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

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Conflict of Interest Disclosure

Lori Guthrie and Jamie Streit

NIDCR receives research funds from Amgen Inc. and QED Therapeutics for studies involving McCune-Albright Syndrome and other disorders.

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 (MAS).

Lori Guthrie, Jamie Streit, Kelly Milligan

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

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 treatments used to manage McCune-Albright Syndrome.
4. Identify three psychosocial aspects related to the challenges of living with McCune-Albright Syndrome.
5. Discussion/Questions.
MAS Natural History Research Study at NIH

- Prospective Cohort Study – detailed phenotyping to define spectrum and natural history
- Largest cohort of MAS patients in the world, >289 on-site
- Range from <1 to 102 years of age
- Current study: 1998 to present
  Prior studies: mid 1980s - 1998

Comprehensive NIH Clinical Evaluation

- History and Physical Exam
- Lab and Urine Endocrine Markers
- Rehabilitation Medicine
- Thyroid Ultrasound
- Gonad Ultrasound
- CT Skull
- Dental
- MRI Pancreas
- History and Physical Exam
- Serum and Urine Endocrine Markers
- Skeletal X-rays
- Rehabilitation Medicine
- Thyroid Ultrasound
- Gonad Ultrasound
- CT Skull
- Dental
- MRI Pancreas
- History and Physical Exam
- Serum and Urine Endocrine Markers
- Skeletal X-rays

Additional Testing as Needed:
- Gynecology
- Pain and Palliative Care
- Dental Blood 
  - Oral Blood 
  - Total Blood
  - 24 hour Guthrie Hormone Sampling (overnight)
  - 3-hour ACTH
  - Kidney Ultrasound
  - MRI Brain
  - MRI Face/Sinus/ENT
  - Pulmonary Function Tests
  - Echocardiogram
  - Neuropsychiatric Testing
  - Overnight Sleep Study
  - Mental Health Interview

Ophthalmology
- Audiology
- Otolaryngology
- Bone scan
- Clinical Photography
- Quality of Life Questionnaires
- Wrap up Meeting
What is McCune-Albright Syndrome?

- 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 their children

MAS Differential Diagnosis

These depend on presentation and may include:

- Neurofibromatosis
- Osteofibrous dysplasia
- Non-ossifying fibromas
- Idiopathic central precocious puberty
- Milder forms of osteogenesis imperfecta
- Ovarian neoplasm
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

How MAS Happens

Mutation occurs by chance

Stem Cell mutation in the gene GNAS

GNAS codes for the protein, Gα

Stem Cell

Mutation occurs by chance

Mutation is now in cells that will give rise to different tissues: skin, bone, thyroid, etc.

Mutated cell proliferates

Migrates & expands as embryo is formed

Skin

Thyroid

Bone
How MAS Happens

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

Stem Cell

The tissues that form from mutated cells determine where the disease is located

How MAS Happens

Skin café-au-lait macules precocious puberty
Bone fibrous dysplasia hyperthyroidism
Thyroid growth hormone excess
Pituitary

In MAS, the hormone receptor get stuck in the “on” position

G\(\alpha\) is the “on and off switch” for many cells
Diagnosis

- Diagnosis most often occurs in early childhood
- May be diagnosed:
  - at birth - presence of café-au-lait macules
  - early childhood - development of precocious puberty, bone fractures, or bone deformities
  - adulthood - incidental finding on imaging
- The name: McCune-Albright Syndrome versus fibrous dysplasia

Clinical Manifestations in MAS

Skin – café-au-lait macules

- 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 macules
Spectrum of café-au-lait macules

- first sign of MAS
- coast of Maine appearance

- Often starts or ends near the midline
- NO correlation with location or extent of bone disease

Clinical Manifestations in MAS

Skin - ectoderm
Bone - mesoderm
Endocrine - endoderm
Fibrous Dysplasia (FD)

- Abnormal scar-like (fibrous) tissue in bones. “Ground glass” appearance
- Monostotic – affecting one bone
  Polostotic – 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

- Wind-swept deformity
- Shepherd’s crook deformity
- Leg-length discrepancy

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 occurs at sites of FD
- Scoliosis is more common with leg length discrepancy
- Worsens with untreated endocrine disorders, especially hyperthyroidism and hypophosphatemia
- 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

