Fibrous Dysplasia in Children

Professor Nick Shaw

Birmingham Children’s Hospital, UK
Overview

• What is Fibrous Dysplasia?
• Clinical Presentations
• Endocrine Problems
• Skeletal Problems
• Treatment Options
Fibrous Dysplasia

- An uncommon skeletal disorder – incidence 1 in 15-30,000
- Replacement of normal bone with fibrous tissue
- Broad spectrum of clinical features - an incidental finding on X-ray or a disabling disease present in early life
- Categories:
  Monostotic (one bone)
  Polyostotic (multiple bones)
  Panostotic (entire skeleton)
- May be associated extraskeletal features:
  McCune Albright Syndrome
Fibrous Dysplasia
Clinical Presentation

- Orthopaedic Surgeon: Limp, fracture, bone pain or coincidental finding on X-ray

- Endocrinologist: Cushing’s Syndrome, Precocious Puberty, Hyperthyroidism

- Dermatologist: Skin Pigmentation
McCune Albright Syndrome

- 2 of 3 features (classic triad):
  - A) polyostotic fibrous dysplasia (PFD)
  - B) café-au-lait skin pigmentation
  - C) autonomous endocrine hyperfunction
- Prevalence $1:10^5$- to $1:10^6$
- Somatic activating mutations of the GNAS gene
- Cannot be inherited
Activating Mutation of $G_s\alpha$ (GNAS) R201(H/C)

Melanin, $E_2$, T, T4, GH, Cortisol

Café-au-lait
Precocious puberty
Fibrous dysplasia

Gigantism/Acromegaly
Hyperthyroid
Cushings

MSH, LH, TSH, GHRH, ACTH

Receptor

$G_s\alpha$

$\gamma\beta\alpha$

ATP

PPI $\xrightarrow{+} cAMP$
**Fig. 94.1.** Café au lait skin pigmentation. (A) A large pigmented macule with a classical appearance on the face, chest, and arm of a 5-year-old girl with McCune-Albright syndrome that demonstrates jagged “coast of Maine” borders, and the tendency for the lesions to respect the midline. (B) Small but typical lesions that are often found on the nape of the neck and crease of the buttocks are shown, which also show a relationship to the midline. (C) Extensive lesions on the back of an infant that follow the developmental lines of Blaschko.
## Prevalence of Major Findings

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous Dysplasia</td>
<td>98</td>
</tr>
<tr>
<td>Café au lait spots</td>
<td>66</td>
</tr>
<tr>
<td>Gonadal abnormalities</td>
<td></td>
</tr>
<tr>
<td>Male (ultrasound)</td>
<td>70</td>
</tr>
<tr>
<td>Female: precocious puberty</td>
<td>50</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>28</td>
</tr>
<tr>
<td>Renal phosphate wasting</td>
<td>43</td>
</tr>
<tr>
<td>Growth hormone excess</td>
<td>21</td>
</tr>
<tr>
<td>Cushing’s Syndrome</td>
<td>4</td>
</tr>
</tbody>
</table>

Collins MT et al. Orphanet Journal of Rare Diseases 2012;7(Suppl 1):S4
Age of Appearance of Features

- Fibrous dysplasia
- Café-au-lait
- Precocious Puberty
- Thyroid
- Phosphaturia
- Growth Hormone Excess
- Cushings

Legend:
- pre-clinical
- clinically evident
- persistent abnormal menses
- spontaneous resolution possible
ENDOCRINE PROBLEMS
Precocious Puberty

• Precocious Puberty: More common in girls – often presents in first 3 years with vaginal bleeding and breast development.

• Characteristic pattern of suppressed gonadotrophins & high oestrogen

• Unilateral ovarian cysts often seen on pelvic ultrasound

• Initial observation – if progressive use of aromatase inhibitors eg Letrozole
Hyperthyroidism

• 2/3rds of subjects with MAS have abnormal thyroid ultrasounds
• However only 50% of these have hyperthyroidism
• May present with thyroid enlargement (goitre), rapid heart rate, poor weight gain, overactivity
• Thyroid function tests – T4, T3 and TSH
• Medical treatment first line eg Carbimazole tablets
• If poor control or long term – surgery or radioactive Iodine ablation of the thyroid gland
Growth Hormone Excess

- Less common problem – can occur in 21%
- Always associated with skull base fibrous dysplasia
- Increased growth rate may be obscured by precocious puberty
- Often associated with raised Prolactin
- Diagnosis: failure of suppression of GH levels on a glucose tolerance test + high IGF1
- Medical treatment: Octreotide injections daily or a long acting analogue monthly eg Lanreotide
GH Excess

Importance of managing GH excess in MAS

• GH excess is associated with a progression of craniofacial fibrous dysplasia & risk of loss of vision.

