FD/MAS Toolkit

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Print your Registry Surveys and store a copy in these folders. These copies can help you communicate your medical history during conversations with your doctors or during intake processes for doctor and hospital visits.

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Other resources

- Physician Nomination Forms
  We invite you to nominate any medical professionals who have provided you with excellent FD/MAS care.

Your FD/MAS Toolkit

About This Resource

The FD/MAS Toolkit is a resource to empower patients and caregivers and help them navigate the best care possible. Between tracking medication dosages, fractures and surgeries, insurance plans and more, fibrous dysplasia and McCune-Albright syndrome (FD/MAS) can be a time consuming disease. That's why we've created this binder, a tool to help you plan and stay organized and up to date.

Keep Your Toolkit Up To Date

Your FD/MAS Toolkit will be most useful if you keep it up to date when new research is published. We'll help you keep this resource up to date by:

- Updating the Library of Published Research on www.fibrousdysplasia.org
- Sharing news about research and treatment in the FDF e-Newsletter

Many of the resources in this binder are personalized tools for your FD/MAS treatment plan. You can keep those resources up to date by:

- Visit www.fibrousdysplasia.org/toolkit to print extra copies of these resources, including
    - Basic Medical Information
    - Medication List
    - Medical Care Team List
    - Appointment Notes and Visit Follow Up Sheet
- Visit www.fdmasregistry.org and update any surveys in your "updateable surveys" tab. Print survey updates and include those updates in your survey sleeves

We recommend updating your Registry surveys and this binder every two years. That way you'll be prepared with a meaningful resource for yourself and you clinicians when you go to any medical appointment and or hospital visit.

Questions and Comments

If you have questions or comments, please reach out to info@fibrousdysplasia.org

Treatment Guidelines for FD/MAS

The following are set of recommendations for the diagnosis, treatment, and follow-up of patients with FD and/or MAS. They are somewhat technical and it may be useful to discuss them with your doctor. Detailed explanations for these recommendations may be found in the Research section of this Toolkit.

Recommendations for Endocrine Follow-up of Patients with FD/MAS

1. **Pituitary:** Growth hormone (GH) and prolactin (PRL) excess are common in MAS (20%). The signs and symptoms can be very subtle. GH excess can worsen craniofacial (CF) bone disease.
    1. All patients should have an oral glucose tolerance test (OGTT) to assess for non-suppressible GH at least once (GH > 2.0 ng/ml at 60 min on standard OGTT is diagnostic).
    2. Non-suppressible GH with elevated insulin-like growth factor-1 (IGF-1) should be treated
    3. What to do with non-suppressible GH and normal IGF-1 is not clear (these patients will have an abnormal overnight GH secretion pattern)
2. **Thyroid:** Hyperthyroidism is common.
    1. Check thyroid function tests (TSH, FT4, T3, T4). T3 dominant hyperthyroidism is most common, 40%)
    2. Treat with an oral anti-thyroidal (methimazole, PTU)
    3. If definitive treatment is needed, we recommend surgery not radioiodine (thyroid cancer in MAS is rare, and radioiodine could be an additional risk factor beyond the Gs mutation).
    4. Annual ultrasound of the thyroid to follow lesions and biopsy clearly dominant, large or changing lesions.
3. **Parathyroid:** Primary hyperparathyroidism is rare, secondary (to vitamin D deficiency) is common.
    1. Check ionized calcium or total calcium and PTH annually.
4. **Adrenal:** Cushings in the neonatal period occurs, but has not been reported past the first year. Some cases of neonatal Cushings resolve spontaneously.
    1. Check adrenal reserve in resolved cases of neonatal Cushings.
5. **Renal:** Phosphate wasting with or without hypophosphatemia, and/or rickets/osteomalacia is common (40%).
    1. Check serum phosphate and renal phosphate handling (second AM void or 24 hour urine for TMP/GFR).
    2. Treat frankly low or low-normal serum phosphate with low TMP/GFR
    3. See separate treatment algorithm.

6. **Gonads:** Precocious puberty (PP) in girls is common, PP in boys is less common, small testicular masses of leydig cell hyperplasia are common.
    1. Treat PP in girls with an aromatase inhibitor (preferred), or tamoxifen.
    2. Treat PP in boys with an aromatase inhibitor and an anti-androgen.
    3. Check for and treat secondary central PP in children with PP with a long-acting GnRH agonist.
    4. Check for Leydig cell masses in men with screening testicular ultrasounds suspicious masses should undergo excisional biopsy to exclude cancer.

Recommendations for Follow-up of Patients with FD/MAS

1. **Craniofacial:** very common, especially skull base, vision loss is uncommon, hearing loss even more uncommon, sarcomatous degeneration is rare, while axial and appendicular FD quiets with age, CF probably continues to slowly progress.
    1. Find a craniofacial and neurosurgical team experienced in treating CF FD!
    2. Avoid surgery in the absence of visual or hearing impairment. (nerves may be surrounded by and unaffected by FD bone for decades).
    3. Severe pain or disfigurement may be an indication for surgery as well.
    4. Annual vision testing by a neuro-ophthalmologist and annual hearing testing are recommended.
    5. Annual CT of skull and mandible are recommended.
    6. Screen for and treat all endocrinopathies which adversely affect bone.
    7. Little evidence that bisphosphonates are effective in CF FD (even for pain).
    8. Bone scan at baseline and at some interval, potentially every few years.
2. **Axial and Appendicular skeleton:** very common, fractures frequent (esp. before 15 y.o.), shepherd's crook deformity common, pain common, sarcomatous degeneration (cancer) rare.
    1. Find an orthopedic surgeon experienced with FD!
    2. In general, less is better in the surgical treatment of FD.
    3. Bracing may potentially be helpful
    4. Screen for and treat all endocrinopathies which adversely affect bone.
    5. Bone scan at baseline and at some interval, potentially every few years.
    6. Bisphosphonates can decrease pain and markers of bone turnover, probably no effect on course of disease or fracture rate.
    7. Maintaining strength is important. Swimming is an excellent exercise, cycling is good also.

Recommendations for Treatment of Rickets/Osteomalacia/Hypophosphatemia

1. **Goal:** Serum phosphorus in the age-appropriate normal range
2. **Treatment:**
    1. **Phosphorus:** 15-60 mg/kg/day (1-3 g/day adults), divided, 4-5 times per day Phosphorus treatment usually causes secondary hyperparathyroidism, so 1,25 vitamin D (calcitriol) is usually added to prevent this.
    2. **Treatment with calcitriol** not only prevents secondary hyperparathyroidism but may also increases GI phosphorus absorption, improve bone healing (especially at high doses, and improve renal tubular maximum for phosphate reabsorption (i.e. increase TmP/GFR).
    3. **Calcitriol**: approximately 30 ng/kg/day (1.5 µg/day, (six 0.25 µg pills/day) for a 70 kg man), range15-60 ng/kg/d (three-twelve 0.25 µg pills/day)
3. **Possible Complications:**
    1. **Hypercalciuria** (high urine calcium). With kidney stones (nephrolithiasis) or kidney calcification (nephrocalcinosis) and decreased kidney function.
    2. **Hypercalcemia** (high blood calcium). Less common than hypercalciuria.
    3. **GI upset.** Due to the phosphate. Dividing the doses over 4-5 times per day and with food helps.
4. **Follow-up:**
5. Baseline ultrasound of the kidneys to rule out nephrolithiasis or nephrocalcinosis (which some patients are at risk for at the outset).
6. Every 3 month urine test (second A M void) for calcium (Ca) and creatinine (Cr), if Ca/Cr >= 0.20, check urine for blood, if presnt, decrease calcitriol, and obtain 24 hour urine for calcium and creatinine with the goal to keep urinary calcium in the normal range. If it is high, decrease calcitriol again. If Ca/Cr <= 0.20 and serum phos and PTH ok, maintain regimen (pediatric urinary calcium: Ca/Cr upper limit: < 7mo 0.86, 7-18 mo 0.6, 19 mo – 6 y 0.42: 24 hr urine: < 4mg/kg/24hr).
7. Every 3 month serum calcium, phosphorus, and PTH.

FD/MAS Toolkit: Medical Background

FD FIBROUS DYSPLASIA FOUNDATION

Patient Information

Name:_____
DOB:_____
Phone:_____
Address:_____
Email:_____

Emergency Contact

Contact & Relationship:_____
Phone:_____
Contact & Relationship:_____
Phone:_____

Primary Physician

Name:_____
Affiliated Hospital:_____
Phone:_____

Allergies

_____
_____
_____

Medical Condition and Considerations

Include affected bones, systems, and chronic conditions for consideration. Also list any primary physician who manages your rare disease diagnosis

Insurance Information

Primary Carrier:_____ Group #:_____ ID#:_____
Customer Service #:_____ Notes:_____
Secondary Carrier:_____ Group #:_____ ID#:_____
Customer Service #:_____ Notes:_____

FD/MAS Toolkit: Medication List

FIBROUS DYSPLASIA FOUNDATION

Medication	Dosage & Frequency	Purpose	Prescriber	Start Date	Stop Date

Be sure to include any over the counter medications, natural remedies, vitamins and supplements you take regularly.

FD/MAS Toolkit: Clinician List

FIBROUS DYSPLASIA FOUNDATION

Type of Care/ Speciality	Name	Address	Phone	Fax	Affiliated Hospital	Follow Up Schedule

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Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.

Fibrous Dysplasia/McCune-Albright Syndrome

Synonym: FD/MAS

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Summary

Clinical characteristics. Fibrous dysplasia/McCune-Albright syndrome (FD/MAS), the result of an early embryonic postzygotic somatic activating pathogenic variant in *GNAS* (encoding the cAMP pathway-associated G-protein, $G_s\alpha$), is characterized by involvement of the skin, skeleton, and certain endocrine organs. However, because $G_s\alpha$ signaling is ubiquitous, additional tissues may be affected.

Café au lait skin macules are common and are usually the first manifestation of the disease, apparent at or shortly after birth. Fibrous dysplasia (FD), which can involve any part and combination of the craniofacial, axial, and/or appendicular skeleton, can range from an isolated, asymptomatic monostotic lesion discovered incidentally to severe disabling polyostotic disease involving practically the entire skeleton and leading to progressive scoliosis, facial deformity, and loss of mobility, vision, and/or hearing. Endocrinopathies include:

- Gonadotropin-independent precocious puberty resulting from recurrent ovarian cysts in girls and autonomous testosterone production in boys;
- Testicular lesions with or without associated gonadotropin-independent precocious puberty;
- Thyroid lesions with or without non-autoimmune hyperthyroidism;

- Growth hormone excess;
- FGF23-mediated phosphate wasting with or without hypophosphatemia in association with fibrous dysplasia; and
- Neonatal hypercortisolism.

The prognosis for individuals with FD/MAS is based on disease location and severity.

Diagnosis/testing. In most individuals, the diagnosis of FD/MAS is based on the finding of two or more typical clinical features. In individuals whose only clinical finding is monostotic fibrous dysplasia, identification of a somatic activating pathogenic variant in *GNAS* by molecular genetic testing is required to establish the diagnosis. Variant detection depends on the level of mosaicism in the tissue and the sensitivity of the technique.

Management. *Treatment of manifestations:* Management is most effectively accomplished by a multidisciplinary team of specialists.

- FD. Management focuses on optimizing function and minimizing morbidity related to fractures and deformity (including scoliosis).
- Precocious puberty. Treatment prevents bone age advancement and compromise of adult height. For girls, the aromatase inhibitor letrozole is used; for boys, treatment options are less well established.
- Thyroid disease. Methimazole effectively manages hyperthyroidism; however, because hyperthyroidism is persistent, thyroidectomy is common.
- Growth hormone excess. Medical therapy is the preferred first-line treatment; options include (alone or in combination) octreotide and the growth hormone receptor antagonist pegvisomant.
- Hypercortisolism. Treatment varies by the presentation of neonatal Cushing syndrome.

Surveillance:

FD/MAS. Monitor for the following:

- Infants: clinical signs of hypercortisolism
- All children: growth acceleration and other clinical signs of precocious puberty and/or growth hormone excess
- Children:
  - Age <5 years: thyroid function abnormalities
  - With thyroid abnormalities on ultrasound examination but normal thyroid function: periodic monitoring of thyroid function
- Males: testicular lesions (physical examination and testicular ultrasound)
- Individuals on:
  - Pegvisomant: hepatotoxicity
  - Somatostatin analogs: signs and symptoms of gallbladder disease
- Females: breast cancer (earlier than is recommended for the general population)

FD

- Periodic radiographs to monitor existing FD and development of new lesions

- Periodic serum phosphorus (for development of hypophosphatemia) and 25-hydroxyvitamin D levels
- Craniofacial FD: yearly vision and hearing evaluations; periodic skull CT; routine serum IGF-1 levels through young adulthood
- Spine FD: close monitoring for progressive scoliosis

Agents/circumstances to avoid: Contact sports and other high-risk activities (when skeletal involvement is significant); prophylactic optic nerve decompression (in individuals with craniofacial FD); surgical removal of ovarian cysts; radiation therapy for treatment of FD; risk factors for malignancy (e.g., radiation exposure).

Genetic counseling. FD/MAS is not inherited. No parent of a child with FD/MAS has been demonstrated to have any significant, distinctive manifestations of the disorder. The risk to sibs is expected to be the same as in the general population. There are no verified instances of vertical transmission of FD/MAS.

Diagnosis

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is usually diagnosed on clinical grounds, although formal diagnostic criteria have not been published.

Suggestive Findings

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) **should be suspected** in individuals with any of the following skin, skeletal, or endocrine features.

Skin. Individuals may have characteristic café au lait skin macules.

- Borders are jagged and irregular, often referred to as resembling the "coast of Maine" (in contrast to the smooth-bordered "coast of California" lesions seen in neurofibromatosis type 1).
- Distribution shows an association with ("respecting") the midline of the body and following the developmental lines of Blaschko, which reflect patterns of embryonic cell migration (see Figure 1).

Skeletal. Fibrous dysplasia (FD), a condition in which normal bone and bone marrow are replaced by fibroosseous tissue, results in an increased risk of fractures, deformity, functional impairment, and pain.

- FD can be classified as monostotic (i.e., involvement of 1 bone) or polyostotic (i.e., involvement of >1 bone).
- FD can involve any part and combination of the craniofacial, axial, and/or appendicular skeleton (see Figure 2).
- The initial radiologic evaluation for FD should include a 99Tc-MDP bone scan.
    - Areas of skeletal involvement identified on scintigraphy should be further evaluated with radiographs and head computerized tomography (CT), depending on the location and extent of the disease.
    - See Figure 3 for the suggested evaluations used to diagnose FD.

Endocrine. Findings may include the following:

- Gonadotropin-independent precocious puberty
- Testicular lesions including Leydig and/or Sertoli cell hyperplasia with characteristic ultrasonographic features, with or without associated gonadotropin-independent precocious puberty (see Figure 4B)
- Thyroid lesions with characteristic ultrasonographic features, with or without non-autoimmune hyperthyroidism (see Figures 4C and 4D)
- Growth hormone excess

- Fibroblast growth factor 23 (FGF23)-mediated phosphate wasting with or without hypophosphatemia
- Neonatal hypercortisolism

Establishing the Diagnosis

The diagnosis of FD/MAS **is established** in individuals who have two or more typical clinical features of FD/MAS. In individuals whose only clinical finding is monostotic fibrous dysplasia, identification of a somatic activating *GNAS* pathogenic variant is required to confirm the diagnosis (see Table 1).

Molecular genetic testing approaches include **targeted analysis** of codons p.Arg201 and p.Gln227. Testing a **sample of the lesional tissue**, if possible, has the highest clinical sensitivity in PCR-sequencing-based diagnostic methods:

- ~80% in lesional tissue
- ~20%-30% in peripheral blood lymphocytes

Note: (1) Variant detection depends on the level of mosaicism in the tissue and the sensitivity of the technique. Detection frequency of a variant at p.Arg201 using standard PCR was highest in endocrine organs and lowest in affected skin specimens [Lumbroso et al 2004]. The ability to detect mosaicism affects the detection rate of the assay (see Table 1 and Table 8). (2) Targeted analysis may be performed by sequencing of *GNAS* exons 8 and 9. *GNAS* variants other than those previously reported to be associated with FD/MAS would likely be interpreted as variants of unknown significance. (3) $G_s\alpha$ is expressed in nearly all tissues from both maternal and paternal *GNAS* alleles. However, *GNAS* is a complex locus where alternative transcripts and additional phenotypes may result from *GNAS* imprinting (see Genetically Related Disorders and Molecular Genetics).

Table 1.

Molecular Genetic Testing Used in Fibrous Dysplasia/McCune-Albright Syndrome

Gene [1]	Test Method	Variants Detected	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method
GNAS	Targeted analysis of lesion biopsy of exons 8 and 9 [3, 4]	p.Arg201His, p.Arg201Cys [5, 6]	8%-90% [7] 75%-100% [8]
		p.Gln227Leu [6]	5% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Targeted analysis may be performed by sequence analysis. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Testing tissue from a lesion biopsy has a higher clinical yield than testing a blood sample. The detection rate for a blood sample is ~20%-30% [Lumbroso et al 2004, Kalfa et al 2006].
5. Somatic *GNAS* missense variants in individuals with FD/MAS are known to occur at only one of two amino acid residues: p.Arg201 (>95% of pathogenic variants) [Lumbroso et al 2004] or p.Gln227 (<5%) [Idowu et al 2007].
6. Rarely, other amino acid substitutions at p.Arg201 and at p.Gln227 have been detected (see Molecular Genetics).
7. Variant detection depends on the level of mosaicism in the tissue and the sensitivity of the technique. Variant detected at p.Arg201 using standard PCR was highest in endocrine organs and lowest in affected skin specimens [Lumbroso et al 2004].
8. When modified primers (peptide nucleic acid) [Bianco et al 2000] and next-generation sequencing [Narumi et al 2013] technologies are combined [Narumi et al 2013], a p.Arg201 variant can be detected in virtually all affected tissues and in leukocytes of up to 75% of

individuals.

Clinical Characteristics

Clinical Description

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) results from mosaic somatic activating pathogenic variants in *GNAS*, which encodes the cAMP pathway-associated G-protein, $G_s\alpha$. Affected tissues can include those derived from ectoderm, mesoderm, and endoderm, and commonly include skin, skeleton, and certain endocrine organs. However, because $G_s\alpha$ signaling is present in virtually every tissue, additional sites may be affected.

The phenotypic spectrum of FD/MAS ranges from asymptomatic incidental findings to neonatal lethality. There is a high degree of variability between individuals, both in the number of affected tissues and the degree to which they are affected. Disease manifestations depend on the time during embryogenesis that the somatic pathogenic variant occurred, the tissue involved, and the role of $G_s\alpha$ in the affected tissue. Pathogenic variants occurring early in development lead to widespread disease, while those occurring later in development lead to limited disease.

Pigmented macules. Café au lait skin macules are common and are usually the first manifestation of the disease, apparent at or shortly after birth. There is no correlation between the size of the skin lesions and the extent of disease, nor between the distribution of skin lesions and the location of fibrous dysplasia.

Fibrous dysplasia of bone. As with skin, fibrous dysplasia demonstrates a mosaic pattern: it can involve any part and combination of the craniofacial, axial, and/or appendicular skeleton. The bones most commonly involved are the skull base and proximal femurs [Kelly et al 2008]. While there is generally a central-to-peripheral gradient, any combination of involved bones is possible.

Fibrous dysplasia can manifest along a wide spectrum: from an isolated, asymptomatic monostotic lesion discovered incidentally to severe, disabling polyostotic disease involving practically the entire skeleton and leading to loss of vision, hearing, and/or mobility.

Individual bone lesions typically manifest during the first few years of life and expand during childhood. The vast majority of clinically significant bone lesions are detectable by age ten years, with few new and almost no clinically significant bone lesions appearing after age 15 years [Hart et al 2007]. In adulthood, fibrous dysplasia lesions typically become less active, likely related to apoptosis of pathogenic variant-bearing cells [Kuznetsov et al 2008].

The clinical presentation and course of fibrous dysplasia (FD) depends on the location and extent of the affected skeleton:

- **Appendicular skeleton**
  - Children with fibrous dysplasia in the appendicular skeleton typically present with a limp, pain, and/or pathologic fractures.
  - Recurrent fractures and progressive deformity may lead to difficulties with ambulation and loss of mobility.
- **Craniofacial region**
  - FD may present as a painless "lump" or facial asymmetry.
  - Expansion of craniofacial lesions may lead to progressive facial deformity (see Figure 2B), and in rare cases (usually in association with growth hormone excess) loss of vision and/or hearing due to compromise of the optic nerves and/or external auditory canals [Cutler et al 2006, Boyce et al 2018].
- **Vertebrae**

- FD involving the vertebrae is common, and may lead to scoliosis, which in rare instances may be severe, progressive, and even lethal [Leet et al 2004b].
- Untreated, progressive scoliosis is one of the few features of FD that can lead to early morbidity.

Bone pain is a common complication of fibrous dysplasia. Although bone pain may present at any age, it is common for bone pain to be absent in childhood, occur in adolescence, and progress into adulthood [Kelly et al 2008].

Aneurysmal bone cysts are rapidly expanding fluid-filled lesions that form within preexisting areas of FD. Such lesions are best detected by MRI. Affected individuals experience acute onset of severe pain, rapidly expanding localized deformity, and rarely – when cysts compress the optic nerve – rapid loss of vision. Aneurysmal bone cysts thus carry a high risk of morbidity (see Management).

Malignant transformation of FD lesions is a rare complication. Many instances of malignant transformation were reported in association with previous radiation treatment [Ruggieri et al 1994]. Growth hormone excess may be a predisposing factor [Salenave et al 2014].

Radiographic appearance of fibrous dysplasia varies according to location:

- Radiographs of the appendicular skeleton show expansive lesions with endosteal scalloping, thinning of the cortex, and a "ground glass" appearance (Figure 2A).
- Fibrous dysplasia in the craniofacial skeleton is typically expansile and appears sclerotic on x-ray, but demonstrates a typical "ground glass" appearance on computed tomography (Figure 2C).
- With aging, fibrous dysplasia lesions in the appendicular skeleton tend to become sclerotic on radiographs and craniofacial fibrous dysplasia lesions develop a "cystic" appearance (Figure 2D).

