Largest cohort of McCune Albright Syndrome patients in the world, >215
- Range from <1 to 98 years of age
- Current study: 1998 to present
  Prior studies: mid 1980s - 1998
Objectives

1. Name the gene mutation associated with McCune Albright Syndrome.

2. List the three body systems most commonly affected by McCune Albright Syndrome.

3. Discuss the current medical management and medications used to manage fibrous dysplasia and McCune Albright Syndrome.

4. Identify two psychosocial aspects related to the challenges of living with McCune Albright Syndrome.

5. Discussion/Questions.

McCune Albright Syndrome

Differential Diagnosis

These depend on presentation and may include:

- Neurofibromatosis
- Osteofibrous dysplasia
- Non-ossifying fibromas
- Idiopathic central precocious puberty
- Milder form of osteogenesis imperfecta
- Ovarian neoplasm
What is McCune Albright Syndrome (MAS)?

- Rare genetic disorder
- Affects 1 in 100,000 to 1 in 1,000,000 people worldwide
- No known "cause" for the mutation
- The mutation did not come from either parent and will not be passed to children

MAS Gene Mutation

- GNAS (guanine nucleotide binding protein, alpha stimulating activity polypeptide 1)
- Spontaneous mutation: long arm (q) arm of chromosome 20 at position 13.3
- Mutates cells within variously affected tissues
- Highly variable presentations – depends on specific tissues involved and extent of involvement

$G_s$ is the “on and off switch” for many cells

- Skin
  - Café-au-lait
  - Precocious puberty
- Ovary
  - Fibrous dysplasia
- Bone
- Thyroid
  - Hyperthyroidism
- Pituitary
  - Growth hormone excess
Skin

Thyroid

Bone

How
MAS
Happens

Mutation occurs by chance

Mutated cell proliferates

Mutated cells migrate & expands as embryo is formed

Stem Cell
Where and when the mutation occurs determines what manifestations the person will and won’t have.

How MAS Happens

- Mutation occurs by chance
- Mutated cell proliferates
- Mutated cells migrate & expands as embryo is formed

Diagnosis

- Diagnosis most often occurs in early childhood
- May be diagnosed:
  - at birth - presence of café-au-lait spots
  - early childhood - in cases with severe polyostotic fibrous dysplasia or development of precocious puberty
  - adulthood - incidental finding on imaging

Clinical Manifestations in MAS

- Skin – ectoderm
- Bone – mesoderm
- Endocrine – endoderm
Skin – café-au-lait spots

- Light brown patches of skin, often present at birth
- Irregular edges are often compared to a map of the coast of Maine
- Not specific for MAS - 10% of healthy population have café-au-lait spots

Spectrum of café-au-lait spots

- First sign of MAS
- Coast of Maine appearance

Spectrum of café-au-lait spots

- Often starts or ends near the midline
- No correlation with location or extent of bone disease
Clinical Manifestations in MAS

Fibrous Dysplasia (FD)

- Abnormal scar-like (fibrous) tissue in bones. "Ground glass" appearance.
- Monostotic – affecting one bone
- Polyostotic – affecting multiple bones
- No medical treatments known to alter the course of FD
- Surgery - correct deformity and repair fractures
- Physical therapy and occupational therapy - optimize mobility and function

Fibrous Dysplasia

Deformity, Pain, Limp, Fractures, Disability

Shepherd's crook deformity
Wind-swept deformity
Fragility fractures
Fibrous Dysplasia

Virtually any bone in the body may be affected.

Most common are:
– facial and skull bones
– pelvis
– femur
– tibia
– humerus
– ribs
– small bones in hands and feet

FD – variations in severity

FD in the spine: scoliosis

- Scoliosis is common; may be progressive.
- Scoliosis occurs at sites of FD
- Progression can be stopped by rods
FD - Craniofacial

In the craniofacial area (bones of the skull and face), most complications are related to FD expansion. This may lead to facial asymmetry, and very rarely, loss of vision and hearing.

Craniofacial fibrous dysplasia: progression
**Fibrous Dysplasia and Pain**

- Common; can occur in any FD location
- FD pain may be due to fracture or hypophosphatemia, or it may be related to the FD itself
- Treatment:
  1. Over the counter medications (such as acetaminophen, ibuprofen, and naproxen) - mild to moderate pain
  2. Intravenous bisphosphonates (such as pamidronate or zoledronic acid)
  3. Narcotic medications - last resort

**Clinical Manifestations in MAS**

- Skin – ectoderm
- Bone – mesoderm
- Endocrine – endoderm

**McCune-Albright Syndrome**

- Café-au-lait
- Fibrous Dysplasia
- Precocious Puberty
- Growth Hormone Excess
- Hyperthyroid
- Cushing Syndrome
- Phosphate Wasting
Peripheral Precocious Puberty in Girls
arises from early activation of ovaries

- Recurrent ovarian cysts
- Breast development
- Vaginal bleeding
- Increased growth velocity
- Bone age advancement
- Reduced final adult height
- Some teens/women have menstrual irregularities
- Women with MAS are often able to become pregnant and have healthy children

Peripheral Precocious Puberty in Boys
arises from early activation of testicles

- Less common in boys, than girls
- Increased growth velocity
- Bone age advancement
- Reduced final adult height
- Pubic and axillary hair
- Increased growth of testicles/penis
- Early sexual behavior/aggression
- Leydig or Sertoli cell hyperplasia in testicles

Precocious Puberty - Treatment

**Peripheral Precocious Puberty:**
- Commonly used medication is letrozole, which blocks the formation of estrogen. Boys may be treated with a combination of letrozole and spironolactone, which blocks the action of testosterone.