Common; can occur in any FD location

Pain may be due to the expansion in the FD bone, fracture or hypophosphatemia

Treatment:
- Prevention: strength training, range of motion, correction of leg length discrepancies (orthotics, shoe lifts)
- Over the counter medications (such as acetaminophen, ibuprofen, and naproxen) - mild to moderate pain
- Pain specialist to guide pharmacologic (narcotics for acute issues - fractures or surgery) and non-pharmacologic therapies (massage, acupuncture)
- Intravenous bisphosphonates (such as pamidronate or zoledronic acid) – ONJ link
Clinical Manifestations in MAS

Skin – ectoderm

Bone – mesoderm

Endocrine – endoderm

McCune-Albright Syndrome

Café-au-lait

Fibrous Dysplasia

Precocious Puberty

Growth Hormone Excess

Hyperthyroid

Neonatal Cushing Syndrome

Phosphate Wasting

Peripheral Precocious Puberty in Girls

- Breast development
- Vaginal bleeding
- Recurrent ovarian cysts
- 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

Pelvic Ultrasound
Peripheral Precocious Puberty in Boys

- 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 on testicular ultrasound

Peripheral Precocious Puberty:

- Girls – letrozole (blocks action of estrogen)
- Boys – combination of letrozole and spironolactone (blocks action of testosterone)

Central Precocious Puberty:

- When a child who was previously well-controlled on peripheral precocious puberty meds, presents with signs of “breakthrough” puberty (pituitary gland turns on too early)
- Leuprolide is added (suppresses the pituitary gland)

Growth Hormone (GH) Excess

- Production of high levels of growth hormone from the pituitary gland
- Main symptoms - accelerated growth rate and FD expansion
- If untreated, GH excess leads to higher risk of vision and/or hearing 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

Gigantism due to GH excess
Short stature due to precocious puberty
**Hyperthyroid**

- Production of excess thyroid hormone, resulting in hyperthyroidism
- Other thyroid abnormalities: goiter, cysts, and nodules
- Very slight increased risk of thyroid cancer
- Treatment:
  - Methimazole - drug that blocks thyroid hormone production
  - Most patients with MAS and hyperthyroidism will eventually have a thyroidectomy, and will then need standard thyroid hormone replacement
  - Some patients may regrow thyroid tissue after thyroid removed

**Neonatal 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 is sometimes fatal
- In a few cases in MAS, neonatal Cushing has resolved on its own
- Treatment: depends on age of the child and severity of illness
  - Drugs that 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, rickets
- 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

- Fibrous dysplasia
- Café-au-lait macules
- Precocious puberty
- Thyroid Phosphate
- Growth hormone excess
- Neonatal Cushing Syndrome

- Spontaneous resolution possible
- Clinically evident
- Subclinical

Age: 0 5 10 15 20 30 50+

→ Complete staging after age 5 allows for determination of affected and unaffected tissues

NIH MAS cohort

<table>
<thead>
<tr>
<th>Findings</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Fibrous dysplasia</td>
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<tr>
<td>Café-au-lait macules</td>
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<tr>
<td>Gonads/precocious puberty male</td>
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<tr>
<td>female</td>
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<td>Thyroid</td>
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<td>Phosphate wasting requiring treatment</td>
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<td>Growth hormone excess</td>
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<tr>
<td>Neonatal Cushing Syndrome</td>
<td>7</td>
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NIH Collaborative Research Related to MAS

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

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

- **Sleep/Psychiatric/Neuropsychological**
  - collaboration with NIMH to determine incidences of sleep, psychiatric, and neuropsychological differences in the NIH MAS population

- **Novel Therapies**
  - denosumab drug trials (for bone pain)
Psychosocial Considerations Related to MAS

- Impaired physical function
  +/− physical limitations
  - Low risk activities to avoid fracture/injuries to bone (modified PE/Gym; encourage activities such as swimming, recreational dance)
  - Adaptations if necessary - cane, crutches, wheelchair, orthotics, shoe lifts, etc.

Psychosocial Considerations - continued

- Self esteem/mental health impact
  - QOL: MAS perception versus parents’ perception
  - Recommend counseling for specific concerns - coping with physical signs of early puberty, teasing/bullying, life transitions (e.g., high school to college, long-term relationships, adaptations to work, etc.)

- Knowledge deficit related to disease process
  - Education
  - Support groups - Magic Foundation, Fibrous Dysplasia Foundation

When parents search the internet for “McCune-Albright Syndrome,” what do they see?
Resources for Patients and Families

The MAGIC Foundation

http://www.magicfoundation.org/www

Resources for Clinicians

GenesReviews: Fibrous Dysplasia/McCune-Albright Syndrome, Bone, Florence, F de Castro, Collins, August 16, 2018

Selected References


Questions?