Endocrinopathies can include any of the following:

- **Precocious puberty.** Precocious puberty is common in girls with FD/MAS (~85%), and is often the presenting feature. Recurrent ovarian cysts (Figure 4A) lead to intermittent estrogen production resulting in breast development, growth acceleration, and vaginal bleeding; during the intervals between cyst formation, breast tissue typically regresses and estrogen levels fall to prepubertal levels. Ovarian cysts typically continue into adulthood, leading to irregular menses. This has the potential to interrupt ovulatory cycles, which may increase the time to conception in adult women. Ovarian torsion has been seen rarely in girls and women with large and persistent cysts [Clark et al 2000].

  Precocious puberty is less common in boys with FD/MAS (~10-15%), and is due to autonomous testosterone production [Boyce et al 2012a], which leads to progressive pubertal development including growth acceleration, pubic and axillary hair, acne, and aggressive and/or inappropriately sexual behavior.

  In both girls and boys, prolonged autonomous sex steroid production typically leads to activation of the hypothalamic-pituitary axis and the development of central precocious puberty.

- **Fertility.** The effects of autonomous sex steroid production on pituitary-gonadal function and fertility in adults are not well characterized. Women with FD/MAS may have recurrent cysts leading to irregular menses in adulthood [Lala et al 2007]. While many women in the NIH cohort have achieved successful pregnancies, it is possible that interruption of ovulatory cycles could decrease fertility and increase the time to conception [Authors, personal observation].
- **Testicular abnormalities.** Testicular abnormalities are seen in the majority of boys and men with MAS (~85%), and typically manifest as unilateral or bilateral macroorchidism [Boyce et al 2012a]. Ultrasound examination demonstrates discrete hyper- and hypoechoic lesions and microlithiasis, corresponding to areas of Leydig and/or Sertoli cell hyperplasia (see Figure 4B).

The potential for malignant transformation of testicular lesions is unknown, but appears to be low [Boyce et al 2012a].

- **Thyroid disease.** Thyroid involvement in FD/MAS is common. Approximately half of individuals with FD/MAS have ultrasound findings consistent with thyroid involvement, including mixed cystic and solid lesions interspersed with areas of normal-appearing tissue (Figure 4C and 4D) [Celi et al 2008, Tessaris et al 2012a].

  Hyperthyroidism is present in 10% to 30% of individuals with FD/MAS, and results from both increased hormone production and increased conversion of thyroxine (T4) to triiodothyronine (T3) [Celi et al 2008].

  Hyperthyroidism is typically mild to moderate, but may be severe, and if undetected can lead to thyroid storm during anesthetic induction for surgery [Lawless et al 1992].

  Uncontrolled hyperthyroidism may lead to bone age advancement, elevated bone turnover, and fractures.

  Malignant transformation of affected thyroid tissue has rarely been reported [Collins et al 2003].

- **FGF23-mediated phosphate wasting.** In the majority of individuals with FD, increased production of the phosphaturic hormone FGF23 in FD tissue results in a renal tubulopathy with some degree of phosphate wasting [Collins et al 2001]. However, frank hypophosphatemia in persons with FD is infrequent, in part due to alterations in FGF23 processing that takes place in FD tissue and results in increased cleavage of FGF23 to its inactive fragments [Bhattacharyya et al 2012]. The degree of FGF23 overproduction in FD correlates with disease severity and skeletal burden; thus, frank hypophosphatemia is only seen in individuals with a substantial FD burden [Riminucci et al 2003].

  In contrast to most other features of FD/MAS, hypophosphatemia may wax and wane over the course of a person's lifetime and become more severe during periods of rapid skeletal growth. Hypophosphatemia may resolve as persons with FD become older, likely reflecting the intrinsic changes in FD that occur with age [Kuznetsov et al 2008].

  Affected individuals with frank hypophosphatemia may develop rickets/osteomalacia, increased fractures, and bone pain [Leet et al 2004a].

- **Growth hormone excess.** Approximately 15%-20% of individuals with FD/MAS harbor *GNAS* pathogenic variants in the anterior pituitary that can lead to autonomous growth hormone production; approximately 80% of affected individuals with autonomous growth hormone production will also have hyperprolactinemia [Salenave et al 2014].

  Affected individuals typically present with linear growth acceleration, and may develop features of acromegaly. Clinically, growth hormone excess must be distinguished from precocious puberty and hyperthyroidism, which also present with growth acceleration.

  Untreated growth hormone excess is associated with expansion of craniofacial fibrous dysplasia, leading to macrocephaly and increased risk of vision loss [Boyce et al 2013] (see Figure 2B).

- **Hypercortisolism.** Infants with FD/MAS may rarely present with Cushing syndrome due to excess cortisol production from the fetal adrenal gland [Brown et al 2010, Carney et al 2011]. Clinical symptoms typically develop in the neonatal period, and may be severe, leading to critical illness and death. Spontaneous regression has been reported in approximately half of survivors, presumably related to fetal adrenal involution.

Liver

- Hepatitis and neonatal cholestasis may be pronounced in infants, and generally wane with age to a mild persistent form [Silva et al 2000, Ikawa et al 2016].

- Hepatic adenomas with an identifiable *GNAS* activating pathogenic variant have also been reported [Gaujoux et al 2014].
- Liver failure in adults with FD/MAS has not been described.

Gastrointestinal

- Gastroesophageal reflux manifests in childhood and may be severe.
- Upper gastrointestinal polyps have been recently described as a common finding in individuals with FD/MAS [Wood et al 2017].

Pancreas. Approximately 15% of individuals with FD/MAS have pancreatic complications:

- Pancreatitis
- Intraductal papillary mucinous neoplasms (IPMN), which may present with variable grades of dysplasia [Gaujoux et al 2014, Wood et al 2017]

  An individual with pancreatic carcinoma derived from an intestinal subtype of IPMN has been described [Parvanescu et al 2014].

Myxomas. Intramuscular myxomas are benign, usually asymptomatic, and often found incidentally.

Hematology

- Bone and bone marrow are, to varying degrees, replaced by fibroosseous tissue typically devoid of hematopoietic marrow.
- There have been reports of bone marrow failure with pancytopenia and extramedullary hematopoiesis requiring splenectomy in individuals with FD/MAS [Mahdi et al 2017, Robinson et al 2018].

Breast cancer. The risk of breast cancer in women with FD/MAS may be increased and it can occur at a **younger** age compared to the general population. However, pathogenic activating *GNAS* variants were identified in only half of the breast tumors from women with FD/MAS studied [Majoor et al 2018a].

Health-related quality of life. Several series have shown impaired physical functioning in individuals with FD/MAS, strongly correlated with disease severity. Nevertheless, individuals with this condition show preserved social and emotional functioning. This finding is important for prognosis and parental reassurance [Kelly et al 2005, Majoor et al 2018b].

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations.

To date, only activating *GNAS* somatic pathogenic variants at residues p.Arg201 and p.Gln227 have been identified in individuals with FD/MAS.

Disease severity is likely correlated with the degree of mosaicism and the tissues that are affected.

Nomenclature

The association of intramuscular myxomas with FD/MAS has been termed Mazabraud syndrome [Cox et al 2017].

Prevalence

FD/MAS is rare. While reliable data of prevalence are not available, estimates range between 1:100,000 and 1:1,000,000.

In contrast, fibrous dysplasia (particularly the monostotic form) is not rare, and has been estimated to account for as much as 7% of all benign bone tumors.

FD/MAS affects both sexes and shows no predilection for any particular populations.

Genetically Related (Allelic) Disorders

In contrast to somatic activating (gain-of-function) variants at specific *GNAS* residues resulting in FD/MAS, germline inactivating (loss-of-function) *GNAS* variants are associated with multiple phenotypes. Furthermore, since *GNAS* is an imprinted gene, the phenotype associated with germline inactivating pathogenic variants depends on the parent of origin (maternal vs paternal) for the mutated allele and the degree of imprinting that occurs in a given tissue. Table 2 lists phenotypes with germline inactivating *GNAS* pathogenic variants (see Disorders of *GNAS* Inactivation).

Table 2.

Allelic Disorders Caused by Germline Inactivating (Loss-of-Function) *GNAS* Variants

Phenotype	***GNAS* Variant**	**OMIM / Reference**
Pseudopseudohypoparathyroidism	Inactivating heterozygous pathogenic variant of the paternal *GNAS* allele	612463
Pseudohypoparathyroidism Ia	Inactivating heterozygous pathogenic variant of the maternal *GNAS* allele in exons 1-12	103580
Pseudohypoparathyroidism Ib	Imprinting defect: heterozygous deletion of regulatory elements in the maternal *GNAS* complex locus [1]	603233
Pseudohypoparathyroidism Ic	Inactivating heterozygous pathogenic variant in exon 13 of the maternal *GNAS* allele	612462
Progressive osseous heteroplasia	Inactivating heterozygous *GNAS* pathogenic variant of the paternal allele	166350

1. Pseudohypoparathyroidism Ib can also be caused by heterozygous deletion of *STX16*.

Sporadic tumors (including pituitary, pancreatic, breast, and colorectal tumors) occurring as single tumors in the absence of any other findings of FD/MAS frequently harbor somatic activating variants in *GNAS* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Neurofibromatosis type 1 (NF1) and FD/MAS have several overlapping features, including café au lait macules and skeletal abnormalities. Skin findings in NF1 include six or more café au lait macules, which are generally smooth bordered ("coast of California," as opposed to the irregularly bordered "coast of Maine" lesions seen in FD/MAS). Skeletal features of NF1 include kyphoscoliosis, sphenoid dysplasia, cortical thinning of long bones, and bowing and dysplasia, particularly of the tibia, which may result in pseudarthroses. Distinct features of NF1 include tumors of the nervous system such as neurofibromas and optic gliomas, pigmented iris hamartomas, and axillary freckling. NF1 is caused by heterozygous pathogenic variants in *NF1* and is inherited in an autosomal dominant manner.

Cutaneous-skeletal hypophosphatemia syndrome is a mosaic disorder resulting from somatic activating pathogenic variants in *HRAS* and *NRAS* [Lim et al 2014]. Affected individuals develop cutaneous lesions (epidermal and large congenital melanocytic nevi) following a mosaic distribution, a mosaic skeletal dysplasia, overproduction of FGF23

resulting in rickets/osteomalacia, and variable other associated anomalies of the eye, brain, and vasculature [Ovejero et al 2016].

Fibroosseous skeletal lesions may have radiologic and/or histologic features similar to fibrous dysplasia. These lesions are typically solitary, are not associated with extraskeletal features, and do not harbor pathogenic variants in *GNAS*.

- **Giant cell tumors of bone** are acquired lesions with histopathologic features similar to fibrous dysplasia, including proliferation of bone marrow stromal cells and the presence of multiple multinucleated giant cells. Giant cell tumors are typically benign, but may result in localized bone destruction and (rarely) metastases.
- **Ossifying fibromas** are benign lesions typically affecting the mandible and maxillae and presenting with local expansion of a firm, painless mass. Ossifying fibromas are generally more aggressive than craniofacial fibrous dysplasia lesions, and are treated with surgical excision.
- **Osteofibrous dysplasia** lesions typically occur in children younger than age ten years, and most commonly affect the anterior tibia. Affected children present with painless localized swelling and, in rare cases, with fracture or progressive deformity. Radiographs show a well-circumscribed radiolucent lesion with a characteristic sclerotic rim along the intra-cortical surface.
- **Cherubism** is characterized by progressive fibroosseous lesions of the mandible and maxilla primarily. It typically presents in early childhood with bilateral symmetric enlargement of the lower face leading to a characteristic "cherubic" appearance in which the eyes appear to gaze upward because of maxillary involvement. Facial deformity progresses during childhood and early puberty, after which it sometimes spontaneously regresses. In most cases, cherubism arises from heterozygous pathogenic variants in *SH3BP2*. Inheritance is autosomal dominant.

Management

Evaluations Following Initial Diagnosis

After the initial diagnosis, all individuals with fibrous dysplasia/McCune-Albright syndrome (FD/MAS) should be evaluated to determine the extent of disease. The presence of any features of FD/MAS should prompt more detailed clinical evaluation for additional manifestations. The authors recommend the studies detailed in Table 3 if they have not already been completed.

Table 3.

Recommended Evaluations Following Initial Diagnosis in Individuals with Fibrous Dysplasia/McCune Albright Syndrome

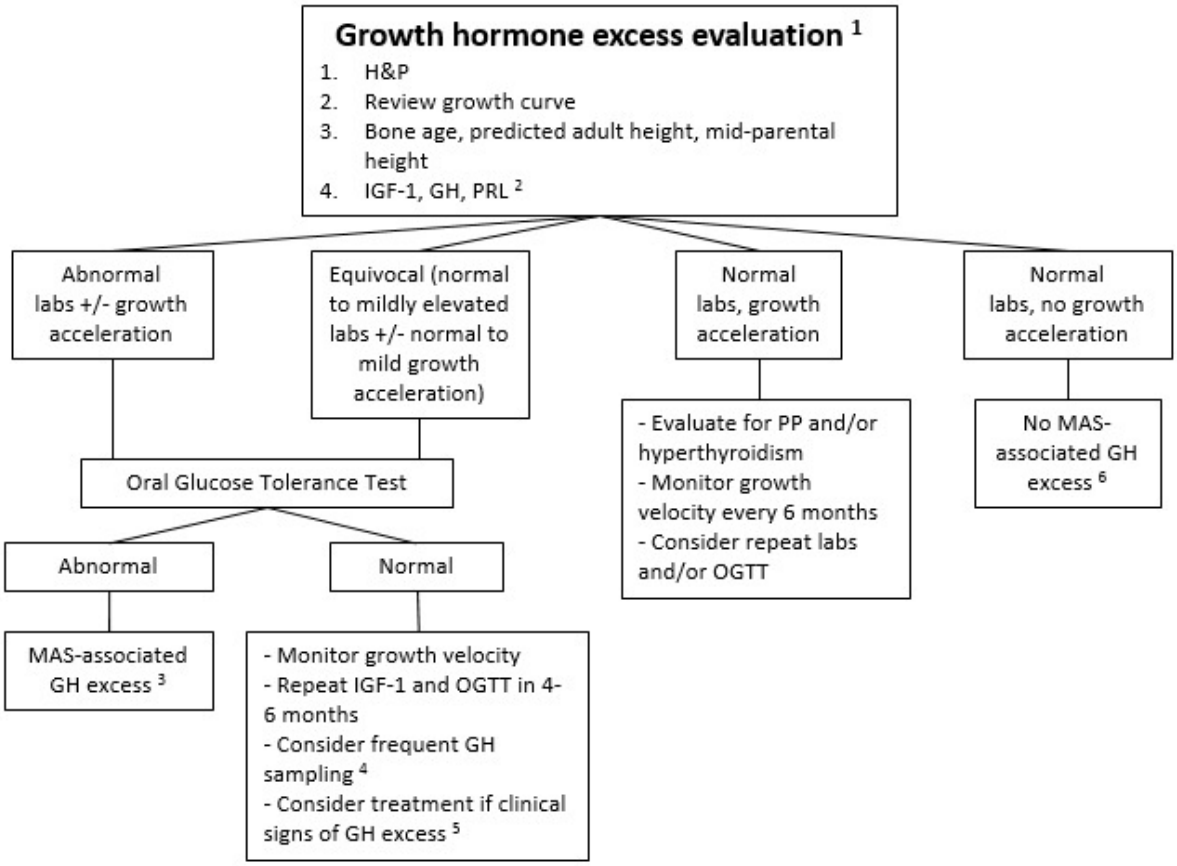
Organ System	Evaluation	Comment
Constitutional (growth) (see Figure 5)	Review growth [1]	For signs of poor growth, which could suggest hyperthyroidism
		For signs of rapid growth, which could indicate growth hormone excess &/or precocious puberty
	IGF-1, random growth hormone, prolactin levels	
	Bone age	Advanced bone age may suggest the presence of precocious puberty.
Musculoskeletal [2]	Clinical evaluation for scoliosis	Further radiographic confirmation may be necessary.

Organ System		Evaluation	Comment
		Total body bone scintigraphy [3]	The majority of clinically significant skeletal lesions are apparent on bone scan by age 5 yrs.
		Radiographs (axial & appendicular) &/or CT (craniofacial) of areas of FD	To more clearly evaluate extent & anatomy of lesions
Endocrine	**Puberty (females)**	Evaluation for signs & symptoms of precocious puberty (see Figure 6)	
	Puberty (males)	Evaluation for signs & symptoms of precocious puberty (see Figure 7)	
		Serum LH, FSH, & testosterone levels	
		Testicular ultrasound	To evaluate for discrete hyper- & hypoechoic lesions & microlithiasis
	Thyroid (see Figure 8)	Thyroid ultrasound	For signs of mixed cystic & solid lesions (see Figures 4C, 4D)
		T3, free T4, & TSH levels	The primary biochemical abnormality is elevated T3 production, which may occur in the setting of normal T4 and free T4.
	Adrenal	Assessment for signs & symptoms of Cushing syndrome (see Figure 9)	e.g., hypertension, facial plethora, abdominal obesity, developmental delay, failure to thrive
			If no signs or symptoms of hypercortisolism after age 3 yrs, no further evaluation needed
Renal		Serum phosphorus level	Verification by calculating tubular reabsorption of phosphorus
Eyes		Evaluation by neuroophthalmologist	In those w/craniofacial FD
ENT		Evaluation by otolaryngologist	In those w/craniofacial FD
		Evaluation by audiologist	
Gastrointestinal		Serum amylase, lipase, AST, & ALT	See Figure 10
		Screening for symptoms of GERD	
Other		Consultation w/clinical geneticist &/or genetic counselor	

CT = computed tomography

GERD = gastroesophageal reflux disease

1. Including determining predicted adult height and mid-parental height
2. See Figure 3 for recommended evaluations of the skeletal system after diagnosis.
3. Collins et al [2005]

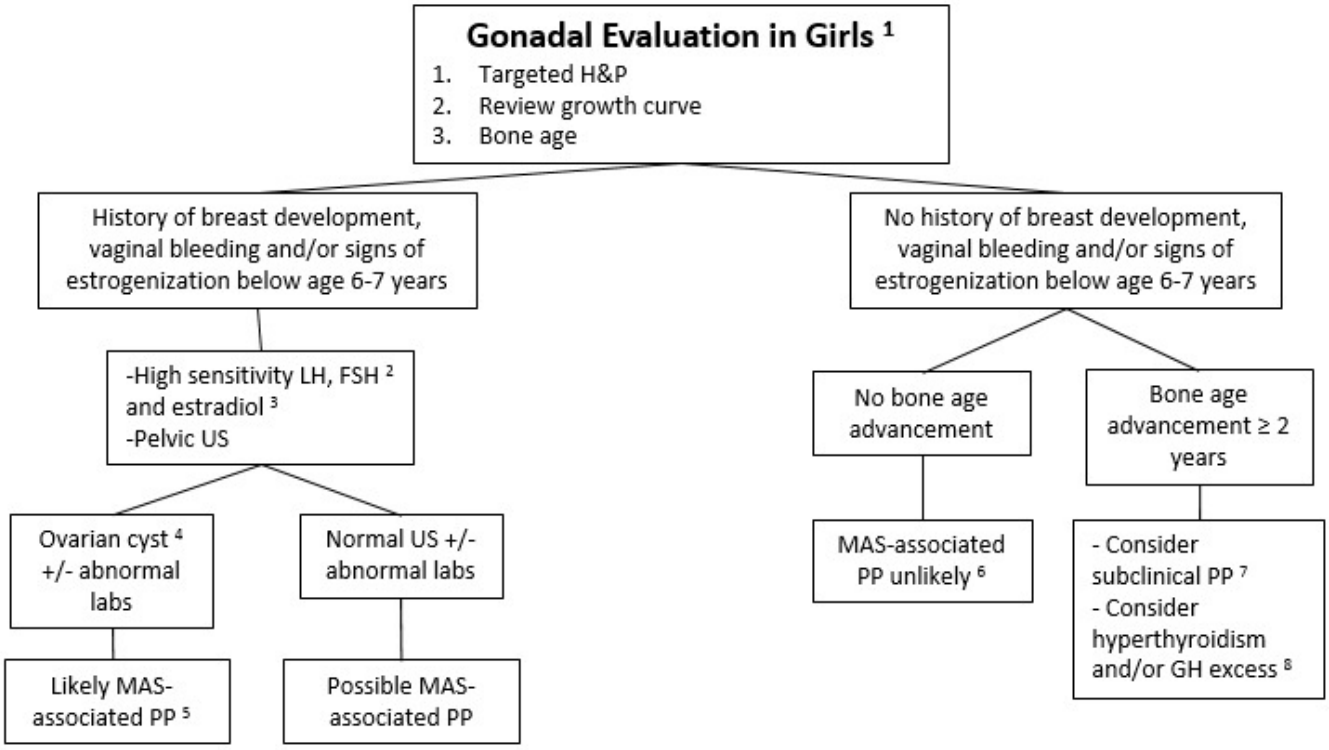


H&P = history and physical examination
IGF-1 = insulin-like growth factor-1
GH = growth hormone
PRL = prolactin
OGTT = oral glucose tolerance test
MAS = McCune-Albright syndrome
PP = precocious puberty

1. To be performed at initial presentation in all individuals with MAS, regardless of clinical symptoms.
2. The majority of individuals with MAS-associated GH excess will have prolactin co-secretion [Salenave et al 2014].
3. Practitioners may consider pituitary MRI in individuals suspected of having MAS-associated GH excess, however findings may be non-specific and rarely change management [Salenave et al 2014].
4. There are a variety of techniques for frequent GH sampling. Collecting GH samples every 20 minutes for 12 hours from 8 PM to 8 AM, with a lack of nadir below 1.0 ng/mL, is considered consistent with GH excess.
5. In those with craniofacial FD it is prudent to have a low threshold for initiating treatment, as uncontrolled GH excess is associated with increased craniofacial morbidity [Boyce et al 2012b].
6. MAS-associated GH excess may rarely present as late as young adulthood, therefore ongoing monitoring with periodic IGF-1 levels is prudent in those with significant craniofacial FD.

Figure 5.

