Date: Wednesday, October 16, 2013, 7:00 pm – 8:45 pm

Topic: VACCINES: MYSTERIES: FOP – WHEN BODIES TURN TO BONE

Speaker: Joseph A. Kitterman, MD, Professor Emeritus of Pediatrics and the Cardiovascular Research Institute

Joseph A. Kitterman, M.D. is Professor Emeritus of Pediatrics and the Cardiovascular Research Institute at UCSF and a staff physician at UCSF Benioff Children’s Hospital. He received a B.A. in Zoology from UC Berkeley and received his medical degree from McGill University in Montreal, Quebec, Canada. After interning at the Montreal General Hospital, he completed a residency in Pediatrics and a fellowship in cardiopulmonary physiology at UCSF. He is board certified in Pediatrics and Neonatal-Perinatal Medicine. While a UCSF faculty member (1970 to 2007), he was an attending physician in the William H. Tooley Intensive Care Nursery, directed the Neonatology Fellowship Program for 19 years, and was Medical Director of the Neonatal Clinical Physiology Laboratory for 20 years. He has extensive experience in clinical research and in laboratory research (developmental lung biology). Since 2000, he has been active in clinical research in FOP and in the care of patients with the disease.

Bibliography:

*International FOP Association: www.ifopa.org


Genetic Mysteries: 
Fibrodysplasia Ossificans Progressiva (FOP), 
When Bodies Turn to Bone

UCSF Mini-Medical School 
October 16, 2013

Joseph A. Kitterman, M.D. 
Professor Emeritus of Pediatrics and 
the Cardiovascular Research Institute

What is FOP?
• Rare, devastating genetic condition in which 
skeletal muscles, tendons and ligaments progressively and permanently turn to bone
• Almost all cases are new mutations
• Characterized by:
  – Distinctive malformations of the great toes: short with lateral deviation (hallux valgus)
  – “Flare-ups,” tumor-like lesions that progress to ossification (bone formation)
• Most cases are initially given incorrect diagnoses
• No effective treatment

Major Clinical Features of FOP

Why is an old, retired neonatologist and lung biologist speaking about a very rare bone disease that is almost never diagnosed before age 3 years?
Born at term with unusual short great toes
- Pediatrician asked: "Whose toes does he have, mom's or dad's?"
- Played Little League baseball
- Tried out for high school football team
- Avid wake-boarder
- Age 17, fell while wakeboarding and felt pain in neck
- Mass arose on back
- Biopsies: (1) probable lymphoma; (2) aggressive fibromatosis
- Chemotherapy
- Follow-up CT scan: Dx'ed by radiologist as FOP

FOP is not a new disease
- 1692: Patin (France) described a woman who gradually became "hard like wood."
- 1738-40: Three cases described in letters to the Royal Society (England)
- 1918: Rosenstirn reported a case and reviewed 120 cases from the literature (Annals of Surgery 68:485).

Julius Rosenstirn, M.D.
Mt. Zion Hospital, San Francisco
Fibrodysplasia Ossificans Progressiva

- Rare genetic disease characterized by:
  - malformations of the great toes
  - episodic progressive heterotopic ossification
- Incidence: one in 2 million worldwide
  (no differences by gender, race, ethnicity, or geographical location)
- Autosomal dominant, 100% penetrance with variable expressivity
- Progressive & permanent loss of mobility
- Cause is an activating mutation of the Type 1 BMP receptor, ACVR1
- No effective treatment
Malformations of the Great Toes in FOP

- Short great toes
- Hallux valgus deformity
- Absent or hypoplastic 1st phalanx
- Malformations are present at birth

Early FOP Lesions (Flare-ups)

- Most commonly occur first on back, head, neck or shoulders
- Lesions are warm, red and tender
- Appear very rapidly, often overnight

FOP is a Metamorphosis

- Intramuscular lymphocytic infiltration
- Perivascular lymphocytic infiltration
- Muscle degradation

FOP Bone

**Normal**
- Histologically
- Biochemically
- Metabolically
- Physically
- Radiographically

**Abnormal**
- Wrong time
- Wrong places

**Progression of FOP**

- FOP affects:
  - Striated muscle
  - Tendons
  - Ligaments
  - Fasciae

- FOP spares:
  - Diaphragm
  - Extra-ocular muscles
  - Tongue
  - Cardiac & smooth muscle
  - Small muscles of hand (usually)

- Progression of FOP:
  - Cranial to caudal
  - Axial to peripheral


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**Clinical Aspects of FOP**

- Toe malformations are present at birth
- Onset of flare-ups usually in first decade of life
- Usually misdiagnosed initially
- Flare-ups may be:
  - Spontaneous
  - Triggered by trauma:
    - Falls
    - IM injections
    - Biopsies
    - Surgery
  - A result of a viral infection
- Surgical removal of FOP bone causes rapid, explosive regrowth of bone

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**Progression of FOP**

Repeated flare-ups
Increasing heterotopic ossification
Progressive & permanent loss of mobility

**Progressive Heterotopic Ossification**
(In an 11 year old boy)
Other Features of FOP

• Mild hearing loss in ~50% of patients
• Neurological complications
  – Headaches*
  – Neuropathic pain*
  – Sensory abnormalities*
  – Myoclonus*
  – Demyelinating lesions of CNS
• Characteristic facial pattern
  – Receding jaw
  – Under-developed mid-facial area
  * Only in post-pubertal females

