Extraskletal manifestations of fibrous dysplasia

FIBROUS DYSPLASIA FOUNDATION'S
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Extraskeletal manifestations of fibrous dysplasia

- Phosphate
- Pancreas
- Cancer
- Brain
Why do we care about Phosphate?

**Phosphate** → **Calcium**

mineralization; the hard stuff the makes up bone

hydroxyapatite

bone is mostly hard stuff

with a few cells
FD overproduces FGF23

FGF23 made by FD, acts at the kidney to regulate blood phosphate and active vitamin D levels

fibroblast growth factor 23

↓ blood phosphate

↓ blood active vitamin D (1,25-D)

urinary phosphate
What are the effects of too much FGF23 on FD?

- Earlier fractures
- More fractures
- More pain

- the more FD, the more FGF23
- probably need >1/2 if the skeleton to be FD to get ↑ FGF23

(Leet, JBMR, 2004)
Treatment of low phosphate

• Oral phosphate + active vitamin D
  • 3-5 times per day
  • diarrhea common
  • risk of kidney stones

• May go get better/go away with time

• New drugs on the horizon
Pancreas in FD/MAS

- Some patients reported a history of pancreatitis
- We and a group in Paris began looking at the pancreas in MAS
- We found IPMNs (intraductal papillary mucinous neoplasms)
  - IPMNs are benign cyst-like lesions seen fairly commonly
  - may be a “precancerous” lesion
IPMNsa - MRCP

IPMN

normal

IPMN

normal

common bile duct

pancreatic duct

duodenum

common bile duct

pancreatic duct

duodenum
Pancreatic disease in MAS

54 patients screened with MRI (MRCP)

30 (56%) with abnormal MRCP

- 25 (83%) IPMNs
  - 7 endoscopy
  - 2 surgery
    - both high grade dysplasia
      - one pancreas
      - one esophagus

24 (44%) normal MRCP

5 (17%) with other pathology
- 2 adenomas
- 2 fatty liver
- 1 biliary cysts (<1cm)

7 endoscopy

2 surgery

both high grade dysplasia
- one pancreas
- one esophagus
Recommendations: Pancreas in FD/MAS

• Baseline screening with MRCP
• If negative – you’re done
• If abnormal → referral to a center with experience in complicated pancreas disease
• This is an evolving story...
Cancer in MAS

• The gene mutation that causes FD/MAS, $G\alpha_s$, is a weak “oncogene” (a gene mutation that promotes tumor growth); the $gsp$ oncogene

• It is NOT sufficient to cause cancer

• Cancer only occurs after several to dozens of mutations occur in a cell/tissue
Cancers that have been seen in association with FD/MAS

- Bone
  - An increase noted following a period when FD was treated with high dose, radiation
- Thyroid
  - Only 2 cases reported ever
- Testicular
  - Only one case reported
- Pancreas
  - 2 cases reported
- Breast
Breast Cancer in MAS

• Study of breast cancer in 2 large groups of women with FD/MAS
  – Leiden University Medical Center, Netherlands (134 women)
  – NIH (121 women)

• 15 cases of breast cancer identified

• 3.4-3.9-fold increase compared to the general population
Breast Cancer in MAS

• Average age 41 years (range 27-54)
• GNAS mutation found in only 4/9 cancers
• Risk factors:
  – Precocious puberty
  – FD in the thorax (chest region)
Breast Cancer in MAS

• Treatment: surgery, chemo, radiation
• 100% survival, 0 metastases
  – average 8.5 years follow-up, range 2-15
• Conclusions:
  – Women with MAS may be at increased risk of breast cancer
  – Compared to the general population, occurred at a younger age, less aggressive, with excellent long-term outcomes
  – Recommend: regular self-exams, and screening mammograms starting at age 40
FD/MAS and the brain

• $G\alpha_s$ is found throughout the brain
• Mice with mutant $G\alpha_s (gsp)$ expressed in certain regions of the brain have abnormal behavior
• In the NIH patients we have observed abnormal behavior/functioning in <10% of the patients
• Area of active research – more work needed...
Thank you: to the patients, families, and co-workers

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