Recommended evaluations for growth hormone excess in individuals with fibrous dysplasia/McCune-Albright syndrome

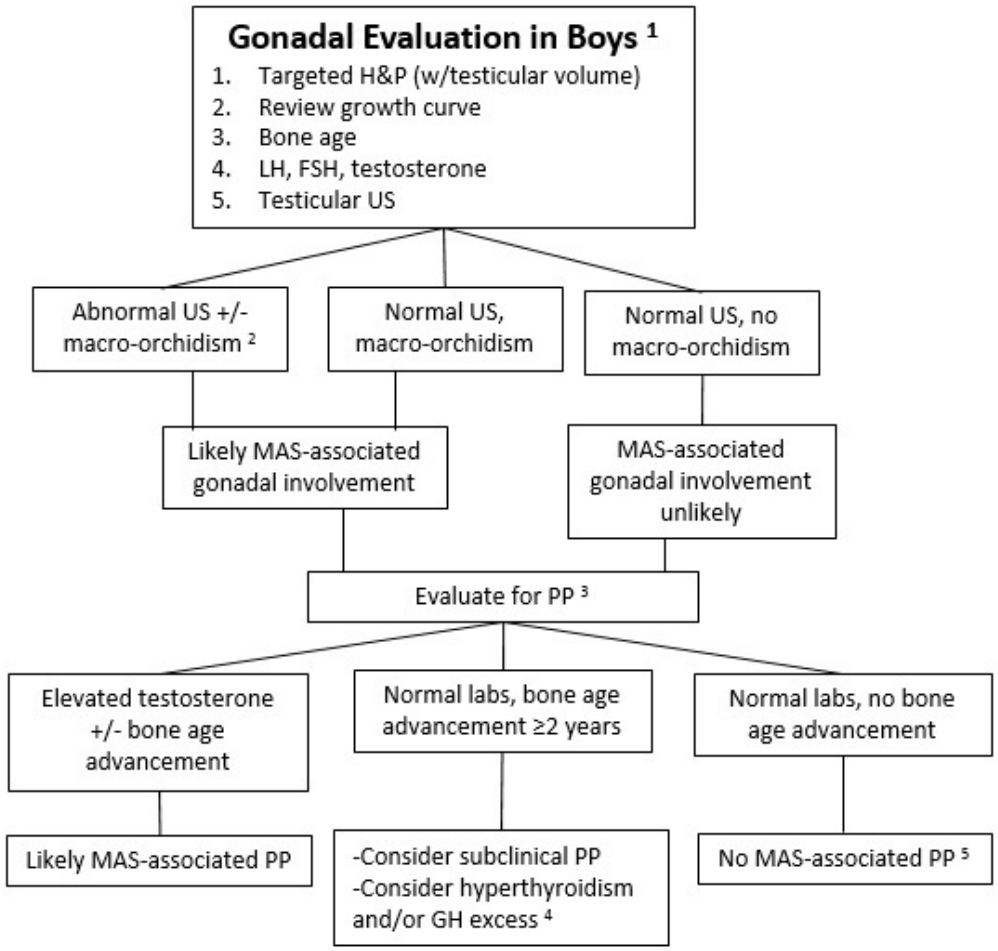


H&P = history and physical examination
LH = luteinizing hormone
FSH = follicle-stimulating hormone
US = ultrasound
MAS = McCune-Albright syndrome
PP = precocious puberty
GH = growth hormone

1. To be performed at initial presentation in all girls with MAS, regardless of clinical symptoms.
2. Gonadotropins should be suppressed in those with precocious puberty, unless autonomous estrogen production has induced central precocious puberty [Collins et al 2012].
3. Estrogen production in MAS-associated precocious puberty is intermittent, and undetectable levels do not eliminate the possibility of disease.
4. Ovarian cysts are suggestive of MAS-associated precocious puberty, however absence of cysts does not eliminate the possibility of disease [Authors, personal observation].
5. In isolated peripheral precocious puberty, the differential diagnosis includes estrogen-producing tumors. Evaluation for additional features of MAS may establish the diagnosis.
6. Unlike other features of MAS, autonomous ovarian activity may present at any time during infancy or childhood. Girls should continue to be monitored clinically for signs of peripheral precocious puberty, however routine labwork and imaging is not recommended.
7. Affected females may rarely present with intermittent ovarian activity with only subtle signs of estrogenization (mild intermittent breast development without vaginal bleeding).
8. Hyperthyroidism and growth hormone excess may present with an advanced bone age compared to chronologic age.

Figure 6.

Recommended evaluations for gonadal abnormalities in females with fibrous dysplasia/McCune-Albright syndrome

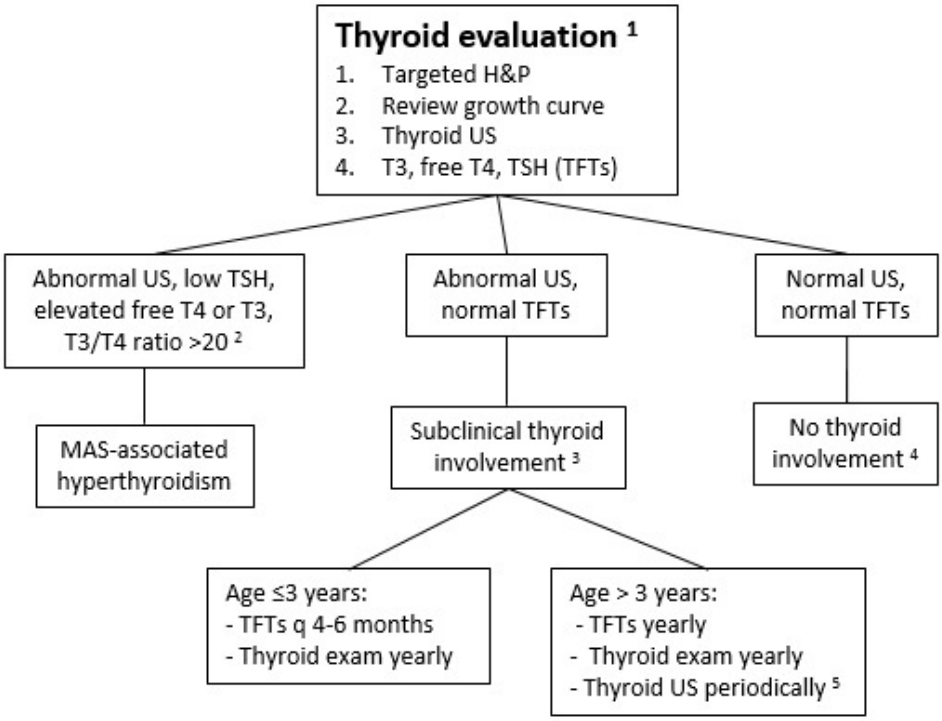


H&P = history and physical examination
LH = luteinizing hormone
FSH = follicle stimulating hormone
US = ultrasound
MAS = McCune-Albright syndrome
PP = precocious puberty
GH = growth hormone

1. Performed at initial presentation in all boys with MAS, regardless of clinical symptoms.
2. Typical MAS-associated macro-orchidism presents with uniform, unilateral or bilateral testicular enlargement without discrete palpable masses.
3. Precocious puberty is less likely to occur in males who do not have evidence of testicular involvement on ultrasound. The presence of macroorchidism is typically associated with ultrasound abnormalities.
4. Hyperthyroidism and growth hormone excess may present with an advanced bone age compared to chronologic age.
5. Autonomous testicular activity may present at any time during childhood. Boys should continue to be monitored clinically for signs of peripheral precocious puberty, however routine labwork and imaging is not recommended [Boyce et al 2012a].

Figure 7.

Recommended evaluations for gonadal abnormalities in males with fibrous dysplasia/McCune-Albright syndrome

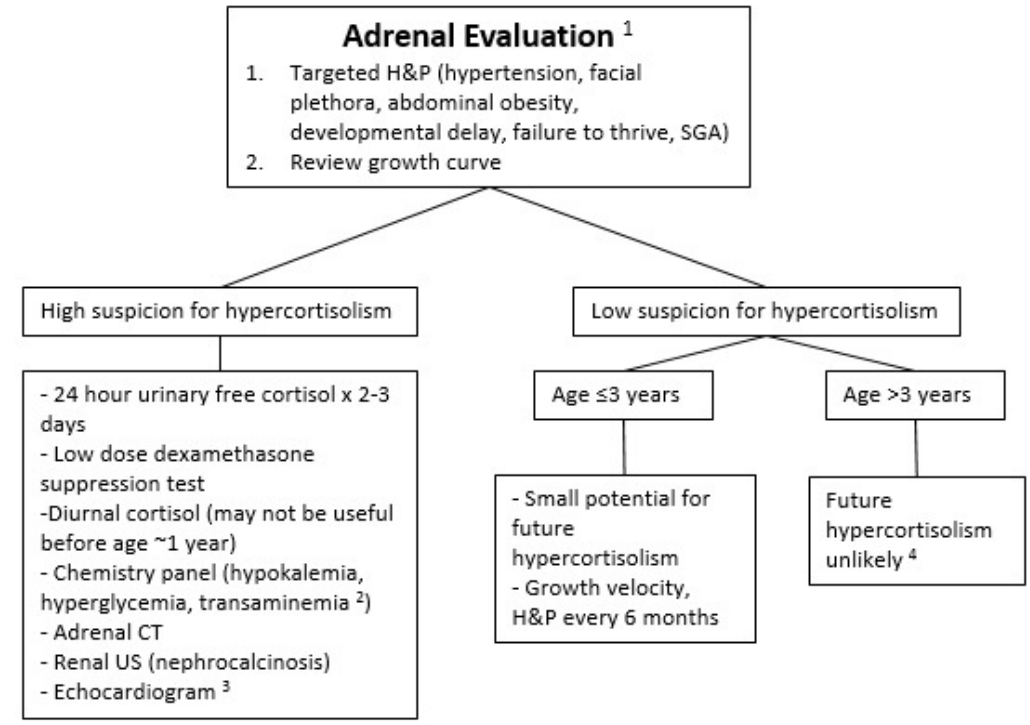


H&P = history and physical examination
US = ultrasound
TSH = thyroid stimulating hormone
T3 = triiodothyronine
T4 = thyroxine
TFTs = thyroid function tests
MAS = McCune-Albright syndrome

1. To be performed at initial presentation in all individuals with MAS, regardless of clinical symptoms.
2. An elevated T3/T4 ratio is suggestive of autonomous T3 production in individuals with MAS [Celi et al 2008].
3. A small percentage of affected individuals with radiologic disease and normal TFTs will develop hyperthyroidism at some point during childhood.
4. The absence of biochemical or radiologic thyroid abnormalities after age 5 years likely eliminates the possibility of MAS-associated thyroid disease, and no further routine monitoring is required.
5. MAS-associated thyroid disease is correlated with a slightly increased risk of thyroid cancer. See Surveillance. Those with radiologic disease should be monitored with yearly physical examination and thyroid US every 2-5 years [Collins et al 2003].

Figure 8.

Recommended evaluations for thyroid abnormalities in individuals with fibrous dysplasia/McCune-Albright syndrome

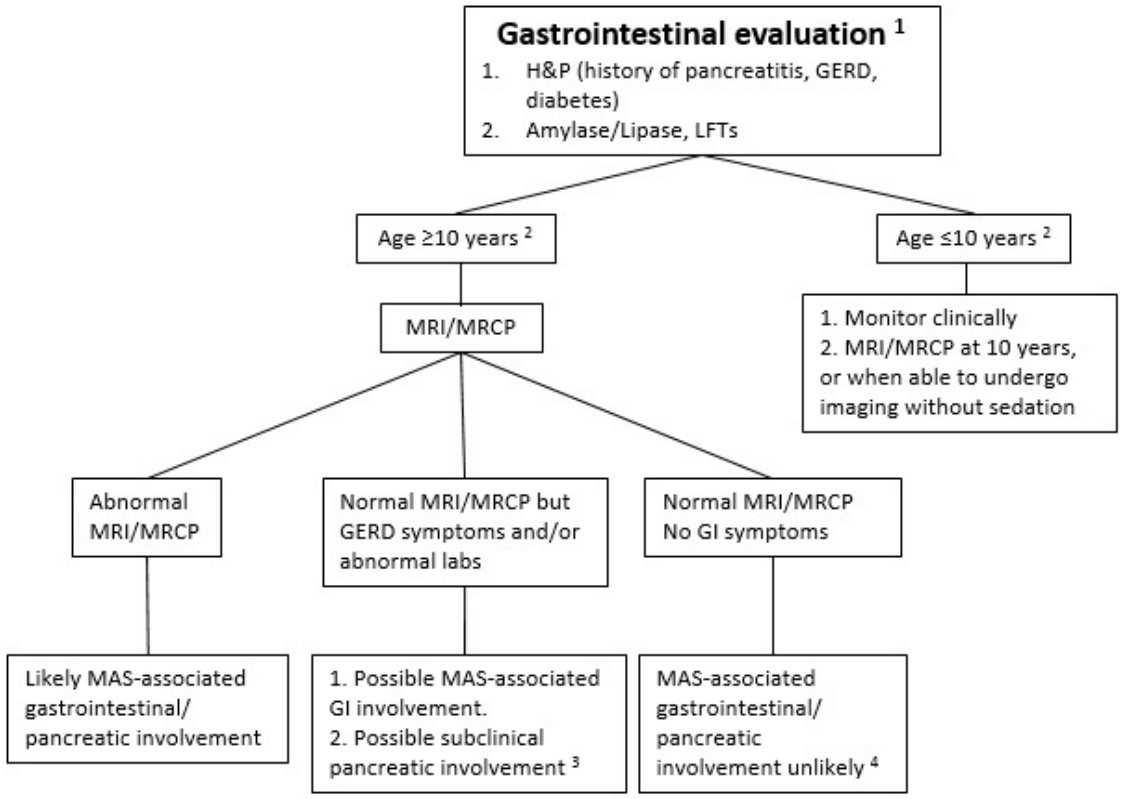


H&P = history and physical examination
SGA = small for gestational age
CT = computerized tomography
US = ultrasound

1. To be performed at initial presentation in all individuals with MAS, regardless of clinical symptoms.
2. Liver disease is highly correlated with MAS-associated hypercortisolism.
3. Prognosis of hypercortisolism is negatively correlated with the presence of comorbid heart disease [Brown et al 2010]. Since hypercortisolism may lead to heart disease, the presence of hypercortisolism makes the prognosis for heart disease worse.
4. Hypercortisolism in MAS results from autonomous activity of the adrenal fetal zone, which involutes rapidly after birth and is typically gone by age 1 year [Carney et al 2011]. MAS-associated hypercortisolism is unlikely after age 1 year and the risk is effectively gone after age 3 years [Brown et al 2010].

Figure 9.

Recommended evaluations for adrenal gland dysfunction in individuals with fibrous dysplasia/McCune-Albright syndrome



H&P = history and physical examination
MRI = magnetic resonance imaging
MRCP = magnetic resonance cholangiopancreatography
GERD = gastroesophageal reflux disease
GI = gastrointestinal
MAS = McCune-Albright syndrome

1. Performed at initial presentation, regardless of clinical symptoms.
2. Age is not based upon clinical evidence, but on age at which affected individuals may undergo MRI/MRCP without requiring sedation, and should be individualized based on clinical judgement.
3. Age of onset of pancreatic cyst development is not established; therefore clinical monitoring for gastrointestinal symptoms in these affected individuals is indicated.
4. Affected individuals should continue to be monitored clinically for new signs of gastrointestinal/pancreatic involvement including pancreatitis and diabetes [Gaujoux et al 2014, Parvanescu et al 2014, Wood et al 2017].

Figure 10.

Recommended evaluations for gastrointestinal issues in individuals with fibrous dysplasia/McCune-Albright syndrome

Treatment of Manifestations

Management is most effectively accomplished through the input of a multidisciplinary team of specialists including an endocrinologist, orthopedic surgeon, physiatrist, ophthalmologist, audiologist, endocrine surgeon, craniofacial surgeon, and clinical geneticist. No consensus management guidelines have been published.

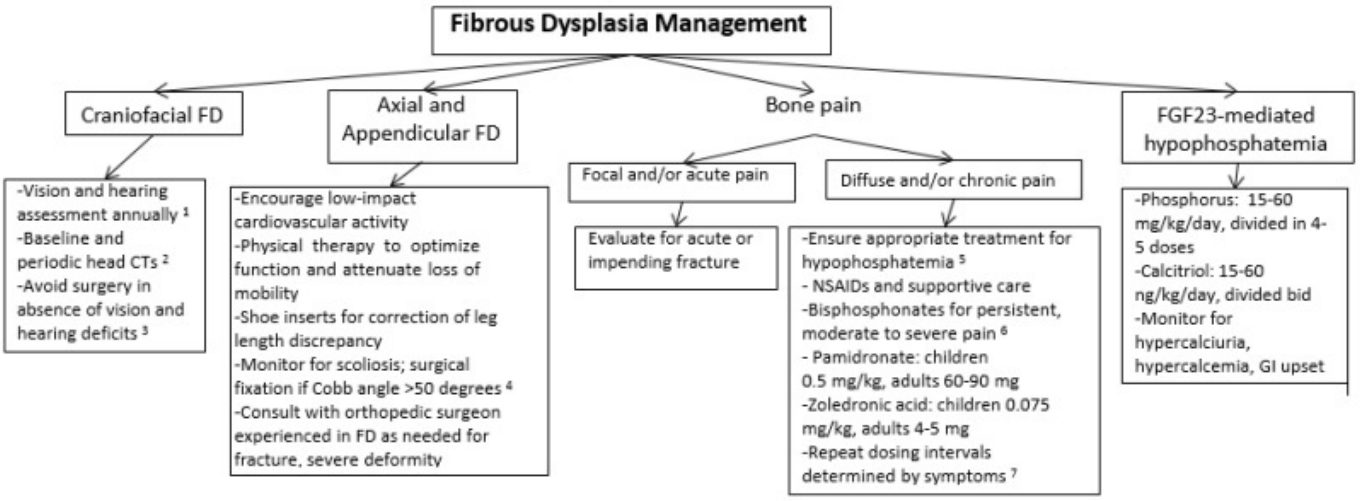
Table 4.

Treatment of Fibrous Dysplasia in Individuals with Fibrous Dysplasia/McCune Albright Syndrome

Manifestation	Treatment	Considerations/Other

Manifestation	Treatment	Considerations/Other
Fibrous dysplasia (see Figure 11)	No available medical therapies alter disease course; management is focused on optimizing function & minimizing morbidity.	
Fractures / bone deformity	Orthopedic surgery	A surgeon experienced in FD should be consulted, as approaches previously considered "standard," (e.g., curettage, grafting, external fixation) are frequently ineffective. [1]
Scoliosis	Surgical fusion in those w/rapidly progressive scoliosis [2]	Rarely, rapidly progressive scoliosis can lead to fatal respiratory compromise.
Aneurysmal bone cysts	Urgent evaluation by a surgeon [3]	Particularly for lesions affecting the face or eyes, which can lead to optic nerve compression [4]
Limited function & mobility	Physical therapy	Therapies to address hip girdle weakness, range of motion, & leg length discrepancies in those w/lower-extremity FD [5]
Bone pain	Intravenous bisphosphonates (e.g., zoledronic acid, pamidronate) [6, 7]	Dosing should be based on symptoms, not on a fixed interval or bone turnover markers.
Acute or rapidly expanding FD lesions	Evaluation for malignancy [8] & aneurysmal bone cyst	

1. Stanton et al [2012], Leet et al [2016]
2. Leet et al [2004b], Mancini et al [2009]
3. Lee et al [2012], Manjila et al [2013]
4. Prophylactic optic nerve decompression to reduce the risk of vision loss can in fact increase the risk of vision loss and is thus contraindicated [Lee et al 2002, Cutler et al 2006, Amit et al 2011].
5. Paul et al [2014]
6. The oral bisphosphonate alendronate has been shown to be ineffective for treatment of bone pain [Boyce et al 2014].
7. Denosumab (a human monoclonal antibody to RANKL) may reduce pain, bone turnover markers, and tumor growth rate. However, Denosumab has been associated with clinically significant disturbances of mineral metabolism both while on treatment and after discontinuation [Boyce et al 2012b, Benhamou et al 2014, Ganda & Seibel 2014]; use should be limited to experienced centers only.
8. Atypical radiographic features (e.g., compromise of the bony cortex with an associated soft tissue mass) should also prompt an evaluation for malignancy.



CT = computerized tomography
NSAIDs = nonsteroidal anti-inflammatory drugs
IV = intravenous
kg = kilograms
mg = milligrams
ng = nanograms
bid = twice daily
GI = gastrointestinal

1. Affected individuals should be evaluated yearly by a neuro-ophthalmologist; less frequently once stability is demonstrated. Those with evidence of optic neuropathy should be referred to an experienced craniofacial surgical team.
2. Repeat head CT approximately every 5 years, potentially sooner in younger individuals, those with severe disease, or if vision or hearing deficits develop [Boyce et al 2017].
3. Optic nerve encasement is common and usually asymptomatic. Prophylactic optic nerve decompression in the absence of optic neuropathy is contraindicated [Lee et al 2002, Amit et al 2011].
4. Scoliosis may be progressive and potentially fatal in severe cases. All affected individuals with scoliosis should be followed regularly by an orthopedic surgeon [Leet et al 2004b].
5. Inadequately treated hypophosphatemia may significantly worsen bone pain, and must be addressed before considering bisphosphonates [Leet et al 2004a, Paul et al 2014].
6. Bisphosphonates have not been shown to affect disease progression, and use should be limited to treatment of FD-related bone pain [Hart et al 2007, Boyce et al 2014].
7. Doses should be repeated as needed when pain returns rather than on a set dosing schedule. In absence of significant benefit on pain, bisphosphonate treatment should be discontinued.

Figure 11.

Recommended management for fibrous dysplasia in individuals with fibrous dysplasia/McCune-Albright syndrome

Table 5.