FOP patients at UCSF in past 13 years

• 2000, 17 y.o. male with masses on neck, back and chest presented at Pediatric Tumor Board
• 2003, 3 y.o. male with neck masses
• 2005, 17 y.o. male seen in Orthopaedics Clinic
• 2006, 23 y.o. female admitted to Medicine with severe flare-up of arm
• 2006, 18 month male admitted to Pediatrics with a stiff neck and masses on neck, back and forehead
• 2007, 29 y.o. Swedish female admitted to Orthopaedics with multiple fractures from MVA
• 2007-2013, 19 y.o. female admitted 25 times to Pediatrics with neurological symptoms

Harry Eastlack
1935 to 1972

Harry’s skeleton can be seen in the Mütter Museum in Philadelphia

4 years 7 years 9 years

11 years 18 years 1973

Chin-on Chest Deformity in FOP

8 year old girl: Deformity developed over 3 years
Diagnostic Errors in FOP

- Survey: 138 individuals with FOP from 25 countries
- 87% initially received incorrect diagnoses
- Physicians seen before correct DX: 
  \( \bar{x}=6, \text{ range: 1 to 51} \)
- Incorrect diagnoses included
  - Cancer (32): lymphoma
  - Fibromatosis (19): aggressive fibromatosis and desmoid tumors
  - Bunions or hallux valgus (9)
  - Overuse injuries (7)
  - 43 other diagnoses
- 67% underwent biopsies
- 49% reported permanent loss of function due to inappropriate medical interventions

(Kitterman, et al. Pediatrics, 2005)

Paucity of FOP Information in Medical Textbooks

<table>
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</table>
Medical Management of FOP

- Make an accurate diagnosis
- Avoid trauma (IM injections, biopsies, surgery, falls, fatigue)
- Muscle relaxants
- NSAIDs for pain relief (Vioxx was banned)
- For flare-ups involving new joints or airway, jaw, or throat:
  - High dose adrenal corticoids for 3 to 4 days
  - Repeat if flare-up persists
- Amino-bisphosphonates may help in flare-ups
- Currently, no proven effective treatment

Special Considerations in FOP

- Dental procedures: Avoid permanent locking of jaw
  - No mandibular blocks
  - Do not stretch mouth open
- General anesthesia
  - No oro-tracheal intubation
  - Use naso-tracheal intubation
  - Careful positioning to avoid pressure trauma

Outcome in FOP

- Recurrent flare-ups leading to ossification
- Progressive & permanent loss of mobility
- Most are wheelchair bound by the 3rd decade
- May need assisted care for basic personal functions
- Malnutrition, especially after inappropriate dental work
- Progressive worsening of cardio-pulmonary function due to restrictive lung disease
- Early death (median age 40 years, range 3 - 77 years)
- Causes of death:
  - Cardio-respiratory failure (54%)
  - Pneumonia (15%)
  - Falls (11%)
  (Kaplan, et al., J Bone Joint Surg Am, 2010)

Genetic Cause of FOP

- Activating mutation in gene encoding for the type 1 bone morphogenetic protein (BMP) receptor, ACVR1 (Alk2), on chromosome 2q
- Identical single nucleotide change in 45 individuals with FOP
- Mutation was absent in 159 individuals without FOP
  (Shore, et al., Nature Genetics, 2006)
- Mutation results in:
  - Over-expression of BMP4 mRNA
  - Failure to upregulate BMP antagonists
  - Ligand independent BMP signaling
  - ↑ responsiveness in presence of ligand
  - ↓ BMP receptor internalization/degradation
  (Shore & Kaplan, Bone, 2008)
Recent Research Advances in FOP

- 2004 FOPPY mouse over-expresses BMP4
- 2006 Discovery of FOP gene
- 2007 Flare-up cells are endothelial in origin
- 2010 Conversion of endothelial cells to stem cells
- 2011 RAR-γ agonists inhibit H.O.
- 2011 Substance P mediates BMP dependent H.O.
- 2012 Transgenic mouse model of FOP
- ? Clinical trial of treatment for FOP

Transgenic Mouse Model of FOP

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<tr>
<td>Short, broad femoral necks</td>
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<tr>
<td>Inflammationn/lymphocyte infiltration</td>
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(Chakkalakal, et al, 2012)
FOP Research and Care at UCSF

Edward Hsiao, M.D., Ph.D.
Division of Endocrinology
Dept. of Medicine

- Stem cell research in FOP
- Metabolic Bone Clinic  (415) 353-2350
- In-patient care of FOP patients

International FOP Association (IFOPA)

- Founded in 1988 by Jeanie Peeper (Florida)
- >500 members worldwide (50 countries)
- Mission:
  - Fund research to find a cure for FOP
  - Support and education of individuals and families
  - Public awareness and advocacy
- Funds from family fundraising events and donations
- IFOPA supports research at ~$500,000/year
  (~75% of budget for FOP laboratory at U. Penn)

Find-A-Cure Benefit

Santa Maria, CA
FOP Summary

• Rare, debilitating, genetic disease
• Main clinical features:
  – Characteristic malformations of great toes
  – Rapidly appearing tumor-like swellings that turn to bone
• No effective treatment
• Research support through IFOPA families
• With recent research advances, probable clinical trial of treatment in relatively near future