**Central Precocious Puberty:**
- Occurs when a child who was previously well-controlled on medications, presents with signs of "breakthrough" puberty. Occurs when the pituitary gland turns on too early. Treated with an injectable medication called leuprolide, which suppresses the pituitary gland.
Find photo of adult female standing
Estrada, Andrea (NIH/NICHD) [E], 2/25/2015
**Growth Hormone (GH) Excess**
- Production of high levels of growth hormone from the pituitary gland
- Main symptom - accelerated growth rate
- GH excess may cause FD to expand
- Untreated GH excess - higher risk of vision loss in patients with skull disease
- Treatments:
  - Octreotide is a drug that prevents the release of growth hormone from the pituitary
  - Pegvisomant is a medication that blocks the action of growth hormone on its receptor
  - Pituitary surgery or radiation - used rarely

**Hyperthyroid**
- Production of excess thyroid hormone, resulting in hyperthyroidism
- Other thyroid abnormalities: goiter, cysts, and nodules
- Treatment:
  - Methimazole - drug that blocks thyroid hormone production. Most patients with MAS and hyperthyroidism will eventually have a thyroidectomy. After thyroidectomy patients will need standard thyroid hormone replacement.
- Very slight increased risk of thyroid cancer

**Cushing Syndrome**
- Excess cortisol production, a rare complication
- Presents during infancy or the first few years of toddlerhood
- Symptoms vary: low birth weight and abnormal weight gain, especially in the face and trunk
- Can become severely ill, and in rare cases death
- In a few cases, Cushing syndrome in MAS has resolved on its own
- Treatment:
  - Depends on the age of the child, the severity of illness
  - Drugs which may be used to block cortisol production
  - Surgery to remove the adrenal glands
Phosphate Wasting

• Hypophosphatemia: low levels of phosphorus in the blood
• Causes bone pain, muscles weakness, increased fractures
• Occurs when fibrous dysplasia bones produce excess amounts of FGF23, a hormone which causes the kidneys to lose phosphorus in the urine
• Treatment: a combination of oral phosphate supplements and vitamin D

“Map” of Tissues is established in utero and manifests at an early age

<table>
<thead>
<tr>
<th>Findings</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Fibrous dysplasia</td>
<td>99</td>
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<tr>
<td>Café-au-lait</td>
<td>89</td>
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<td>Gonads</td>
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<tr>
<td>male</td>
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<td>female (PP)</td>
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<td>Thyroid</td>
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<td>Phosphate wasting</td>
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<td>requiring treatment</td>
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<tr>
<td>Growth hormone</td>
<td>18</td>
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<tr>
<td>Cushings</td>
<td>7</td>
</tr>
</tbody>
</table>

NIH MAS cohort
Psychosocial Considerations Related to MAS/FD

- Impaired physical function may = physical limitations
- Self Esteem/mental health impact
- Parental/Family Dynamics

Quality of life in children with FD/MAS

* = p < 0.05 MAS vs US
Kelly, Bone, 2005

Quality of life in adults with FD/MAS

* = p < 0.05 MAS vs US norms
Kelly, Bone, 2005
Physical Function Impaired, HRQOL Preserved

- Impaired physical function may = physical limitations
  - low risk activities to avoid fractures/injuries to bone (swimming).
  - Adaptations if necessary - wheelchair
- Self esteem/mental health impact
  - MAS/FD population - perceptions similar to general population
- Parental/Family Dynamics
  - education
  - support groups - Magic Foundation, Fibrous Dysplasia Foundation

Resources for Patients and Families

The MAGIC Foundation

The MAGIC Foundation

http://www.magicfoundation.org/www

http://fibrousdylosis.org/

Comprehensive NIH CC Clinical Evaluation

NIH Natural History Study of FD/MAS
NIH Research Related to FD/MAS: Present and Future

- **Pancreatic**
  - collaboration with Johns Hopkins University
  - prospective research, part of NIH natural study, to determine incidence of pancreatic neoplasms (intraductal papillary mucinous neoplasms (IPMNs) in high risk subjects of the NIH FD/MAS population

- **Dental**
  - collaboration with University of Pennsylvania
  - retrospective study to determine dental outcomes in NIH FD/MAS pediatric population

- **Neurological**
  - study to be developed to examine neurological/neuropsychological effects, if any, of FD/MAS

- **Novel Therapies**
  - denosumab
  - denosumab
  - denosumab

Selected References


Questions?