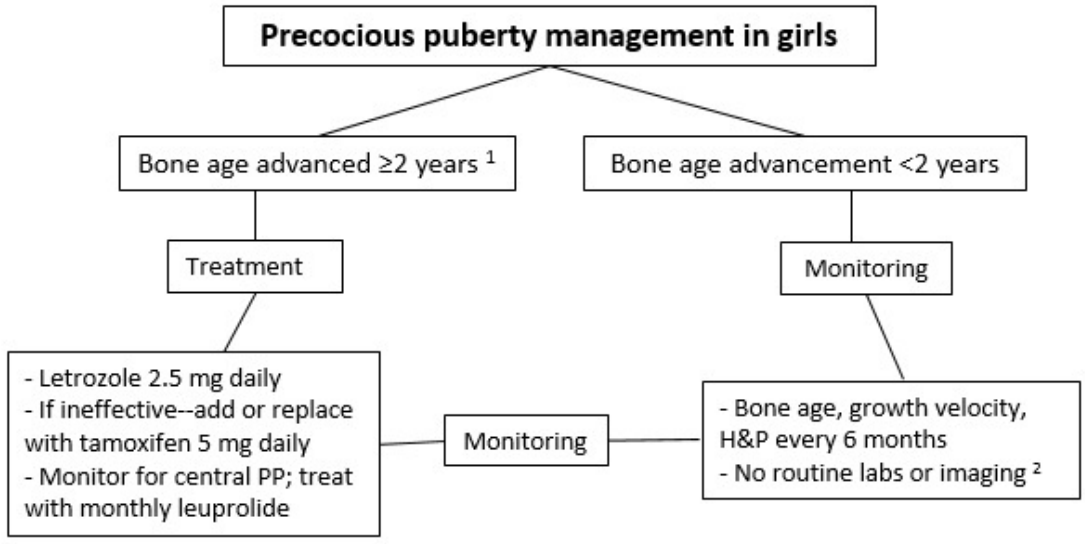
Treatment of Endocrinopathies in Individuals with Fibrous Dysplasia/McCune Albright Syndrome

Manifestation	Treatment	Considerations/Other
Precocious puberty (females) [1]	Letrozole (aromatase inhibitor) [2, 3]	Treatment prevents bone age advancement & compromise of adult height.
Precocious puberty (males) [4]	Combined androgen receptor blocker (e.g., spironolactone or bicalutamid) & an inhibitor of sex steroid synthesis (e.g., letrazole) [5]	Treatment options are less well established.
Central precocious puberty (females & males) [6]	Leuprolide combined w/medications listed above for precocious puberty	

Manifestation	Treatment	Considerations/Other
Persistent ovarian cysts	Prophylactic surgical intervention may be considered for large cysts.	Caution is advised due to risk for recurrent cysts & potential for decreased ovarian reserve.
Hyperthyroidism [7]	Methimazole [8]	Propilthiouracil has been associated w/unacceptable risk for hepatotoxicity in children & thus is no longer recommended. [9]
	Thyroidectomy [10]	Total gland resection is generally recommended due to potential for thyroid tissue regrowth.
FGF23-mediated phosphate wasting	Standard treatment w/oral phosphorus & calcitriol	Therapeutic endpoints include normal growth velocity & radiographic evidence of epiphyseal healing. [11]
Growth hormone (GH) excess (see Figure 15)	Alone or in combination: somatostatin analogs & the GH receptor antagonist pegvisomant [12, 13]	In growing children, the therapeutic goal is to maintain IGF-1 level in the middle of normal range w/an IGF-1 Z-score <0.
		In skeletally mature individuals, goal is to decrease the IGF-1 level to as low as possible.
		Medical therapy is typically continued indefinitely, because options for definitive treatment are associated w/significant morbidity. [14]
Hyperprolactinemia	Dopamine agonists, [15] including cabergoline & bromocriptine	
Hypercortisolism [16]	Medical: Metyrapone [17]	Spontaneous remission has been clearly documented in some affected individuals [Brown et al 2010]; however, it is not possible to identify prospectively which individuals will undergo remission.
	Surgical: Removal of the adrenal glands [18]	
Intraductal papillary mucinous neoplasms of the pancreas	Standard treatment [19]	See Figure 17

1. See Figure 12. Most girls will have a decrease in the number of menstrual bleeding episodes while on treatment.
2. Feuillan et al [2007]
3. Letrozole treatment resulted in sustained beneficial effects on skeletal maturation, growth velocity, and predicted adult height [Estrada et al 2016].
4. See Figure 13. Precocious puberty is rare in affected males.
5. Boyce et al [2012a]
6. Due to premature sex steroid exposure (see Clinical Description), central precocious puberty presents with reappearance of signs of puberty in a child with previously well-controlled peripheral precocious puberty.
7. See Figure 14. Radioabalation is avoided (see Agents/Circumstances to Avoid).
8. Tessaris et al [2012a]
9. Ross et al [2016]
10. Selection of an experienced high-volume endocrine surgeon is critical to minimize complications and optimize outcomes.
11. Bone turnover markers (e.g., alkaline phosphatase) may be constitutively elevated and are not a useful indicator of skeletal response to treatment.
12. Boyce et al [2013], Salenave et al [2014]
13. Radiation treatment may be effective in refractory cases, but has been associated with fatal malignant transformation of craniofacial FD [Hansen & Moffat 2003, Liu et al 2011].

14. Surgery may be technically difficult or precluded due to craniofacial FD. Additionally, given the diffuse pituitary infiltration of GH-producing cells, affected individuals treated surgically require total hypophysectomy with resulting total hypopituitarism [Vortmeyer et al 2012].
15. This class of drugs could also have an effect on growth hormone excess treatment, in affected individuals with modest elevations of GH and IGF-1 levels, with or without concomitant hyperprolactinemia [Katznelson et al 2014].
16. See Figure 16; treatment guidelines are difficult to establish given the rarity of neonatal Cushing syndrome.
17. Preferred over ketoconazole in children with liver abnormalities
18. The decision to pursue or delay adrenalectomy must be made on an individual basis, taking into account the severity of illness, the ability of medications to control cortisol levels, and the potential effect of continued hypercortisolism on neurodevelopment.
19. Tanaka et al [2012]

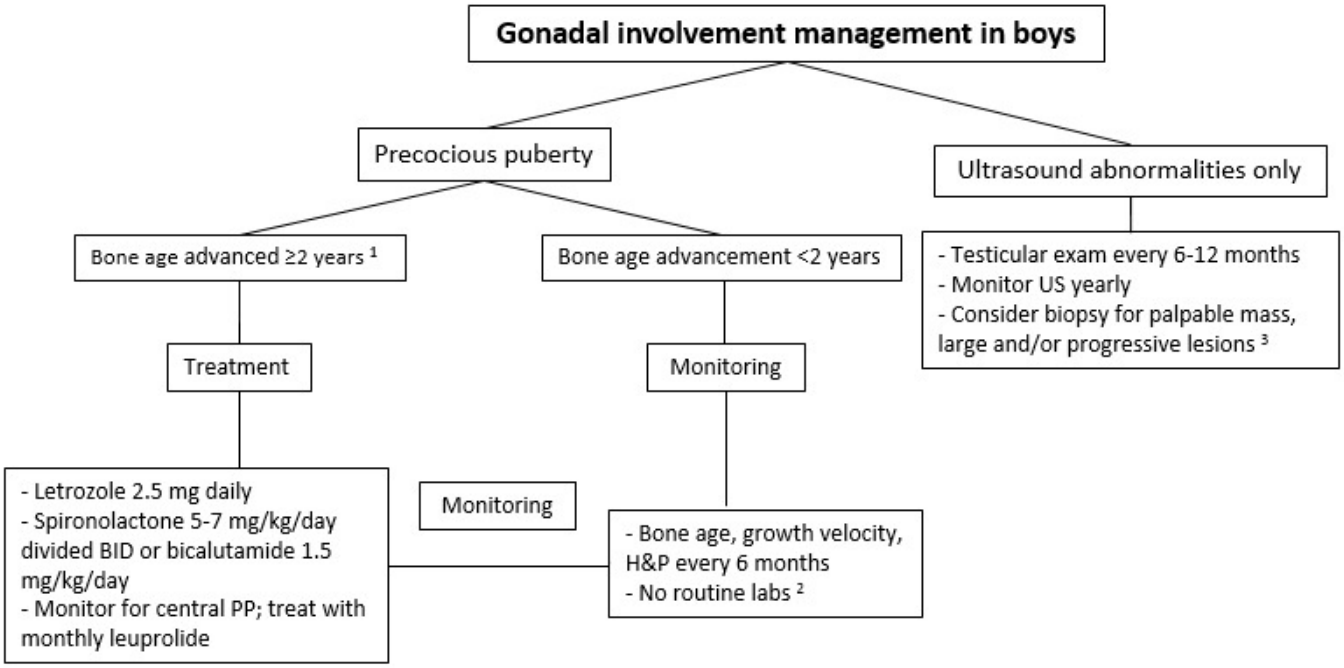


PP = precocious puberty
mg = milligrams
H&P = history and physical examination

1. The primary indication for treatment is to prevent impairment of adult height. Vaginal bleeding in the absence of bone age advancement does not typically warrant treatment. Exceptions may be made for very young children with frequent bleeding episodes deemed likely to lead to bone age advancement, or those who experience significant psychosocial distress related to pubertal episodes [Boyce et al 2016, Eugster et al 2003].
2. The primary endpoint for treatment efficacy is prevention of bone age advancement, which is assessed by growth velocity and bone age examination. Routine laboratory testing and ultrasound are unlikely to change management, and are not recommended.

Figure 12.

Recommended management for precocious puberty in girls with fibrous dysplasia/McCune-Albright syndrome

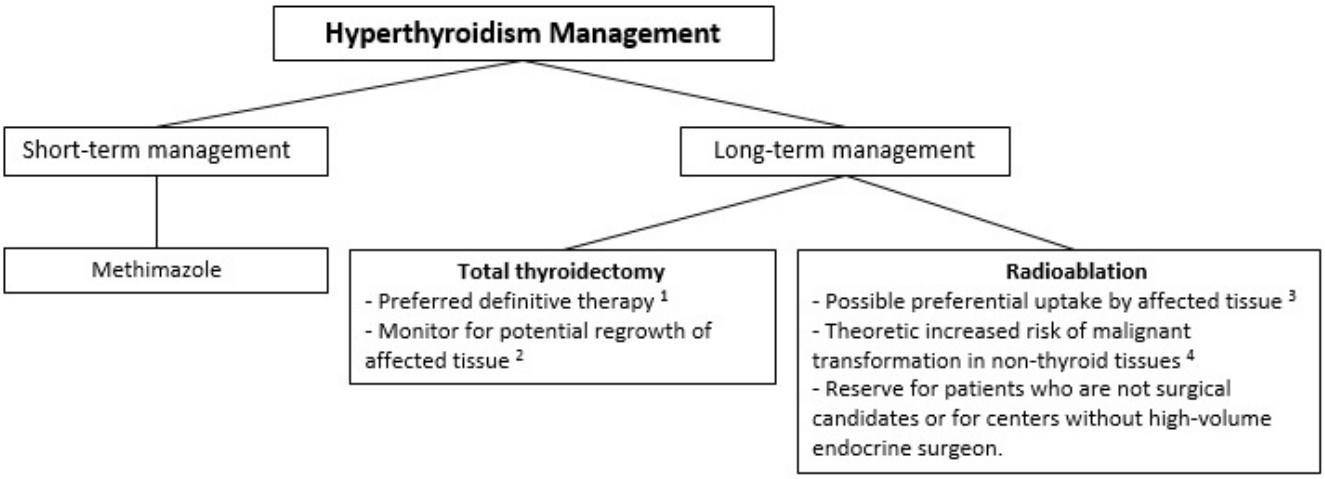


PP = precocious puberty
mg = milligrams
kg = kilogram
H&P = history and physical examination
US = ultrasound

1. The primary indication for treatment is to prevent impairment of adult height. Elevated testosterone levels in the absence of bone age advancement does not warrant treatment. Exceptions may be made for boys with testosterone-induced behavioral changes or progressive masculinization of the genitalia.
2. Routine labwork is unlikely to change management and is not recommended.
3. Routine biopsy of affected testes is not recommended. Lesions should be followed with serial exam and ultrasound. Consider biopsy for lesions with atypical features such as a palpable mass, or for lesions that are large and/or progressive [Boyce et al 2012a, Tessaris et al 2012b].

Figure 13.

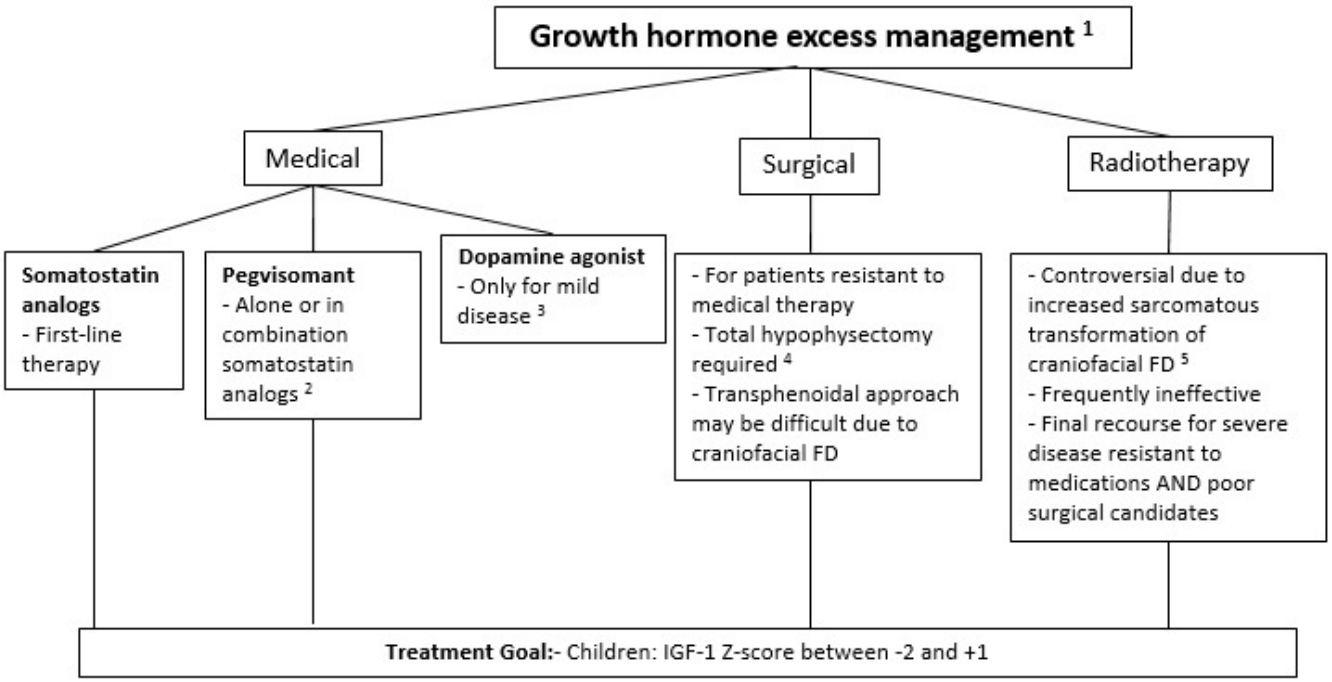
Recommended management for gonadal involvement in boys with fibrous dysplasia/McCune-Albright syndrome



1. Total thyroidectomy is preferred over subtotal as any remaining abnormal tissue has the potential to regrow, with recurrence of hyperthyroidism. Accordingly, radioactive iodine uptake scan will not alter management and is not part of routine pre-operative care.
2. After thyroidectomy affected individuals should continue to be monitored with yearly physical exam and thyroid US.
3. Preferential uptake of radioactive iodine by diseased tissue may lead to a theoretic increased risk of thyroid cancer in the remaining unaffected tissue.
4. Both thyroid and non-thyroidal tissues with an activating pathogenic *GNAS* variant carry a slight increased risk of malignant transformation, which may be increased by radiation exposure [Tessaris et al 2012a, Collins et al 2003].

Figure 14.

Recommended management for hyperthyroidism in individuals with fibrous dysplasia/McCune-Albright syndrome

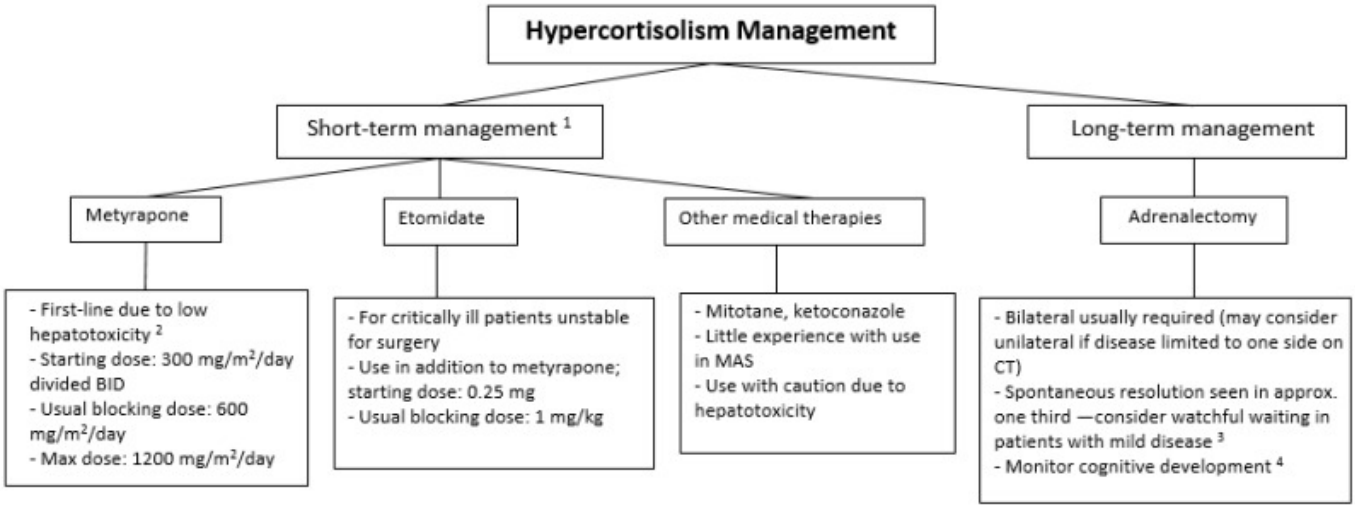


FD = fibrous dysplasia
IGF-1 = insulin-like growth factor-1

1. Hyperprolactinemia accompanies GH excess in approximately 80% of the individuals with MAS. It usually only requires treatment if levels are very high and/or it is interfering with pubertal progression, menses, or sexual function [Salenave et al 2014].
2. The authors's practice is to add pegvisomant after reaching a maximal dose of somatostatin analogs.
3. Effective for treatment of modest elevations of GH and IGF-1 levels, with or without concomitant hyperprolactinemia.
4. Due to characteristic diffuse somatolactotroph hyperplasia of the pituitary, total hypophysectomy is required for successful surgical treatment [Vortmeyer et al 2012].
5. FD of the skull base is nearly universal in individuals with MAS-associated GH excess. There are reports of fatal skull base osteosarcomas arising after pituitary irradiation for treatment of MAS-associated GH excess [Liu et al 2011].

Figure 15.

Recommended management for growth hormone excess in individuals with fibrous dysplasia/McCune-Albright syndrome

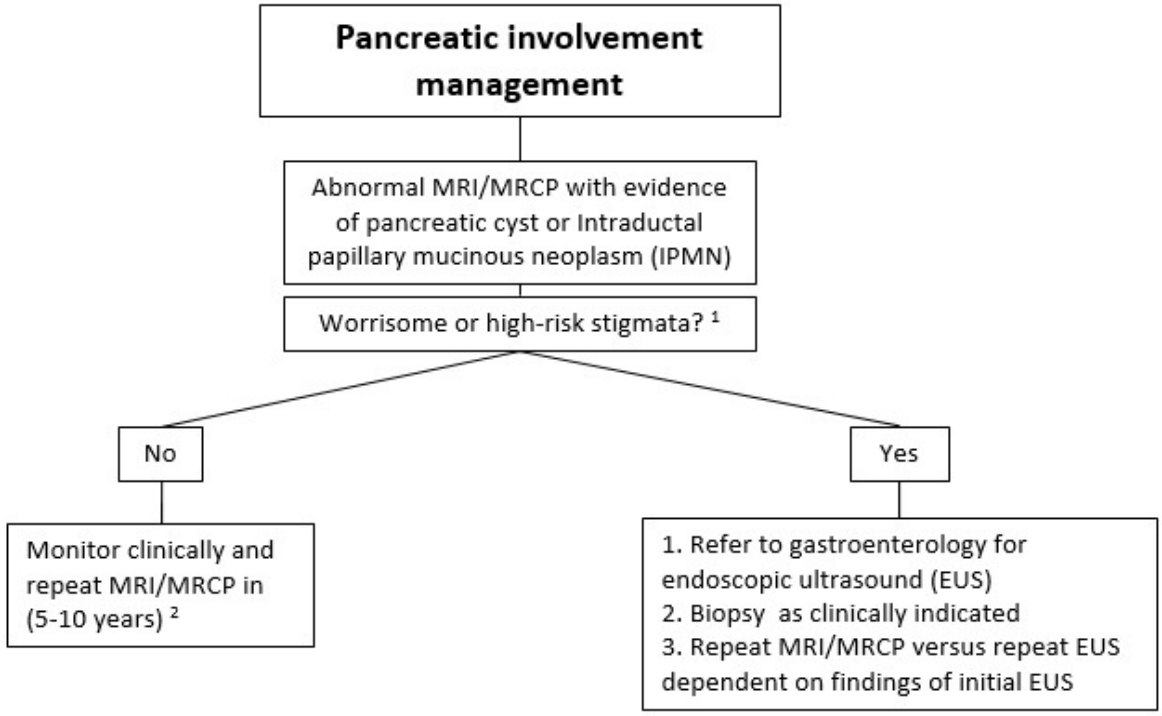


mg = milligrams
m^2 = meters squared
MAS = McCune-Albright syndrome

1. Affected individuals are often critically ill at presentation, which may impact treatment options.
2. Hepatotoxicity is an important consideration due to frequent comorbid liver disease [Brown et al 2010].
3. Spontaneous resolution may occur due to involution of the adrenal fetal zone, which is the source of hypercortisolism in MAS [Carney et al 2011].
4. Children with a current or remote history of MAS-associated hypercortisolism are at increased risk for neurodevelopmental delays, and should be considered for early interventional services [Brown et al 2010].

Figure 16.