• In a cohort of 26 subjects with GH excess early intervention (< 18yrs) prevented optic neuropathy. 57% incidence in late intervention group.

Boyce AM et al, J Clin Endocrinol Metab 2013;98:E1260134
Cushing’s Syndrome

- Rare – only occurs in 4% of MAS subjects
- Always occurs in the neonatal period
- Presents with poor growth, hypertension, high blood sugars, round face and hirsutism
- Can resolve spontaneously
- Often requires surgical removal of the adrenal glands for cure
Phosphate Wasting

- FGF23 produced by fibrous dysplasia lesions
- Excess FGF23 increases renal phosphate wasting
- Skeletal burden related to FGF23 levels
- More likely to have bone pain & fractures
- Treat with Phosphate supplements & Vitamin D analogue eg One Alpha
SKELETAL PROBLEMS
Affected Skeletal Sites

- Skull Base
- Long Bones
- Ribs
- Spine
- Often not apparent clinically until age 4-5 yrs
- Isotope bone scan useful to determine extent
CT Scan
Fracture Incidence in Polyostotic Fibrous Dysplasia and the McCune-Albright Syndrome

![Fracture Incidence Graph](http://onlinelibrary.wiley.com/doi/10.1359/JBMR.0301262/full#fig1)
Fractures

• Study of 172 fractures in patients age 6-53yrs
• Peak fracture rate age 5-10 years
• Reduction in fracture rate in adolescence
• Presence of Phosphate wasting associated with more fractures at an earlier age
Polyostotic Fibrous Dysplasia

• Expanding lesions → pain, deformity & fractures.
• Classical Shepherd’s crook deformity of neck of femur
• Burden of skeletal disease worse in growing years
Polyostotic Fibrous Dysplasia
Panostotic Fibrous Dysplasia
Panostotic Fibrous Dysplasia
Scoliosis

- Scoliosis occurs in 40-52% of patients
- Important to monitor for progression
- Potential role of bracing
- If progressive will require spinal surgery
Management

• Craniofacial disease – yearly vision & hearing tests
• Periodic CT scans for optic nerve compression
• Prophylactic optic nerve decompression not recommended
• Recurrent femoral fractures – use intramedullary rods rather than plate & screws
• Operate when femoral shaft angle reaches 110 degrees
# Prevalence of less common findings

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>7</td>
</tr>
<tr>
<td>History of Hepatitis</td>
<td>4</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>4</td>
</tr>
<tr>
<td>Aortic root dilatation</td>
<td>2</td>
</tr>
<tr>
<td>Haematologic</td>
<td>1</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>4</td>
</tr>
</tbody>
</table>
WHAT CAN BE DONE TO MANAGE THE BONE DISEASE IN MCCUNE ALBRIGHT SYNDROME?
Bisphosphonates & Fibrous Dysplasia

- 18 children/adolescents with fibrous dysplasia
- IV Pamidronate every 4 months for 1 to 9 yrs
- Reduction in bone turnover markers
- Pain relief
- No evidence of filling of lytic lesions
- No change in dysplastic tissue on bone biopsy

Plotkin H et al, J Clin Endocrinol Metab 2003;88:4569-4575
RCT of Alendronate

- 40 subjects with FD
- Randomised to Alendronate or placebo over 2 yrs
- Improvement in bone density in Alendronate group
- No differences in pain scores, skeletal burden or functional outcomes

Boyce AM et al, J Clin Endocrinol Metab 2014;99:4133-40
Denosumab & Fibrous Dysplasia

- 9 yr old boy with MAS
- Required amputation of Rt Femur
- Failure of response to Pamidronate
- Expanding lesion in left femur
- Trial of Denosumab proposed

Boyce AM et al, J Bone Miner Res 2012;27:1462-70
Denosumab & Fibrous Dysplasia

- Monthly injections of Denosumab 1mg/kg
- After 7 months: Marked reduction in bone pain & tumour growth rate
- No impairment of fracture healing
- Rapid rebound in bone turnover & hypercalcaemia on stopping treatment
Summary

• Fibrous Dysplasia is a rare but often challenging condition
• Management requires understanding of possible endocrine and bone complications
• Close cooperation with an orthopaedic surgeon and a multidisciplinary team is critical in successful management
• Collins MT et al, McCune Albright Syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis 2012;7(Suppl 1):S4