Recommended management for hypercortisolism in individuals with fibrous dysplasia/McCune-Albright syndrome



MRCP = magnetic resonance cholangiopancreatography
MRI = magnetic resonance imaging
EUS = endoscopic ultrasound

1. Based on the International Consensus Guidelines 2012 for the management of IPMNs [Tanaka et al 2012]. Worrisome features include: pancreatitis; cyst ≥3 cm; thickened cystic walls; main duct dilatation of 5-9 mm; non-enhanced mural nodules; and abrupt change in caliber of pancreatic duct with distal pancreatic atrophy. High-risk stigmata include: obstructive jaundice in affected individuals with a cystic lesion in the pancreatic head; enhanced solid component within the cyst; and main duct dilatation ≥10 mm.
2. The interval for repeat MRI/MRCP is not established [Gaujoux et al 2014, Wood et al 2017].

Figure 17.

Recommended management for pancreatic involvement in individuals with fibrous dysplasia/McCune-Albright syndrome

Table 6.

Treatment of Other Manifestations in Individuals with Fibrous Dysplasia/McCune Albright Syndrome

Manifestation	Treatment	Considerations/Other
Optic nerve compression	Standard treatment	
Hearing loss	Standard treatment	See Hereditary Hearing Loss and Deafness Overview
Gastroesophageal reflux	Standard treatment	
Pancreatitis	Standard treatment	
Bone marrow failure	Standard treatment	In those w/pancytopenia & extramedullary hematopoiesis, consider splenectomy. [1]

Manifestation	Treatment	Considerations/Other
Breast cancer	Standard treatment	Consider early routine mammography screening. [2]

1. Mahdi et al [2017], Robinson et al [2018]
2. Majoor et al [2018a]

Surveillance

Table 7.

Recommended Surveillance for Individuals with Fibrous Dysplasia/McCune Albright Syndrome

Organ System		Evaluation	Frequency
Musculoskeletal [1]		Monitoring for progression of scoliosis & other skeletal findings by orthopedic surgeon or physiatrist	Routinely
		Computed tomography of the skull	Every 5 yrs or potentially sooner in younger individuals, those w/severe disease, or if vision or hearing deficits develop
		Radiographs to evaluate new or worsening symptoms & to provide additional information about FD anatomy & bone quality	Periodically
Endocrine	**Puberty (females)**	Evaluation for growth acceleration & other clinical signs of precocious puberty [2, 3]	At each visit
		Bone age assessment	Every 6 mos in those w/bone age advancement of ≥2 yrs
	Puberty (males)	Evaluation for growth acceleration & other clinical signs of precocious puberty [2, 3]	At each visit
		Bone age assessment	Every 6 mos in those w/bone age advancement of ≥2 yrs
		Testicular physical examination	At each visit
		Testicular ultrasound	Periodically
	Thyroid	Thyroid function tests (TSH, free T4, T3)	Routinely in all children age <5 yrs; every 4-6 mos in children <3 yrs & annually in children >3 yrs throughout childhood if ultrasound abnormalities are present [4]
		Physical examination of the thyroid	Periodically in those w/retained abnormal thyroid tissue following thyroidectomy [5]
		Thyroid ultrasound	Periodically in those w/abnormalities on thyroid ultrasound or who have undergone thyroidectomy [5, 6]

Organ System		Evaluation	Frequency
	Adrenal [7]	Clinical signs of hypercortisolism [8]	In infants at each visit
		Signs & symptoms of late-appearing adrenal insufficiency in those w/history of Cushing syndrome that has spontaneously resolved [9]	At each visit
		Serum IGF-1 levels	Routinely through young adulthood in those w/craniofacial FD
		For signs & symptoms of gallbladder disease in those treated w/somatostatin analogs	Periodically
Renal		Serum phosphorus & 25-hydroxyvitamin D levels [1, 10]	Periodically
Eyes		Evaluation by ophthalmologist (or neuroophthamologist)	Annually in those w/craniofacial FD
ENT		Evaluation by audiologist	Annually in those w/craniofacial FD
Gastrointestinal		Evidence of hepatotoxicity for those on pegvisomant	Periodically
Oncology		Consider initiating breast cancer screening earlier than recommended for general population. [11]	Periodically

1. See Figure 3.
2. See Figure 5.
3. Growth acceleration can also be a sign of growth hormone excess.
4. Individuals with abnormalities on thyroid ultrasound examination but normal thyroid function tests are at risk for the development of frank hyperthyroidism.
5. See Figure 7.
6. Thyroid tissue can regrow after thyroidectomy.
7. See Figure 8.
8. Routine biochemical surveillance for hypercortisolism is not indicated.
9. See Figure 10.
10. To monitor for the development of FGF23-mediated hypophosphatemia and as part of routine bone health
11. Majoor et al [2018a]

Agents/Circumstances to Avoid

Contact sports and other high-risk activities should be avoided in those with significant skeletal involvement.

Avoid prophylactic optic nerve decompression (see Treatment of Manifestations).

Surgical removal of ovarian cysts should be performed with caution and only in limited circumstances.

Radiation therapy is not indicated for treatment of FD, and radiation exposure to FD lesions should be limited due to potential risk for malignant transformation [Ruggieri et al 1994].

Radioablation for hyperthyroidism is also typically avoided due to potential preferential uptake by tissues bearing a somatic activating *GNAS* pathogenic variant, which may lead to increased risk of malignancy in the remaining unaffected gland.

Evaluation of Relatives at Risk

Because FD/MAS is not inherited, relatives are not at increased risk and do not require evaluation.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

While the effects of pregnancy on bone and endocrine disease in women with FD/MAS are not well studied, in the authors' experience most affected women do not experience a worsening of disease during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is not inherited.

- Verified vertical transmission has never been observed.
- Molecular data indicates that all affected individuals are mosaic for an activating *GNAS* pathogenic variant that arises sporadically early in embryonic development.

Risk to Family Members

Parents of a proband. No parent of a child with FD/MAS has been demonstrated to have any significant, distinctive manifestations of the disorder, nor would such a finding be expected given the somatic nature of the disease.

Sibs of a proband. Given the somatic mutational mechanism of FD/MAS, the risk for an affected sib would be expected to be the same as in the general population.

Offspring of a proband. There are no verified instances of vertical transmission of FD/MAS, potentially the result of embryonic lethality.

Other family members. The risk to other family members is the same as that in the general population.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mosaic pathogenic variant. Counseling for recurrence risks in FD/MAS should emphasize that, while no pregnancy is at zero risk, evidence suggests that the risk of recurrence for this disorder is not increased over that of the general population.

Family planning. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

As FD/MAS is the result of postzygotic somatic mutation of *GNAS* and is not inherited, prenatal testing for FD/MAS is not indicated.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association des Malades Porteurs du Syndrome de McCune-Albright, de Dysplasie Fibreuse des Os**
  France
  Phone: 09 77 39 12 60; 06 76 34 15 69
  Email: assymcal@orange.fr
  www.assymcal.org
- **European Association for McCune-Albright Syndrome and Other Rare Diseases**
  Italy
  Email: info@eamas.net
  www.eamas.net
- **Fibrous Dysplasia Foundation**
  Email: info@fibrousdysplasia.org
  www.fibrousdysplasia.org
- **Fibrous Dysplasia Support Society**
  United Kingdom
  Email: enquiries@FDSSUK.org.uk
  www.fdssuk.org.uk
- **MAGIC Foundation**
  6645 West North Avenue
  Oak Park IL 60302
  Email: ContactUs@magicfoundation.org
  McCune-Albright Syndrome / Fibrous Dysplasia
- **Medline Plus**
  McCune-Albright syndrome
- **Patiëntenvereniging Fibreuze Dysplasie**
  Netherlands
  Email: info@fibreuzedysplasie.eu
  www.fibreuzedysplasie.eu

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Fibrous Dysplasia/McCune-Albright Syndrome: Genes and Databases

Gene	Chromosome	Protein	Locus-Specific Databases	HGMD	ClinVar

	Locus				
GNAS	20q13.32	Guanine nucleotide-binding protein G(s) subunit alpha isoforms short	GNAS complex locus (GNAS) @ LOVD	GNAS	GNAS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B.

OMIM Entries for Fibrous Dysplasia/McCune-Albright Syndrome (View All in OMIM)

139320	GNAS COMPLEX LOCUS; GNAS
174800	MCCUNE-ALBRIGHT SYNDROME; MAS

Gene structure. *GNAS* is a complex locus with an imprinted expression pattern. Multiple gene products, including maternally, paternally, and biallelically expressed transcripts, are derived from the use of four promoters and 5' exons that splice onto a common set of downstream exons [Weinstein et al 2004] (summarized in OMIM 139320). The major *GNAS* product is the ubiquitously expressed $G_s\alpha$, which is generated by the most downstream promoter (exon 1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Somatic mosaicism for pathogenic missense variants at p.Arg201 has been identified in more than 95% of all published reports of FD/MAS. The most frequent missense pathogenic variants are p.Arg201His and p.Arg201Cys [Lumbroso et al 2004]. Very infrequently, arginine is replaced by serine, glycine, or leucine. Rarely, missense variants at p.Gln227 have been reported [Idowu et al 2007].

There are ongoing experimental approaches to develop methods with increased sensitivity [Bianco et al 2000, Narumi et al 2013, de Sanctis et al 2017] that in the future may enable the use of peripheral blood lymphocytes (PBL) for pathogenic variant detection and also allow the quantification of the mutated to wild type cell ratio within the sample (as opposed to presence-absence in PCR-RFLP techniques):

Table 8.

Techniques to Detect *GNAS* Somatic Variants

Method	Detection Rate	
	Blood	Lesional tissue
Variant-specific amplification by polymerase chain reaction (PCR) &/or restriction enzyme digestion (RFLP) followed by directed sequencing of the variant loci [1]	~20%-30%	~80%
PCR with peptide-nucleic acid probes [2] combined w/next-generation sequencing (PNA-NGS) [3]	~75%	~100%
Co-amplification at lower denaturation temperature and allele-specific PCR-based TaqMan genotyping (real-time COLD-MAMA-PCR) [4]	~75%	~100%

1. Lumbroso et al [2004], Kalfa et al [2006]
2. Bianco et al [2000]
3. Narumi et al [2013]
4. de Sanctis et al [2017]

Recent studies implicate alternate transcripts of *GNAS* in the pathogenesis of FD/MAS. A p.Arg543His variant, corresponding to position p.Arg201His in Gαs, on the large XLαs transcript of Gαs, was detected in individuals with a paternal pathogenic variant, whereas mutated neuroendocrine secretory protein 55 (NESP55) variant transcript was detected in those with a maternal pathogenic variant in the affected tissues. Functional in vitro assays of wild type XLαs showed strong induction of adenyl cyclase activity in transfected cells, suggesting that this *GNAS* variant could be playing a role in the pathogenesis of FD [Mariot et al 2011].

Table 9.

GNAS Somatic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.601C>T	p.Arg201Cys	NM_000516.4 NP_000507.1
c.601C>G	p.Arg201Gly	
c.601C>A	p.Arg201Ser	
c.602G>A	p.Arg201His	
c.602G>T	p.Arg201Leu	
c.679C>A	p.Gln227Lys	
c.680A>T	p.Gln227Leu	
c.680A>G	p.Gln227Arg	
c.681G>T	p.Gln227His	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *GNAS* encodes the cAMP pathway-associated G-protein, $G_s\alpha$. $G_s\alpha$ is a key component of many hormonal and other signal transduction pathways. Its primary role is to couple G-coupled protein receptors to adenylyl cyclase, promoting receptor-stimulated production of intracellular cAMP. $G_s\alpha$ in its inactive state forms a heterotrimer with the $G_s\beta$ and $G_s\gamma$ subunits, with GDP bound to its binding site. Ligand binding to the G-coupled protein receptor promotes release of GDP from the α-subunit and binding of GTP. The GTP-bound $G_s\alpha$ dissociates from the β-γ heterotrimer and translocates to interact with adenylyl cyclase to promote cAMP production. Intrinsic GTPase hydrolyzes the bound GTP to GDP, leading to cessation of cAMP generation and reassembly of the α-β-γ heterotrimer. Downstream, cAMP is metabolized to AMP by one of many tissue-dependent phosphodiesterases.

Abnormal gene product. The FD/MAS-associated *GNAS* variants at residues p.Arg201 and p.Gln227 disrupt the activity of intrinsic GTPase, causing constitutive activity and inappropriately increased cAMP signaling [Landis et al 1989].

The spectrum of FD/MAS ranges from asymptomatic incidental findings to neonatal lethality. The phenotype of FD/MAS is a reflection of the role of $G_s\alpha$ in that tissue and whether or not a given tissue harbors a pathogenic variant in *GNAS*. The distribution of affected tissues is a reflection of the timing of the occurrence of the sporadic pathogenic variant during development and the fate of the specific clone in which the pathogenic variant occurs. It is likely that the stem cells of certain tissues will not tolerate mutated $G_s\alpha$ and are eliminated during development. Therefore, some tissues in which there is significant $G_s\alpha$ signaling will not be affected. For example, $G_s\alpha$ signaling is important in growth plate development, yet the growth plate is virtually never affected.

Activating or gain-of-function *GNAS* pathogenic variants in individuals with FD/MAS are present in the mosaic state, resulting from postzygotic somatic pathogenic variants appearing early in the course of development, which yields a monoclonal population of mutated cells within variously affected tissues. The non-mosaic state for most activating pathogenic variants is presumably lethal to the embryo (modified from OMIM 174800).

Cancer and Benign Tumors

The FD/MAS-associated activating *GNAS* pathogenic variants at residues p.Arg201 and p.Gln227 (collectively referred to as the *gsp* oncogene) have been reported in nonsyndromic benign [Landis et al 1989] and malignant [Wood et al 2007] tumors. However, the presence of the *GNAS* pathogenic variant alone is insufficient for malignant transformation of the affected tissues, but more likely predisposes for additional genetic or epigenetic events.

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Figures

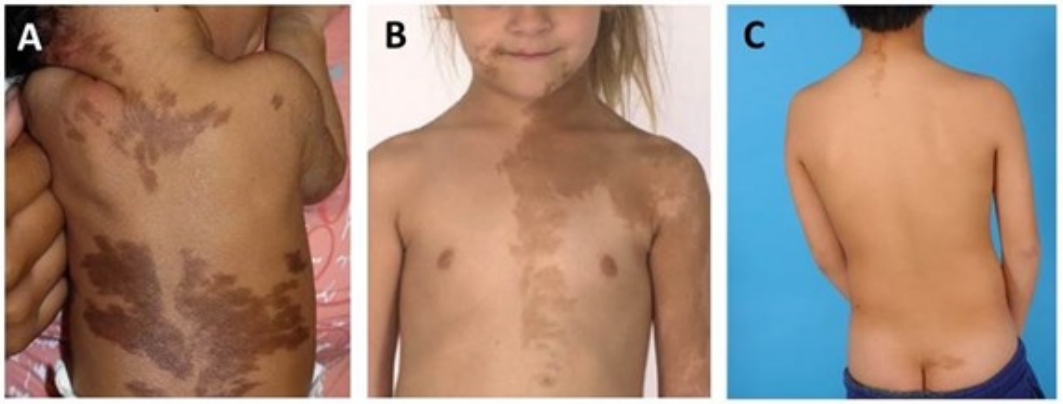


Figure 1.

Café au lait skin pigmentation

A. Skin lesions in a newborn demonstrating the characteristic association with the midline of the body, and distribution reflecting patterns of embryonic cell migration (developmental lines of Blaschko)

B. A typical lesion on the chest, face, and arm demonstrating the irregular "coast of Maine" borders, relationship with the midline of the body, and distribution following developmental lines of Blaschko

C. Typical lesions frequently found on the nape of the neck and crease of the buttocks

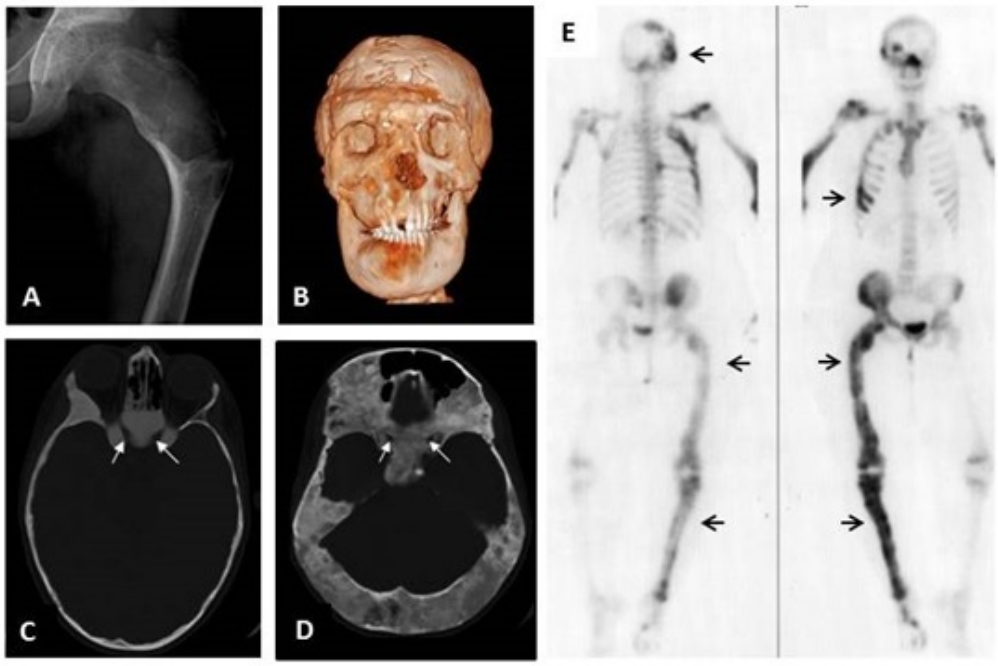


Figure 2.

Fibrous dysplasia (FD)

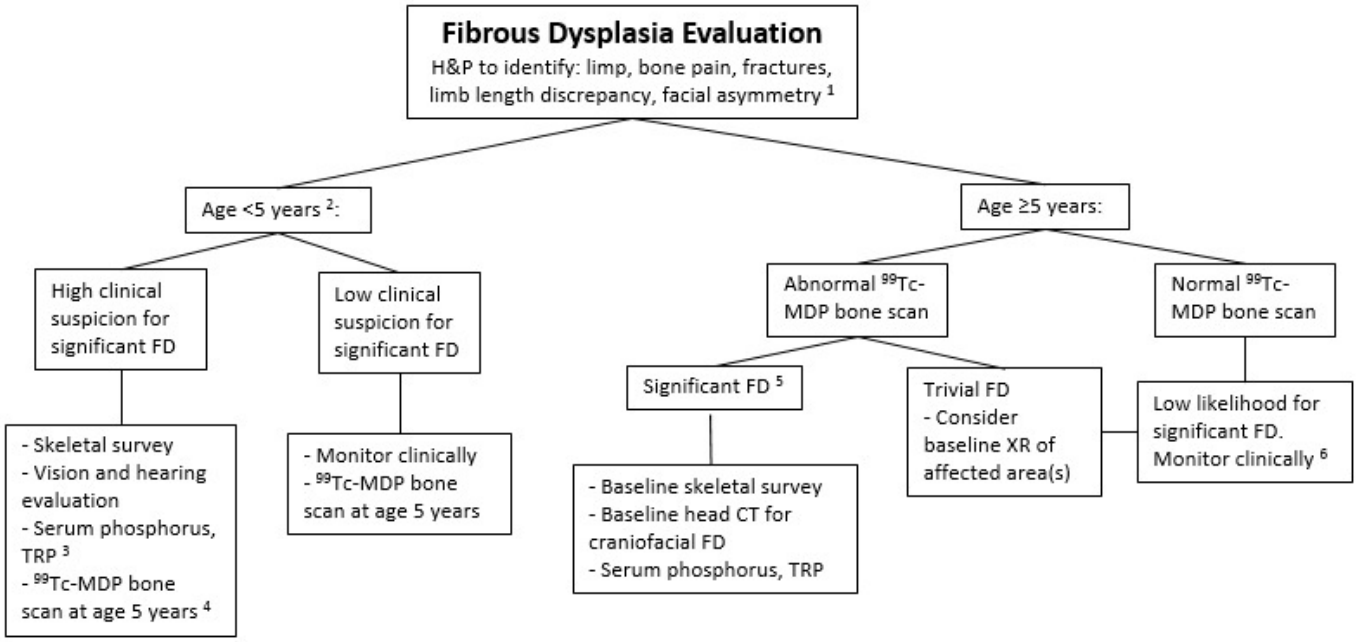
A. Proximal femur FD demonstrating the typical ground-glass appearance with a coxa vara ("shepherd's crook") deformity

B. Three-dimensional reconstructed computed tomography (CT) image of a man age 26 years with craniofacial FD and uncontrolled growth hormone excess, leading to macrocephaly and severe facial deformity

C. CT image from a girl age ten years, demonstrating the typical ground glass appearance of craniofacial FD in younger individuals. The optic canals are typically encased in FD (white arrows) without any visual disturbance.

D. CT image from a woman age 40 years, demonstrating typical features of craniofacial FD in an older individual, including a more sclerotic appearance with mixed solid and cystic components. Again, depicted are the optic nerves encased in FD (white arrows) without visual disturbance.

E. ^{99}Technetium bone scintigraphy, posterior-anterior and anterior-posterior views, left and right panels, respectively demonstrating patchy tracer uptake at affected skeletal sites, including the skull, ribs, femur, and tibia (arrows), consistent with a mosaic pattern of expression



FD = fibrous dysplasia
H&P = history and physical exam
TRP = tubular reabsorption of phosphate
^{99}Tc-MDP = technetium-99 conjugated with methylene diphosphonate
XR = x-ray

1. Performed at initial presentation in all individuals suspected of having FD/MAS.
2. Areas of clinically significant FD will be apparent on bone scan by age 5 years. Prior to age 5, a normal ^{99}Tc-MDP does not eliminate the possibility of significant FD [Hart et al 2007].
3. FGF23-mediated phosphate wasting is associated with a high FD burden. Phosphate wasting may worsen during rapid skeletal growth and improve or resolve in adulthood as FD becomes less active [Riminucci et al 2003].
4. Consider performing ^{99}Tc-MDP bone scan in children < 5 years regardless of clinical suspicion for bone disease in instances where establishing the diagnosis of MAS may alter management – i.e. those for whom diagnostic surgery is being considered, such as skeletal biopsy.
5. Significance of FD is determined by both the amount and location of affected bone [Collins et al 2005]. Clinically significant disease is frequently associated with the craniofacial area, proximal femurs and spine.
6. A normal ^{99}Tc-MDP bone scan at age 5 years or older effectively eliminates clinically significant FD, and no further radiologic monitoring is required [Hart et al 2007].

Figure 3.

Suggested evaluations to determine if fibrous dysplasia (FD) is present and the extent of disease if FD is present.

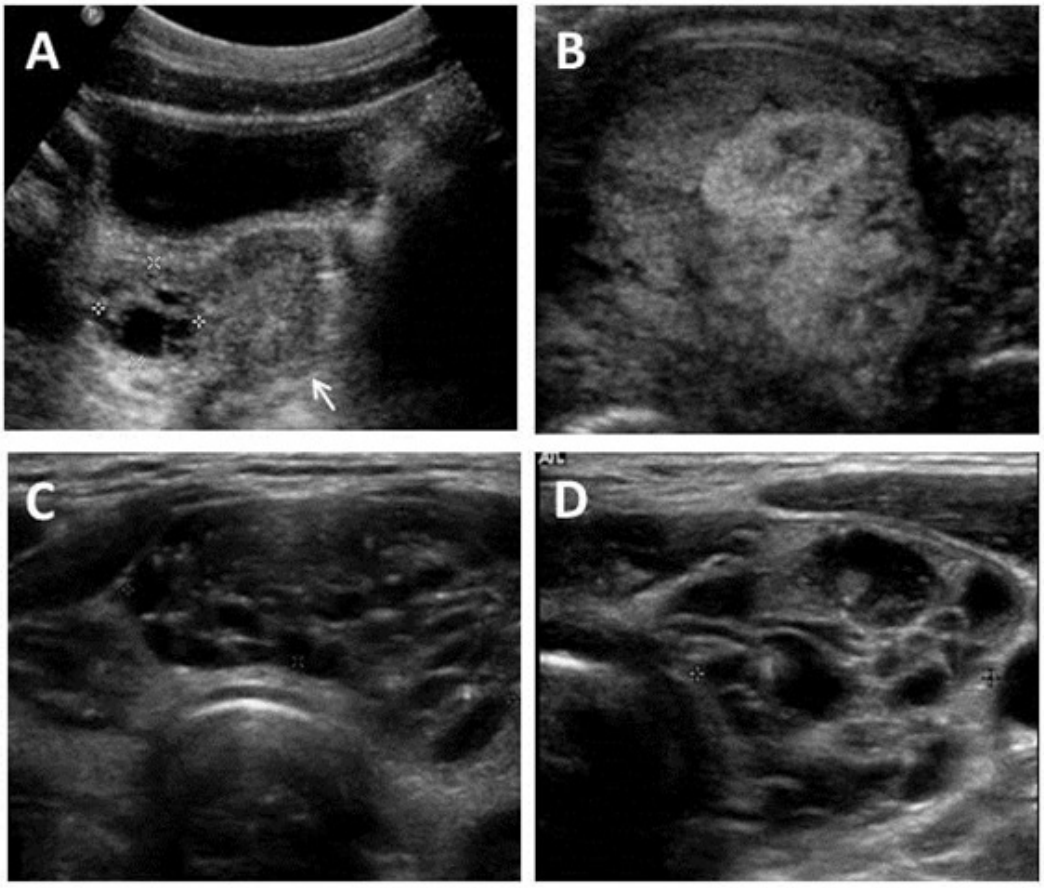


Figure 4.

Ultrasonography

A. Pelvic ultrasound in a girl age seven years, showing a complex unilateral ovarian cyst (defined by cross-hatches). The uterus is prepubertal in size (arrow).

B. Testicular ultrasound in an adult showing a heterogeneous lesion with mixed solid and cystic elements

C&D. Typical thyroid ultrasound findings, including heterogeneity and a cystic ("Swiss cheese") appearance

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Long-term Outcome of Optic Nerve Encasement and Optic Nerve Decompression in Patients with Fibrous Dysplasia: Risk Factors for Blindness and Safety of Observation

OBJECTIVE: Fibrous dysplasia (FD) of bone may occur solely as a skeletal condition or it may occur in association with extraskeletal manifestations, including growth hormone (GH) excess. Uncertainty exists as to the management of FD involving the optic nerves. In an effort to clarify management, the authors studied a large population of patients.

METHODS: One hundred four patients underwent an evaluation that included review of records, endocrine testing, cranial computed tomography, and neuro-ophthalmological examination.

RESULTS: Ninety-one of 104 patients had craniofacial FD; complete records were available for 87 patients (174 nerves). Seventeen percent of the optic nerves were less than 50% encased, 22% were 50 to 99% encased, and 61% were 100% encased. Twelve percent of the nerves that were 100% encased showed evidence of optic neuropathy, but 88% did not. The group with optic neuropathy was not older than the group without. Patients with GH excess were significantly more likely to have nerves that were 100% encased (relative risk, 4.1; 95% confidence interval, 1.5–11.1; $P = 0.0017$) and to have optic neuropathy (relative risk, 3.8; 95% confidence interval, 2.0–7.1; $P = 0.0019$). Six prophylactic optic nerve decompressions were performed; in five patients, vision was stable after surgery, and one patient was blind after surgery. Thirteen interventional optic nerve decompression procedures were performed; six of the 13 patients showed some improvement and seven of the 13 showed no improvement or worsened vision.

CONCLUSION: The vast majority of optic nerves encased with FD do not exhibit symptoms of optic neuropathy and seem to be stable over time. GH excess is associated with increased risk of nerve encasement and optic neuropathy. Patients with craniofacial FD should be screened for GH excess, and optic nerve decompression should be performed only when there is objective evidence of progressive optic neuropathy.

KEY WORDS: Bone, GNAS, Growth hormone, $G_s\alpha$, McCune-Albright syndrome

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Fibrous dysplasia (FD) of bone is a benign skeletal disease in which normal bone is replaced by a benign fibro-osseous tissue (5, 6, 15). It results from postzygotic activating mutations in the signaling protein $G_s\alpha$ (17). It may appear as a condition of the skeleton only or as part of the McCune-Albright syndrome (MAS), which is clinically defined by FD in combination with either café au lait skin pigmentation and/or at least one of a number of hyperfunctioning endocrinopathies, including precocious puberty, hyperthyroidism, growth hormone (GH) excess, and others (4). The craniofacial structures and cranial base are involved in many patients, and the optic nerves are usually involved and are often encased circumferentially as they pass through the cranial base (6, 8, 14). The optimal management of optic nerves circumferentially encased with fibrous dysplastic bone, but without symp-

toms of optic neuropathy, is controversial (3, 9–11, 13, 16). Prophylactic decompression is sometimes performed based on the assumption that the risk of future optic neuropathy outweighs the risks of the operation (3, 7, 10–13), which include postoperative blindness (3, 7, 13). The reason for this controversy is the lack of knowledge of the natural history and the risk for blindness in the absence of intervention. It has been pointed out that this controversy could be resolved by data on the natural history of this condition (9).

We previously demonstrated that significant narrowing of the optic canal with FD was not associated with optic neuropathy (8) and that GH excess may be related to a more severe craniofacial phenotype (1, 8, 19). Herein, we report on a larger group, with a longer follow-up period, who underwent a uniform and comprehensive evaluation. The goal was to better define the natural history of FD encasing the optic nerve and to identify the pathophysiological mechanisms contributing to the development of optic neuropathy.

PATIENTS AND METHODS

All patients seen at the National Institutes of Health since 1998 with a diagnosis of FD were evaluated. The diagnosis of FD was made based on the results of clinical, radiographical, and histological studies. Craniofacial FD was identified by a combination of nuclear medicine bone scans and computed tomographic (CT) analysis. All patients underwent testing of all relevant endocrine axes. A diagnosis of GH excess was made on the basis of a serum GH level of more than 1.0 ng/ml measured 60 minutes after a standard oral glucose tolerance test. Patients without neuro-ophthalmological examination results were excluded from the relevant sections of analysis. All patients were enrolled in an institutional review board-approved protocol and gave informed consent.

All patients were evaluated by a single neuro-ophthalmologist (EJF). Testing included best-corrected visual acuity, according to the Early Treatment Diabetic Retinopathy Study scale (20/20 denotes perfect vision); visual fields obtained using the Humphrey Visual Field Analyzer (Humphrey Instruments, San Leandro, CA) using the Swedish Interactive Thresholding Algorithm (SITA) 30–2 program or Goldmann perimetry testing; color vision, with the use of 14 Ishihara color plates; contrast sensitivity testing using the Pelli Robson charts; and results of examination of the fundus. Because there is no definitive test for optic neuropathy, abnormalities suggestive of optic neuropathy resulting from FD were defined as either an abnormal result on the visual field test (such as scotoma or field deficit) or an abnormal result on two of the three other tests performed (visual acuity less than 20/40, correct identification of fewer than 10 of 14 Ishihara color plates, or evidence of optic atrophy on examination of the fundus).

All patients underwent standardized CT imaging of the cranium, on either a 4- or 8-slice helical scanner, using 2.5- to 3.8-mm collimation. The slice reconstruction interval was 1.25 to 1.50 mm. Soft tissue and bone algorithm reconstructions were reviewed by a single neuroradiologist (JAB). The extent of encasement of optic nerves by FD of bone was evaluated in a semiquantitative manner as less than 50, 50 to 99, and 100%. Statistical analyses were performed using InStat software, version 3 (GraphPad Software, Inc., San Diego, CA).

RESULTS

One hundred four patients with FD and MAS were seen at the National Institutes of Health between 1998 and 2005. Of these, 91 (88%) had craniofacial involvement. Demographics for the group are shown in *Table 1*. Cranial CT scans were available for 91 patients. Neuro-ophthalmological evaluations were available for 87 (96%) of these 91 patients. In two patients, no examination was performed, and, in two patients, the record of the examination was missing. These four patients were excluded from the relevant analyses. Of the four patients excluded from the analysis because of no neuro-ophthalmological examination, four of the optic nerves were 100% encased and four were less than 50% encased with FD of bone.

TABLE 1. Patient demographics[a]

	Craniofacial fibrous dysplasia patients (n = 91)	Patients with 100% optic nerve encasement (n = 61)[b]	Patients with 50 to 99% optic nerve encasement (n = 28)[b]	Patients with <50% optic nerve encasement (n = 24)[b]
Age (yr)[c]				
Average	24.3	22.5[d]	25.7[d]	29.8[d]
Median	19	18	12.5	31
Range	3–84	3–84	6–84	6–69
Sex				
Male	39/91 (43%)	27/61 (44%)	11/28 (39%)	13/24 (54%)
Female	52/91 (57%)	34/61 (56%)	17/28 (61%)	11/24 (46%)
Diagnosis				
MFD	1/91 (1%)	0/61 (0%)	0/28 (0%)	1/24 (4%)
PFD	7/91 (8%)	0/61 (0%)	4/28 (14%)	5/24 (21%)
MAS	83/91 (91%)	61/61 (100%)	24/28 (86%)	18/24 (75%)

[a] MFD, monostotic fibrous dysplasia; PFD, polyostotic fibrous dysplasia; MAS, McCune-Albright syndrome, defined as fibrous dysplasia plus café au lait hyperpigmentation, endocrinopathies, or both.
[b] Some patients may fall into two categories.
[c] Age at date of most recent head computed tomographic scan.
[d] Age differences between groups not statistically significant ($P = 0.16$).

Optic Nerve Encasement

Of the 174 optic nerves, 29 (17%) were less than 50% encased, 38 (22%) were 50 to 99% encased, and 107 were 100% encased with FD of bone (*Fig. 1*). The average age of patients with optic nerves 100% encased was 22.5 years (median, 18 yr; range, 3–84 yr), compared with 25.7 years (median, 12.5 yr; range, 6–84 yr) and 29.8 years (median, 31 yr; range, 6–69 yr) for those with a nerve 50 to 99% encased or less than 50% encased, respectively (*Table 1*). There were no significant age differences between groups with less than 50, 50 to 99, and 100% encasement ($P = 0.16$, Krushkal-Wallis nonparametric analysis of variance), demonstrating a lack of age-related progression. Patients with GH excess were more likely to have optic nerves 100% encased by FD of bone than those without (relative risk, 4.1; 95% confidence interval, 1.5–11.1; $P = 0.0017$). All patients with at least one nerve 100% encased had MAS.

Optic Neuropathy

There was no evidence of optic neuropathy in any of the nerves that were either less than 50% or 50 to 99% encased by FD of bone (*Fig. 1*; *Table 2*). Of the nerves 100% encased by FD of bone, 94 (88%) of 107 exhibited no evidence of optic neuropathy. Optic neuropathy was seen in 13 (12%) of 107 nerves that were 100% encased. Of these, 12 (92%) were surgically decompressed and are discussed below. The remaining one (7%) had only mild neuropathy characterized by a pale fundus and a slow color vision response (10 out of 14 Ishihara color plates correct), which was not noticeable to the patient. This patient's mild optic neuropathy has been stable during 7 years of follow-up. The average age of patients at the time optic neuropathy occurred was 16.3 years (median, 12 yr; range, 5–35 yr), and the average age of those without optic neuropathy was 20.9 years (median, 18 yr; range, 3–84 yr). There was no age difference between the group with and without optic neuropathy ($P = 0.3057$, two-tailed Mann-Whitney *U* test).

Growth Hormone Excess and Aneurysmal Bone Cysts

Seven (54%) out of 13 nerves with optic neuropathy occurred in patients with GH excess (*Fig. 1*; *Table 2*). As such, GH excess represented a statistically significant risk factor for the development of optic neuropathy (relative risk, 3.8;

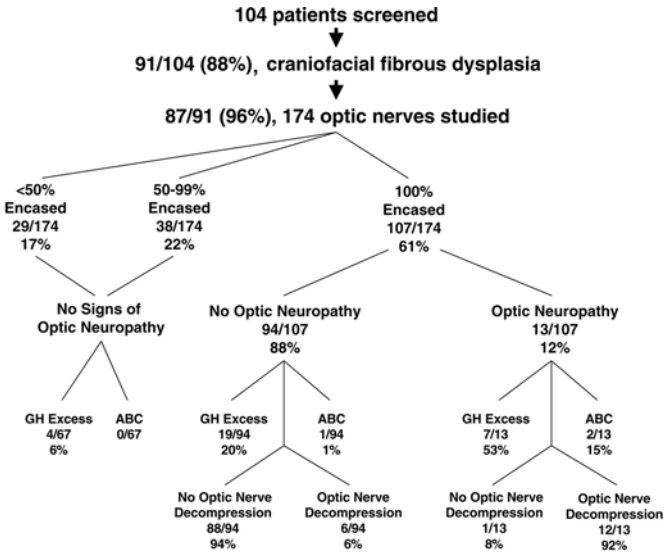

FIGURE 1. *Flowchart showing progress of patients studied. One hundred four patients were screened; 91 patients had craniofacial FD, and complete records were available for 87 patients (96%). The breakdown according to the extent of encasement and the presence or absence of GH excess, aneurysmal bone cyst (ABC), optic neuropathy, or a combination thereof are indicated. Optic neuropathy was defined as either an abnormal result on the visual field test or an abnormal result on two of the three other tests performed (visual acuity worse than 20/40, correct identification of fewer than 10 out of 14 Ishihara color plates, or evidence of optic atrophy on examination of the fundus).*

TABLE 2. Optic nerve encasement, optic neuropathy, growth hormone excess, and bone cysts[a]

	100% encasement	50–99% encasement	<50% encasement
No symptoms of optic neuropathy[b]	94/107 (88%)	38/38 (100%)	29/29 (100%)
Average age (yr)[c]	20.9	24.2	28.1
Median age (yr)	18	12.5	29
Age range (yr)	3–84	6–84	6–56
GH excess	19/94 (20%)	2/38 (5%)	2/29 (7%)
ABC	1/94 (1%)	0/38 (0%)	0/29 (0%)
Symptoms of optic neuropathy[d]	13/107 (12%)	0/38 (0%)	0/29 (0%)
Average age (yr)[c]	16.3 years	—	—
Median age (yr)	12 years	—	—
Age range (yr)	5–35 years	—	—
GH excess[e]	7/13 (54%)	—	—
ABC	3/13 (23%)	—	—

[a] GH, growth hormone; ABC, aneurysmal bone cyst. Preoperative extent of encasement and age at time that symptoms of optic neuropathy occurred were used for patients who had undergone optic nerve decompression.
[b] Optic neuropathy was defined by visual field defect or two of the following: decreased color vision, decreased visual acuity, abnormal appearance of fundus.
[c] Age differences between groups was not statistically significant ($P = 0.31$).
[d] One patient had optic nerve decompression of her right eye twice; both ages at times of optic nerve decompression were counted in these calculations.
[e] Patients with GH were more likely to have optic neuropathy (relative risk, 3.8; 95% confidence interval, 2.0–7.1; $P = 0.0019$).

95% confidence interval, 2.0–7.1; $P = 0.0019$). In two (15%) out of 13 nerves, the development of optic neuropathy was associated with an aneurysmal bone cyst (ABC) that compressed the optic nerves (*Fig. 1*), and one nerve (8%) was associated with both GH excess and an ABC. Therefore, in nine (69%) out of 13 nerves, optic neuropathy was associated with either GH excess or an ABC.

TABLE 3. Demographic data of patients who underwent optic nerve decompression[a]

	Patients without surgery (n = 79)	Surgery patients (n = 12)[b]	Interventional surgery (n = 9)[c]	Prophylactic surgery (n = 4)
Age (yr)[d]				
Average	24.6	14.8	14.8	15.8
Median	19	12	12	5.5
Range	3–84	5–37	5–30	5–37
Sex				
Male	35/79 (44%)	4/12 (25%)	3/9 (33%)	2/4 (50%)
Female	44/79 (56%)	8/12 (75%)	6/9 (66%)	2/4 (50%)
Diagnosis				
MFD	1/79 (1%)	0/12 (0%)	0/8 (0%)	0/4 (0%)
PFD	6/79 (8%)	1/12 (8%)	0/8 (0%)	1/4 (25%)
MAS	72/79 (91%)	11/12 (92%)	8/8 (100%)	3/4 (75%)

[a] MFD, monostotic fibrous dysplasia; PFD, polyostotic fibrous dysplasia; MAS, McCune-Albright syndrome, defined as fibrous dysplasia plus café au lait hyperpigmentation, endocrinopathies, or both.
[b] Age at date of most recent head computed tomographic scan.
[c] Age at date of surgery.
[d] One patient underwent interventional decompression on the same optic nerve at two different times; both ages at time of symptoms were included for calculation.

Optic Nerve Decompression

Optic nerve decompression was performed on 18 nerves. In the 94 patients without optic neuropathy, there were six prophylactic decompression surgeries (6%). Twelve (92%) of the 13 patients with optic neuropathy underwent 13 decompression surgeries (*Fig. 1*). All patients who underwent optic nerve decompression had nerves that were 100% encased. The demographics of the patients who underwent optic neuropathy are shown in *Table 3*. The average age of patients who underwent an interventional optic nerve decompression was 14.8 years (median, 12 yr; range, 5–30 yr). The average age at decompression for those who underwent prophylactic procedures was 15.8 years (median, 5.5 yr; range, 5–24 yr), and the average age of patients who did not undergo optic nerve decompression was 24.6 years (median, 19 yr; range, 3–84 yr).

Optic nerve decompressions were performed 13 times on 12 nerves (one for recurrent symptoms). Vision improved as a result of five (38%) of these procedures. One symptomatic nerve had improved vision after the initial optic nerve decompression, but then optic neuropathy developed 10 years later. The symptoms also resolved after the second optic nerve decompression. This patient had associated GH excess. Slight improvement was seen in one (8%), no improvement was reported in four (31%), and vision loss was reported in two (15%) of 13 procedures (*Table 4*).

Six prophylactic optic nerve decompressions were performed on six nerves that were 100% encased, but in which there were no symptoms of optic neuropathy (*Fig. 1*; *Table 4*). Five (83%) out of six of these nerves were intact after surgery with no change in vision. However, one (17%) of the six sustained intraoperative injury resulting in blindness.

DISCUSSION

The proper handling of optic nerves encased by FD without symptoms of neuropathy has long been controversial. Many authors recommend prophylactic decompression based on the assumption that the disease is progressive and that optic neuropathy is an inevitable complication. This recommendation assumes that the risk of prophylactic decompression—which includes blindness—is less than the risks associated with no treatment for asymptomatic nerves. In a previous study of 67 nerves, we demonstrated that narrowing of the optic canal alone is not necessarily associated with visual loss (8). In this study, we extend these findings to a larger cohort and demonstrate that, in most patients, vision loss is associated with either GH excess or an ABC.

In 93% of the 174 nerves, there was no evidence of optic neuropathy, and there was no optic neuropathy in nerves less than 100% encased. Of the 107 optic nerves that were 100% encased, 88% exhibited no evidence of optic neuropathy. There was no difference in age between groups with less than 50, 50 to 99, and 100% encasement, and patients with optic neuropathy were not older than those without optic neuropathy. These data support the conclusion that encasement does not progress with age and that increasing age does not necessarily bring with it the likelihood of optic neuropathy and blindness. Thus, prophylactic decompression should not be performed on patients without symptoms merely as an effort to prevent possible future optic neuropathy.

Two associations suggested the pathophysiological mechanism of optic neuropathy, namely GH excess and the presence of an ABC. Sixty-nine percent of the patients with optic neuropathy had either GH excess or an ABC of the cranial base. GH (and/or its trophic hormone insulin-like growth factor I) seems to promote growth and expansion of craniofacial FD. Patients with craniofacial FD and GH excess are more prone to macrocephaly, and there is a significant linear correlation between serum GH levels and head circumference in patients

TABLE 4. Optic neuropathy and optic nerve decompression: indications and outcomes[a]

Patient no.	Age (yr)	Eye	Indication at preoperative examination	Postoperative examination findings	Outcome summary	Postoperative encasement (%)	Follow-up (yr)	Endocrinopathies
Interventional optic nerve decompression (n = 9 patients; 12 nerves)								
1	24	R	VF	Moderate: CV; abnormal funduscopic results	Improved vision	100	18	GH excess, PP
2	5	L	VF	Mild: VF, CV; abnormal funduscopic results	Improved vision	100	12	HT, PW, neonatal Cushing's syndrome
3	14	R	VF, decreased VA	Mild: VF	Improved vision	100	25	GH excess, PP
3	24	R	VF, decreased VA, CV	Mild: VF	Improved vision	100	15	GH excess, PP
4	11	R	ABC, VF: vascular occlusion	Normal examination results	Improved vision	100	7	PP
5	12	R	ABC, decreased VA: light perception	Severe: VF, decreased VA, CV; abnormal funduscopic results: finger counting	Slight improvement	100	10	PP, HT
5	12	L	ABC, decreased VA: minimal light perception	Severe: VF, decreased VA, CV; abnormal funduscopic results: light perception, finger counting at 3–4 ft	No improvement	100	10	PP, HT
6	11	L	VF, decreased VA, CV	Moderate: VF, decreased VA, CV; abnormal funduscopic results	No improvement	100	2	PP
7	12	R	VF, decreased VA	Mild: VF, decreased VA	No improvement	100	1.5	GH excess, PP
8	30	R	VF, decreased VA, CV, abnormal funduscopic results	Severe: VF, decreased VA, CV; abnormal funduscopic results	No improvement	100	4	GH excess, PP, PW
3	14	L	Decreased VA	Severe: VF, decreased VA, CV; abnormal funduscopic results	No improvement	100	25	GH excess, PP
9	12	R	Decreased VA	Severe: VF, decreased VA, CV; abnormal funduscopic results	Severe vision loss	100	6	GH excess
9	12	L	Decreased VA	Severe: VF, decreased VA, CV; abnormal funduscopic results	Severe vision loss	100	6	GH excess
Prophylactic optic nerve decompression (n = 4 patients; 6 nerves)								
10	6	R	OC narrowing, right eye proptosis	Normal examination results	Normal visual results	50–99	3	None
11	37	R	OC narrowing: normal	Normal examination results	Normal visual results	<50	2	None
11	37	L	OC narrowing: normal	Normal examination results	Normal visual results	<50	2	None
12	5	R	OC narrowing: normal	Normal examination results	Normal visual results	100	9	GH excess, PP, HT
12	5	L	OC narrowing: normal	Normal examination results	Normal visual results	100	9	GH excess, PP, HT
2	5	R	OC narrowing: normal	Severe: VF, decreased VA, CV; abnormal funduscopic results	Vision loss	100	11	HT, PW, neonatal Cushing's syndrome

[a] R, right; VF, visual field defect; CV, decreased color vision; GH, growth hormone; PP, precocious puberty; L, left; HT, hyperthyroid; PW, phosphate wasting; VA, visual acuity; ABC, aneurysmal bone cyst; OC, optic canal. Data for indications for surgery were obtained by patient report or records. Postoperative examinations were performed by a neuro-ophthalmologist at our institution. Postoperative encasement of optical nerves with FD bone was determined by a neuroradiologist at our institution and was taken from the most recent head computed tomographic examination.

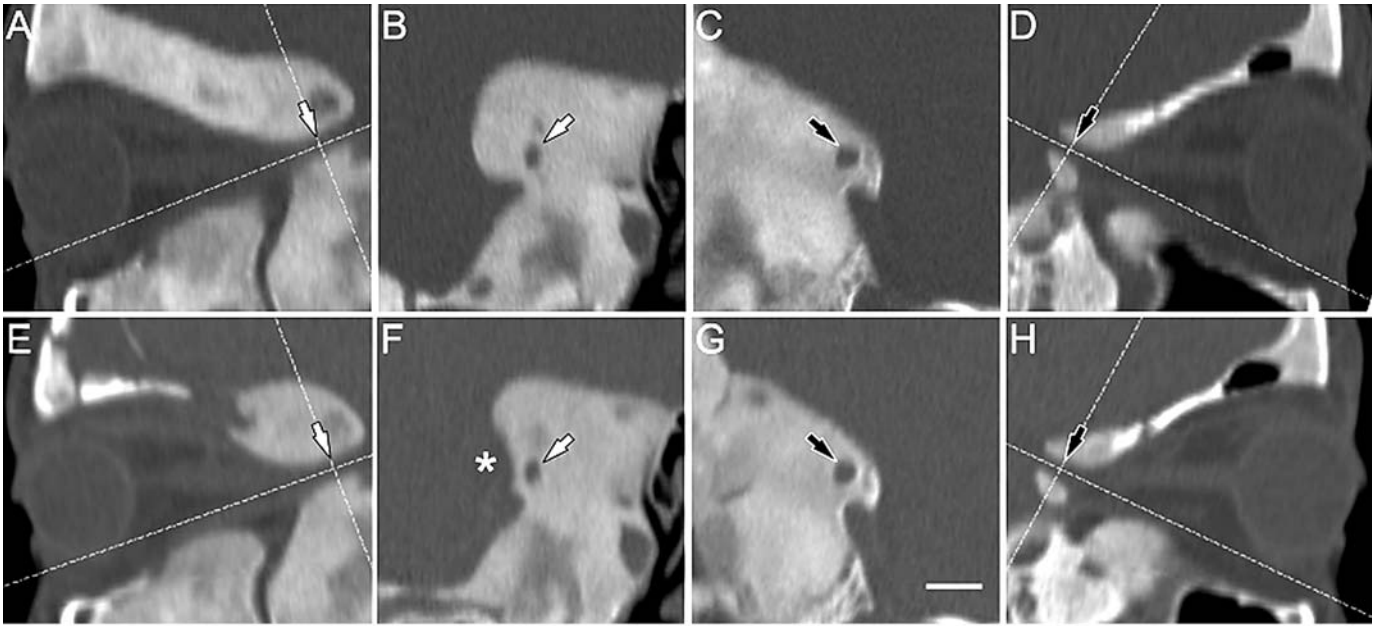

FIGURE 2. *Preoperative (*A–D*) and postoperative (*E–H*)CT scans obtained from a 12-year-old girl with MAS and GH excess (Patient 7,* Table 4*) who underwent optic nerve decompression for a mild visual field defect.* A–D, *preoperative images demonstrating full encasement of both nerves, with marked narrowing of the right optic canal (*A *and* B, white arrows*) as compared to the left (*C *and* D, black arrows*).* E *and* F, *postoperative images obtained 1.5 years after surgery demonstrating that some bone has been removed (*asterisk*), but the optic canal remains encased (*white arrows*).* G *and* H, *no change is noted on the left. There were essentially no differences in the pre- and postoperative neuro-ophthalmological examinations.* A, D, E, *and* H, *parasagittal oblique views along the plane of the optic canal.* B, C, F, *and* G, *coronal oblique views perpendicular to the long axis of the optic canal. Scale bar (*G*), 1 cm.*

with craniofacial FD and GH excess (2). Furthermore, there is evidence that optic nerve stretching resulting from bone expansion may be the mechanism of vision loss in some patients with GH excess and craniofacial FD (8). This is significant because GH excess is a potentially treatable disease (1, 18). Yet, early in the course of MAS, when intervention is perhaps most important to prevent long-term morbidity, GH excess is usually not clinically evident. Its presentation may be as subtle as normal stature in a young adult who experienced precocious puberty and should have short stature as a consequence of early growth plate closure. Therefore, referral for specific testing for GH excess is essential. This suggests that, in the absence of the comorbidities of GH excess, an ABC, or both, the baseline rate of optic neuropathy in craniofacial FD is quite low. With such a low rate of optic neuropathy, the risk of injury to the optic nerve during prophylactic optic nerve decompression becomes an even greater consideration.

Fifteen (83%) out of 18 patients who underwent optic nerve decompression still had 100% encasement of the optic nerve on postoperative cranial CT scans (*Fig. 2; Table 4*). It is not known whether this was the result of incomplete decompression or regrowth. Despite persistent (or recurrent) 100% encasement in these patients, only two out of 15 patients, both of whom had GH excess, experienced symptoms of optic neuropathy. This suggests that, even if FD of bone is removed from around the optic nerve, it is likely to recur, further questioning the prudence of decompression in the absence of symptoms.

It is possible that the low rate of optic neuropathy in the group is the result of referral bias because ours is a medically based treatment group. Against this argument is the fact that, as a group, this was a more severely affected group of patients with FD. The ratio of MAS to polyostotic FD to monostotic FD was 91:8:1, the relative inverse of a random group of patients with FD (6).

CONCLUSION

Complete encasement of the optic nerve in FD of the cranial base is common, but is not commonly associated with optic neuropathy. There does not seem to be an age-related progression to optic neuropathy in patients in whom the optic nerve is encased, suggesting that, in most cases, the condition is stable. The vast majority of cases of optic neuropathy are seen in patients with either GH excess, an ABC, or both. Risk factors for the development of ABCs are not known, but GH excess, which is seen in approximately 20% of the patients with MAS, is relatively easy to diagnose and is treatable. Patients with craniofacial FD should be screened for GH excess, and prophylactic decompression should be reserved for patients with objective signs of optic neuropathy.

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COMMENTS

The authors have presented an excellent retrospective review of their experience of more than 20 years in the management of patients with fibrous dysplasia of the cranial base. Clinical decision making in this group of patients is often difficult in terms of whether or not the optic nerves should be decompressed, when they should be decompressed, and how should they be decompressed. The authors' observations shed considerable light in these areas.

Importantly, they have demonstrated that, despite encasement of the optic nerves by dysplastic bone, the majority of patients do not develop symptoms of optic neuropathy and remain stable over time, except if there is an elevated growth hormone level or aneurysmal bone cyst. A cautionary note is raised in their results of six prophylactic optic nerve decompressions in asymptomatic patients. Although five out of six were intact postsurgically, one patient (17%) experienced blindness from the prophylactic procedure.

The authors fail to discuss their surgical technique for optic nerve decompression, but presumably this was via a transcraniotomy approach. Recently, with the advancement in endoscopic and endonasal approaches to the cranial base, we have had the opportunity to decompress two patients who had failed craniotomy procedures for optic nerve relief that were operated transnasally and endoscopically with excellent decompression. In experienced hands, the medial and inferior walls of the optic canal can be well decompressed with not only preservation, but also enhancement of deteriorating vision. Overall, the data presented in this report represent a significant approach in the management of optic neuropathy secondary to fibrous dysplasia.

Joseph C. Maroon
Pittsburgh, Pennsylvania

In this article, the authors are making recommendations about the treatment of optic neuropathy in association with fibrous dysplasia. The natural history data about optic neuropathy and encasement are invaluable, as this is one of the largest series of fibrous dysplasia with follow-up data.

However, the authors provide no details about the techniques of optic nerve decompression. What techniques were used for the decompression, and what methods were used to prevent optic nerve damage during the decompression? It is surprising that the postoperative computed tomographic scans after the optic nerve decompression still showed 100% bony encasement after the decompression. This strongly suggests that the decompression was inadequate and that the results of decompression could be markedly improved in such cases with better surgical technique. I think that asymptomatic patients must be followed with careful radiological and clinical examinations, and optic nerve decompression should be undertaken when there is evidence of either radiographic or clinical progression.

Laligam N. Sekhar
Seattle, Washington

This is a very interesting report on a relatively rare pathological condition. The authors have collected a large series of patients with a long follow-up period and concluded for the scarce value of a prophylactic optic nerve decompression to prevent visual deterioration. In my experience, the loss of vision that occurred in a few patients was not owing to progressive deterioration, but rather to an abrupt event, namely the expansion of a bone cyst in the proximity the optic pathways (generally the result of a spontaneous intracystic hemorrhage). Also, in our series, subjects with McCune-Albright syndrome tended to experience a more severe clinical course. However, the great majority of our patients showed relatively stable visual deficits for years, with an incidence of progression that diminished significantly after puberty. Consequently, I share the suggestion by the authors to refrain from the prophylactic treatment and consider their advice quite important for our colleagues faced with this rare disease.

Concezio Di Rocco
Rome, Italy

In a follow-up to a previous study of 67 optic nerves, the authors have expanded their retrospective series to include 104 patients. Their study included a review of all medical records, endocrine testing, cranial computed tomographic scans, and neuro-ophthalmological examination. In their previous study, they concluded that significant narrowing of the optic canal with fibrous dysplasia was not associated with optic neuropathy (1). This was an important study in that large individual experiences with fibrous dysplasia and the approach to decompression were varied and based more on personal experience than any true literature base. This was true in our own practice, in which we recommend prophylactic decompression based on the assumption that disease progression would result in optic neuropathy. In the current study, the authors demonstrate that, in the majority of cases, vision loss is associated with either growth hormone (GH) excess or the presence of an aneurysmal bone cyst. In 174 optic nerves reviewed in 104 patients, 93% had no evidence of optic neuropathy. They found no case of optic neuropathy in nerves less than 100% encased. Of the 107 optic nerves that were 100% encased, 88% exhibited no evidence of optic neuropathy. Additionally, there were no age differences between groups, indirectly suggesting that it is unlikely that there will be progression resulting in eventual compromise. Sixty-nine percent of the patients with optic neuropathy had either GH excess or an associated aneurysmal bone cyst. Their evidence suggests that, in the absence of the comorbidities of GH excess and/or an associated aneurysmal bone cyst, the baseline rate of optic neuropathy is low. The conclusion is that testing for GH excess and imaging to evaluate for the presence of an aneurysmal bone cyst is an essential component in the care of these patients. The current study establishes that optic nerve decompression should be performed in the presence of progressive optic neuropathy. In the absence of neuropathy, following patients electively may be a safer course of action given the potential compromise associated with surgical decompression.

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Michael L. Levy
San Diego, California

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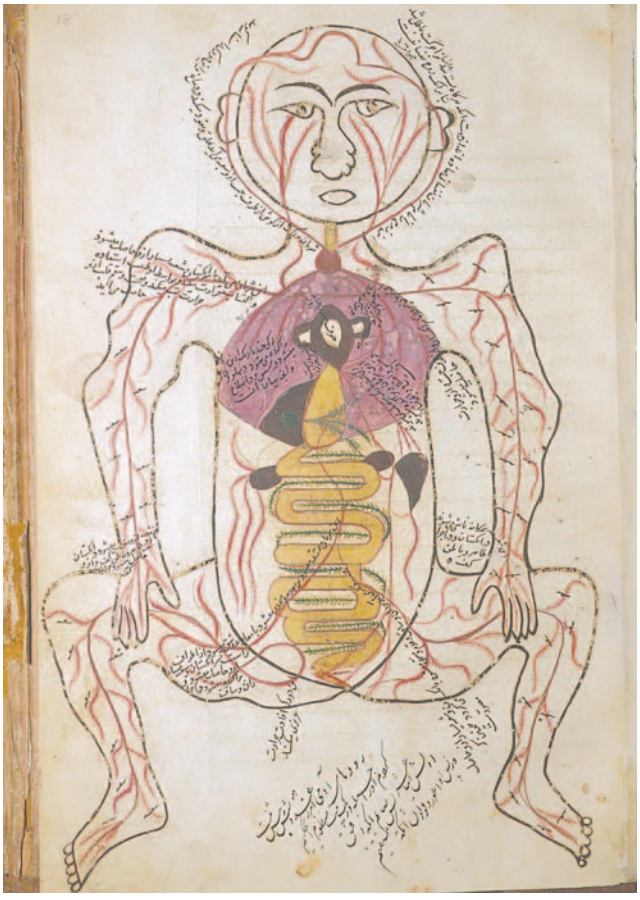

Mansur ibn Ilyas, ***Tashrih-i badan-i insan [Anatomy of the Human Body].*** Iran, ca. 1390. (Courtesy of the U.S. National Library of Medicine, National Institutes of Health, Bethesda, Maryland).

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association of Hearing Loss and Otologic Outcomes With Fibrous Dysplasia

Alison M. Boyce, MD; Carmen Brewer, PhD; Timothy R. DeKlotz, MD; Christopher K. Zalewski, PhD; Kelly A. King, AuD, PhD; Michael T. Collins, MD; H. Jeffrey Kim, MD

IMPORTANCE Fibrous dysplasia (FD) and McCune-Albright syndrome (MAS) are rare bone and endocrine disorders in which expansile fibro-osseous lesions result in deformity, pain, and functional impairment. The effect of FD on hearing and otologic function has not been established.

OBJECTIVES To characterize audiologic and otologic manifestations in a large cohort of individuals with FD/MAS and to investigate potential mechanisms of hearing loss.

DESIGN, SETTING, AND PARTICIPANTS In this natural history study, individuals with craniofacial FD seen at a clinical research center underwent clinical, biochemical, computed tomographic, audiologic, and otolaryngologic evaluations.

MAIN OUTCOMES AND MEASURES Clinical and radiologic features associated with hearing loss and otologic disease were evaluated. Conductive hearing loss was hypothesized to be associated with narrowing of the external auditory canal (EAC), FD involving the epitympanum, and FD crowding the ossicular chain. Sensorineural hearing loss was hypothesized to be associated with FD affecting the internal auditory canal (IAC) and otic capsule.

RESULTS Of the 130 study participants with craniofacial FD who were evaluated, 116 (89.2%) had FD that involved the temporal bone (median age, 19.6 years; range, 4.6-80.3 years; 64 female [55.2%]), whereas 14 (10.8%) had craniofacial FD that did not involve the temporal bone. Of the 183 ears with temporal bone FD, hearing loss was identified in 41 ears (22.4%) and was conductive in 27 (65.9%), sensorineural in 12 (29.3%), and mixed in 2 (4.9%). Hearing loss was mild and nonprogressive in most participants. Whereas EACs were narrower in ears with FD (mean difference [MD], 0.33 mm; 95% CI, 0.11-0.55 mm), this finding was associated with conductive hearing loss in only 4 participants. Fibrous dysplasia crowding of the ossicles was associated with conductive hearing loss (odds ratio [OR], 5.0; 95% CI, 2.1-11.6). The IAC length was not different between ears with and without FD (MD, −0.37; 95% CI, −0.95 to 0.211); however, canals were elongated in ears with sensorineural hearing loss (MD, −1.33; 95% CI, −2.60 to −0.07). Otic capsule involvement was noted in only 4 participants, 2 of whom had sensorineural hearing loss. Both MAS-associated growth hormone excess (OR, 3.1; 95% CI, 1.3-7.5) and neonatal hypercortisolism (OR, 11; 95% CI, 2.5-55) were associated with an increased risk of hearing loss.

CONCLUSIONS AND RELEVANCE Hearing loss in craniofacial FD is common and mild to moderate in most individuals. It typically arises from FD crowding of the ossicular chain and elongation of the IAC, whereas EAC stenosis and otic capsule invasion are less common causes. Individuals with craniofacial FD should undergo otolaryngologic evaluation and monitoring, including assessment to identify those with high-risk features.

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Supplemental content

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Fibrous dysplasia (FD) is an uncommon skeletal disorder in which normal bone and marrow are replaced with fibro-osseous tissue.[1] It arises from somatic mutations in *GNAS* (OMIM 139320) leading to constitutive activation of G_s G-coupled protein receptor signaling.[2] In the skeleton, these mutations impair differentiation of bone marrow stromal cells, resulting in cellular proliferation and formation of abnormal bone prone to expansion, deformity, and fracture.[1,3] Disease may occur in one bone (monostotic) or multiple bones (polyostotic) and may develop in isolation or in combination with café au lait skin macules and hyperfunctioning endocrinopathies, which include precocious puberty, hyperthyroidism, growth hormone excess, hypophosphatemia, and neonatal hypercortisolism.[4] The association of FD with 1 or more of these extraskeletal features is termed McCune-Albright syndrome (MAS).[3]

The temporal bone is frequently affected by FD and has been associated with a variety of otologic and audiologic conditions, including hearing loss, pain, auditory canal stenosis, and cholesteotoma.[5-7] However, the prevalence, spectrum, and natural history of ear-related disease have not been well characterized, and the mechanisms of hearing loss have not been established. A transgenic FD mouse model demonstrated severe and progressive hearing loss attributable to bony overgrowth around the ossicles and otic capsule[8]; however, it is not known whether this model replicates human disease. The purposes of this study are to characterize audiologic and otologic manifestations in a large cohort of individuals with FD/MAS and to investigate potential mechanisms of hearing loss.

Key Points

Question What are the potential mechanisms of hearing loss in individuals with fibrous dysplasia?

Findings In this natural history study of 130 individuals with craniofacial fibrous dysplasia, conductive hearing loss was frequently associated with deformity of the epitympanum and rarely with external auditory canal stenosis, whereas sensorineural hearing loss was most often associated with elongation of the internal auditory canal and rarely with otic capsule involvement. Endocrine features, including growth hormone excess and neonatal hypercortisolism, were associated with hearing loss.

Meaning Individuals with fibrous dysplasia should undergo clinical and radiologic evaluation to identify high-risk features for audio-otologic dysfunction.

Methods

Individuals with FD/MAS were evaluated as part of a longstanding natural history study at the National Institutes of Health.[9] All participants underwent evaluation at the National Institutes of Health Clinical Center, including history and physical examination, biochemical testing, skeletal imaging, and medical treatment for MAS-associated endocrinopathies. Participants were diagnosed with FD/MAS based on previously established clinical guidelines.[3] The protocol was approved by the institutional review board of the National Institute of Dental and Craniofacial Research, and all participants and/or their guardians gave written informed consent or assent.

Participants with craniofacial FD underwent comprehensive otolaryngologic and audiologic evaluation. Standard audiometric measures, including air- and bone-conduction pure-tone thresholds for 250 to 8000 Hz and 226-Hz tympanometry, were conducted. Clinically significant hearing loss was determined using established definitions[10] by a 4-frequency pure-tone average (0.5/1/2/4 kHz) greater than 20 dB hearing level (HL), and degree of hearing loss was further categorized as mild (21-40 dB HL), moderate (41-70 dB HL), severe (71-90 dB HL), and profound (>90 dB HL). Type of hearing loss was determined using a 3-frequency pure-tone average (0.5/1/2 kHz) and was classified as conductive (difference between 3-frequency pure-tone average by air and bone conduction >10 dB and normal hearing for bone conduction and hearing loss by air conduction), sensorineural (difference between 3-frequency pure-tone average by air and bone conduction <10 dB and hearing loss by air and bone conduction), or mixed (difference between 3-frequency pure-tone average by air and bone conduction >10 dB and hearing loss by both air and bone conduction). In addition, ears with normal hearing by air conduction were classified as subclinical conductive when there was a mean air bone gap greater than 10 dB. For participants with multiple audiograms, the most recent, most complete audiogram was used for evaluation of cross-sectional data.

Head computed tomographic scans with a section width of 3 mm or smaller were evaluated in the axial and coronal reconstructed planes. Tomographs were evaluated for factors selected a priori as potential causes of hearing loss. Conductive hearing loss was hypothesized as potentially associated with deformities of the outer and middle ears, including narrowing of the external auditory canal (EAC), FD involvement of the epitympanum, and FD crowding the ossicular chain. Sensorineural hearing loss was hypothesized as potentially associated with FD that affected inner ear structures, including the internal auditory canal (IAC) and the otic capsule. Dimensions of the IACs and EACs were recorded by a single reader (A.M.B.), as were specific areas of FD involvement within the temporal bone (H.J.K.). Readers were masked to auditory status at the time of computed tomography evaluation.

Comparisons were made between ears affected and unaffected by temporal bone FD and between ears affected and unaffected by hearing loss, as indicated. For participants followed up longitudinally, clinical and radiologic data from the initial and most recent evaluations were analyzed for progression. Statistics and figures were prepared using GraphPad Prism 6 for Windows, version 6.02 (GraphPad Software Inc). Comparisons between groups were made using effect size metrics and 95% CIs. Data are presented as mean, SD, and SE.

Results

Participant Characteristics

A total of 130 individuals with craniofacial FD were identified. Of these, 116 (89.2%) had FD that involved the temporal

Table. Characteristics of Participants With Temporal Bone FD

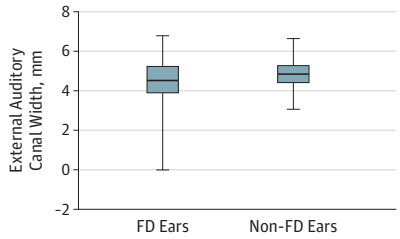
Characteristic	Finding (N = 116)[a]
Female	64 (55.2)
Age, median (range), y	19.6 (4.6-80.3)
Length of follow-up, mean (range), y[b]	6.2 (0.9-15.2)
Polyostotic FD	110 (94.8)
MAS-associated endocrinopathies	96 (82.8)
Precocious puberty	71 (61.2)
Hyperthyroidism	45 (38.8)
Growth hormone excess	28 (24.1)
Hypophosphatemia	42 (36.2)
Neonatal hypercortisolism	8 (6.9)
Symptoms	
Skull pain	45 (38.8)
Tinnitus	21 (18.1)
Aural fullness	12 (10.3)
Otalgia	4 (3.4)
Vertigo	7 (6.0)

Abbreviations: FD, fibrous dysplasia; MAS, McCune-Albright syndrome.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

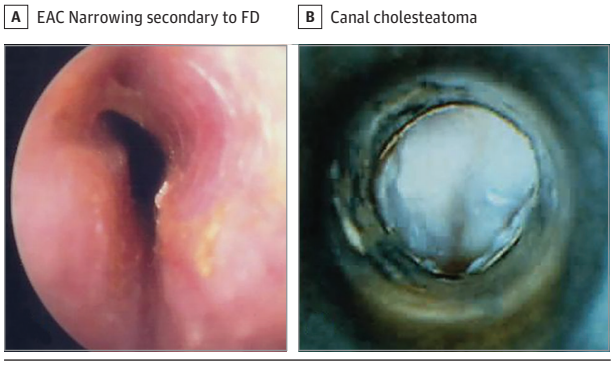
[b] Longitudinal data available for 72 participants.

Figure 1. Bony External Auditory Canal Axial Diameter as Measured by Computed Tomography in Normal Ears and Those Affected by Temporal Bone Fibrous Dysplasia (FD)



Horizontal line in box indicates median; box, interquartile range; and whiskers, range.

Figure 2. External Auditory Canal (EAC) and Canal Cholesteatoma in Ears With Fibrous Dysplasia (FD)



bone (median age, 19.6 years; range, 4.6-80.3 years; 64 female [55.2%]), whereas 14 (10.8%) had craniofacial FD that did not involve the temporal bone. Temporal bone FD was bilateral in 67 individuals and unilateral in 49 individuals, affecting 183 total ears. A total of 77 ears were unaffected by temporal bone FD. Two individuals (1 with unilateral temporal bone FD and 1 without temporal bone FD) were eliminated from the analyses because of the presence of sinusitis at the time of evaluation.

Participant characteristics and clinical symptoms are given in the **Table**. Most participants had polyostotic FD and MAS-associated endocrinopathies. The most common concern was skull pain, whereas otologic symptoms were uncommon.

Audiologic Findings

Hearing loss was identified in 41 of 183 ears (22.4%) with temporal bone FD. Conductive hearing loss was most frequent, affecting 27 ears (65.9%). Of these, there was a subclinical conductive component in 13, and the hearing loss was mild in 11, moderate in 2, and profound in 1 ear. Sensorineural hearing loss affected 12 ears (29.3%), which was mild in 10 and moderate in 2 ears. Mixed hearing loss occurred in 2 ears, including 1 with a moderate and 1 with a severe degree of hearing loss.

Longitudinal audiologic data were available for 72 participants, with 112 ears affected by temporal bone FD for a mean period of 6.2 years (SD, 4.4 years; SE, 0.5 years; range, 0.9-15.2 years). The categorical degree of hearing loss worsened in 13 ears, improved in 14 ears, and remained unchanged in 85 ears during the follow-up period.

Hearing loss was detected in 7 of 77 ears (9.1%) in participants with craniofacial FD without temporal bone involvement, which was significantly less prevalent compared with ears with temporal bone FD (41 of 183 ears [22.4%]) (odds ratio [OR], 3.2; 95% CI, 1.4-7.7). This hearing loss included mild unilateral conductive hearing loss of unclear origin in an 11-year-old participant. Sensorineural hearing loss occurred in 6 ears: 3 in elderly participants (>80 years of age) with moderate to severe hearing loss and 3 in participants aged 53, 22, and 19 years with mild hearing loss of unclear origin.

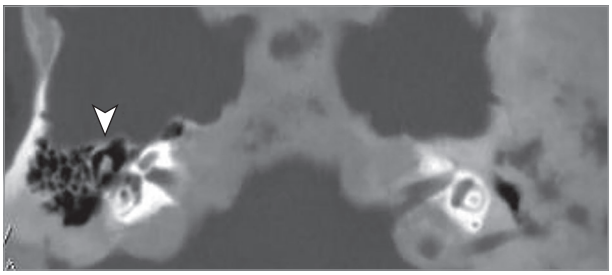
Imaging Results

External Auditory Canal

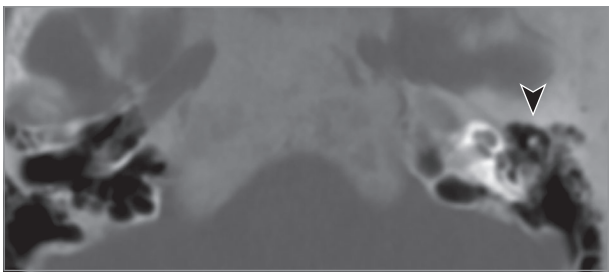
The EAC diameters were compared between the 183 ears affected by temporal bone FD and the 77 ears that were unaffected by temporal bone FD. Ears affected by temporal bone FD were significantly narrower (mean, 4.49 mm [SD, 10.9 mm; SE, 0.08 mm] vs 4.82 mm [SD, 0.69 mm; SE, 0.08 mm]; mean difference [MD], 0.33 mm; 95% CI, 0.11-0.55 mm) and variable among participants (**Figure 1**). No difference was found between EAC diameter and the presence of conductive hearing loss at any frequency (mean EAC diameter, 4.69 mm [SD, 1.13 mm; SE, 0.21 mm] for participants with conductive hearing loss vs 4.52 mm [SD, 1.03 mm; SE, 0.08 mm] for participants without conductive hearing loss; MD, 0.17 mm; 95% CI, −0.63 to 0.30 mm). On clinical evaluation, severe EAC stenosis (**Figure 2**) was believed to be directly contributory to conductive hearing loss in 4 participants, all of whom underwent canalplasty. Two of these participants had improvement in hearing at 4 years postoperatively and no recurrence of EAC

Figure 3. Axial Computed Tomography of the Epitympanum

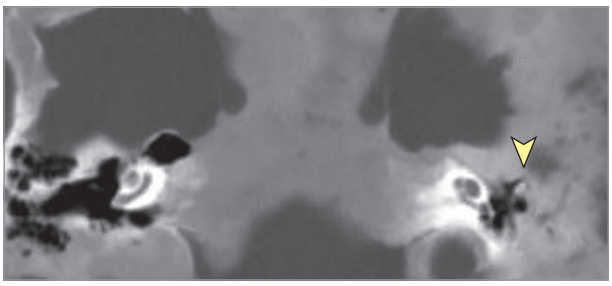
A Normal epitympanum



B FD surrounding the epitympanum



C Epitympanum with FD and crowding the ossicular chain



A, White arrowhead indicates normal epitympanum. B, Black arrowhead indicates fibrous dysplasia (FD) involvement surrounding the epitympanum. C, Yellow arrowhead indicates an epitympanum that is involved with FD and is crowding the ossicular chain.

stenosis at 11 years postoperatively. A third participant underwent canalplasty with removal of cholesteotoma (Figure 2B). Postoperatively, his conductive hearing loss improved from severe to mild and remained stable after 3 years. One participant underwent another operation 2 years after her initial canalplasty because of postoperative FD regrowth. She continues to have normal hearing 5 years after her second operation.

Epitympanum

Fibrous dysplasia involvement of the epitympanum was common, affecting 150 of 183 ears (82.0%) with temporal bone FD. In 86 (57.3%) of those ears, FD was limited to the area surrounding the ossicles, whereas 64 (42.7%) had crowding of the ossicular chain (**Figure 3**). No correlation was found between the presence of FD surrounding the epitympanum and the presence of hearing loss; however, ossicular crowding was associated with conductive hearing loss (OR, 5.0; 95% CI, 2.1-11.6). There was no association between ossicular crowding and sensorineural hearing loss (OR, 2.1; 95% CI, 0.61-7.1). Although the presence of sensorineural hearing loss was nearly double among those with ossicular crowding and the true difference could be as big as 7 times, the precision of the estimate was low and the lower bound crossed the null effect value. Differences in air conduction pure-tone thresholds were observed at both low and high frequencies (eFigure, A in the Supplement), whereas there were no differences in bone conduction thresholds between participants with and without ossicular crowding (eFigure, B in the Supplement).

Tympanometry demonstrated that ears with epitympanic FD had stiffened middle ear systems, as evidenced by lower peak admittance levels (median, 0.4 cm^3 [95% CI, 0.4-0.5 cm^3] for participants with epitympanic FD vs 0.8 cm^3 [95% CI, 0.6-0.8 cm^3] for participants without epitympanic FD; absolute median difference, 0.4 cm^3; 95% CI of difference, 0.2-0.4 cm^3). Peak admittance data were not included for ears with middle ear effusion (n = 2), pressure equalization tubes (n = 6), or tympanic membrane perforation (n = 1).

Internal Auditory Canal

No difference was found in IAC length from the fundus to the porous in ears with and without temporal bone FD (mean, 11.05 mm [SD, 2.32 mm; SE, 0.17 mm] for ears with temporal bone FD vs 10.68 mm [SD, 1.77 mm; SE, 0.20 mm] for ears without temporal bone FD; MD, −0.37 mm; 95% CI, −0.95 to 0.21 mm). When ears affected by sensorineural hearing loss were analyzed separately, these IACs were found to be elongated compared with ears with temporal bone FD and normal hearing or conductive hearing loss (mean, 12.28 mm [SD, 2.88 mm; SE, 0.77 mm] for ears with sensorineural hearing loss vs 10.91 mm [SD, 2.25 mm; SD, 0.71 mm] for ears without sensorineural hearing loss; MD, −1.33 mm; 95% CI, −2.60 to −0.07 mm) (**Figure 4**). No difference was found in IAC width in ears with and without FD (mean, 5.31 mm [SD, 1.42 mm; SE, 0.10 mm] vs 5.29 mm [SD, 1.11 mm; SE, 0.12 mm]; MD, −0.02 mm; 95% CI, −0.37 to 0.33 mm) or those with and without hearing loss (mean, 5.34 mm [SD, 0.96 mm; SE, 0.21 mm] vs 5.30 mm [SD, 1.35 mm; SE, 0.09 mm]; MD, −0.04 mm; 95% CI, −0.65 to 0.56 mm).

Otic Capsule

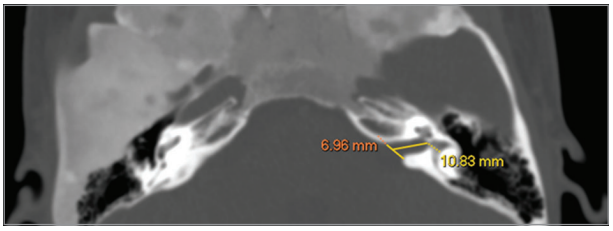
The area surrounding the otic capsule was a frequent site for FD involvement, affecting 120 of 183 ears (65.6%) with temporal bone FD. No association was found between sensorineural hearing loss and the presence of FD in this area (OR, 0.79; 95% CI, 0.32-1.89). Extension of FD to the membranous labyrinth, such as the semicircular canals and cochlea, was rare, occurring in only 4 ears; however, 2 of these had sensorineural hearing loss and 2 had normal hearing.

Clinical Features and Hearing Loss

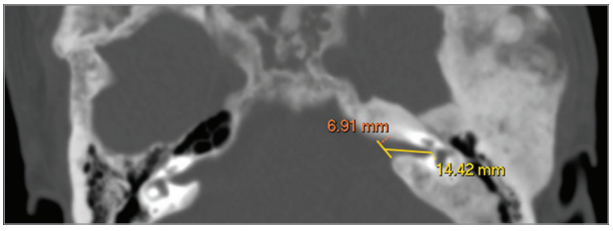
No statistical difference in age was found between participants with and without hearing loss (median, 19.3 years [95% CI, 15.7-22.8 years] vs 20.6 years [95% CI, 16.8-21.1 years]; actual median difference, −0.2 years; 95% CI of median difference, −5.1 to 1.8 years). Hearing loss was associated with MAS-associated growth hormone excess, which

Figure 4. Axial Computed Tomography of the Internal Auditory Canal (IAC)

A Patient with normal hearing



B Patient with temporal FD and sensorineural hearing loss



Axial computed tomographs show the technique for measuring IAC width. A, Normal left IAC is shown in a participant with normal hearing. B, Elongated and distorted IAC in a participant with temporal fibrous dysplasia (FD) and sensorineural hearing loss.

affected 12 of 29 participants (41.4%) with hearing loss and 16 of 87 participants (18.4%) without hearing loss (OR, 3.1; 95% CI, 1.3-7.5). Hearing loss was also associated with a history of MAS-associated neonatal hypercortisolism, which affected 6 of 29 participants (20.7%) with hearing loss and 2 of 87 participants (2.3%) without hearing loss (OR, 11; 95% CI, 2.5-55). No important associations were found between hearing loss and other MAS-associated endocrinopathies.

Discussion

Data from this largest series of individuals with FD to date demonstrate that the causes of audio-otologic dysfunction are multifactorial and largely determined by the extent and location of skeletal involvement. Conductive hearing loss was most commonly associated with FD that involves the bony epitympanum, leading to crowding of the ossicular chain. This finding is supported functionally by tympanometry studies, which demonstrated decreased tympanic membrane mobility in ears with epitympanic involvement. Stenosis of the EAC was a less common cause of conductive hearing loss, accounting for only 15% of cases and affecting only 2% of the total cohort. Sensorineural hearing loss was most commonly associated with elongation of the IAC and rarely with invasion of the otic capsule and membranous labyrinth. Understanding the association between these radiographic features and hearing loss will allow clinicians to more accurately identify at-risk patients and ensure monitoring in those with higher-risk features.

These findings provide insight into potential mechanisms of hearing loss in individuals with FD. Differences in hearing sensitivity were observed for the low and high frequencies by air conduction but not by bone conduction in participants with and without ossicular crowding in the epitympanum. This finding suggests a potential mechanism in which stiffening of the ossicles may lead to low-frequency hearing loss, whereas high-frequency hearing loss may result from mass effect on the ossicles related to the surrounding FD. The association of sensorineural hearing loss with IAC length (but not width) suggests that stretching of its contents may be a potential mechanism of hearing loss in FD. Of interest, this mechanism is analogous to the development of optic neuropathy, which occurs rarely in patients with craniofacial FD, resulting from elongation of the optic canal with traction on the optic nerve.[11] Future investigations into the anatomical and functional effects of FD on the IAC and its contents could include advanced imaging techniques with 3-dimensional reconstruction and auditory brainstem response testing.

Our findings are consistent with those of the ColI(2,3)+/Rs1+ mouse model, in which invasive FD formation developed. In this transgenic mouse model, observed progressive hearing loss was attributable to FD-like lesions that surrounded the ossicular chain and obliterated the oval and round window of the cochlea. Because the organ of Corti showed no abnormality in histologic and immunocytochemical findings, the progressive hearing loss in this model was conductive in nature rather than sensorineural.[8]

The extensive phenotyping performed in this FD/MAS natural history study also offers an opportunity to identify clinical features associated with audio-otologic disease. This study was the first, to our knowledge, to demonstrate an increased risk of hearing loss in patients with MAS-associated growth hormone excess. Overproduction of growth hormone is presumed to drive expansion of craniofacial FD and has also been linked with optic neuropathy[12,13] and postsurgical regrowth after craniofacial procedures.[14] The correlation between hearing loss and neonatal hypercortisolism is another novel finding; however, the cause of this association is unclear. Of interest, a history of neonatal hypercortisolism has been linked to developmental abnormalities in patients with MAS and, in particular, with disorders of speech and language.[15] Further investigation is needed to determine whether hearing deficits are a contributor to developmental delays in this population.

Findings from this study expand on the relatively limited audio-otologic literature in FD.[16-18] The largest previous series was a retrospective review of 66 patients referred for otolaryngologic evaluation at tertiary care centers that reported a higher prevalence of otologic symptoms and hearing loss compared with our series.[5] Most in that series were managed nonsurgically, and those authors concluded that conservative management with serial evaluation and imaging review is warranted in most patients. Findings from our series expand on this approach by identifying specific radiologic and clinical features that place patients at increased risk for disease.

Strengths and Limitations

Strengths of this study include large participant numbers for this rare disease, making it the largest series in the literature to date. Participants underwent extensive clinical phenotyping and longitudinal follow-up as part of a longstanding natural history study. Because participants were evaluated systematically as part of a research protocol, the prevalence and spectrum of audio-otologic disease were less likely to be affected by referral bias compared with clinical series. Limitations include the inherent weakness in retrospective reviews. In addition, because of the paucity of procedures performed in our cohort, this series was unable to define surgical indications in patients with FD-related audio-otologic disease.

Conclusions

Hearing loss in craniofacial FD is common and typically mild and nonprogressive. The mechanisms of hearing loss are multifactorial based on the location and extent of FD lesions. Deformities of the epitympanum and IAC are most frequently associated with conductive and sensorineural hearing loss, respectively, whereas less common associations include EAC stenosis and otic capsule involvement. Patients with craniofacial FD should undergo evaluation and serial monitoring for audio-otologic disease, including clinical and radiologic evaluation to identify those with high-risk features.

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Study concept and design: Boyce, Brewer, DeKlotz, Zalewski, Collins, Kim.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Boyce, Brewer, Collins, Kim.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Boyce.
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Clinical guidelines for the management of craniofacial fibrous dysplasia

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From International Meeting on Fibrous Dysplasia/McCune-Albright Syndrome and Cherubism: Best Clinical Practice and Future Research
Bethesda, MD, USA. 3-5 October 2010

Abstract

Fibrous dysplasia (FD) is a non-malignant condition caused by post-zygotic, activating mutations of the *GNAS* gene that results in inhibition of the differentiation and proliferation of bone-forming stromal cells and leads to the replacement of normal bone and marrow by fibrous tissue and woven bone. The phenotype is variable and may be isolated to a single skeletal site or multiple sites and sometimes is associated with extraskeletal manifestations in the skin and/or endocrine organs (McCune-Albright syndrome). The clinical behavior and progression of FD may also vary, thereby making the management of this condition difficult with few established clinical guidelines. This paper provides a clinically-focused comprehensive description of craniofacial FD, its natural progression, the components of the diagnostic evaluation and the multi-disciplinary management, and considerations for future research.

Definition

Fibrous dysplasia (FD) is a non-malignant condition in which normal bone and marrow are replaced by fibrous tissue and haphazardly distributed woven bone [1,2]. Patients may exhibit involvement of one bone (monostotic FD; MFD), multiple bones (polyostotic FD; PFD) or they may have McCune-Albright syndrome (MAS), which has been classically defined by the triad of PFD, café-au-lait skin macules and endocrinopathies, including among others, precocious puberty [3]. FD is caused by somatic activating mutations in the α subunit of the stimulatory G protein encoded by the gene *GNAS* [4,5]. A related disorder, cherubism, is manifest by expansile, multiloculated, radiolucent fibro-osseous lesions with multiple giant cells located bilaterally and symmetrically in the jaws. Cherubism is genetically distinct from FD and will be discussed elsewhere in the Proceedings of this meeting.

Prevalence

MFD is reported to be the most common manifestation of the disease, in some references it is estimated to occur four times more often than PFD [6]. However, in other series PFD is reported to be more common than MFD [7,8]. While the prevalence of MFD is probably greater than PFD, in none of the studies that define the relative prevalence of MFD versus PFD have the subjects undergone thorough skeletal and/or endocrine screening to determine the full extent of the skeletal and/or endocrine involvement. The most common locations are the craniofacial bones, proximal femur, and rib [2,8-11]. In MFD, the zygomatic-maxillary complex is reported to be the region most commonly involved (Figure 1A&B) [12]. In the less prevalent PFD and MAS, the craniofacial region is involved in 90% of the cases and the anterior cranial base is involved in over 95% of cases. (Figure 2) [13]. Depending on the type and location of FD, the signs and symptoms vary and include facial deformity and asymmetry, vision changes, hearing impairment, nasal congestion and/or obstruction, pain, paresthesia, and malocclusion. Many patients are asymptomatic and the diagnosis is made when a family member, friend or health care provider who has not seen the patient for a period of time notices asymmetry, or there is an incidental abnormality noted on dental or panoramic x-rays or on a head and neck computed tomogram (CT).

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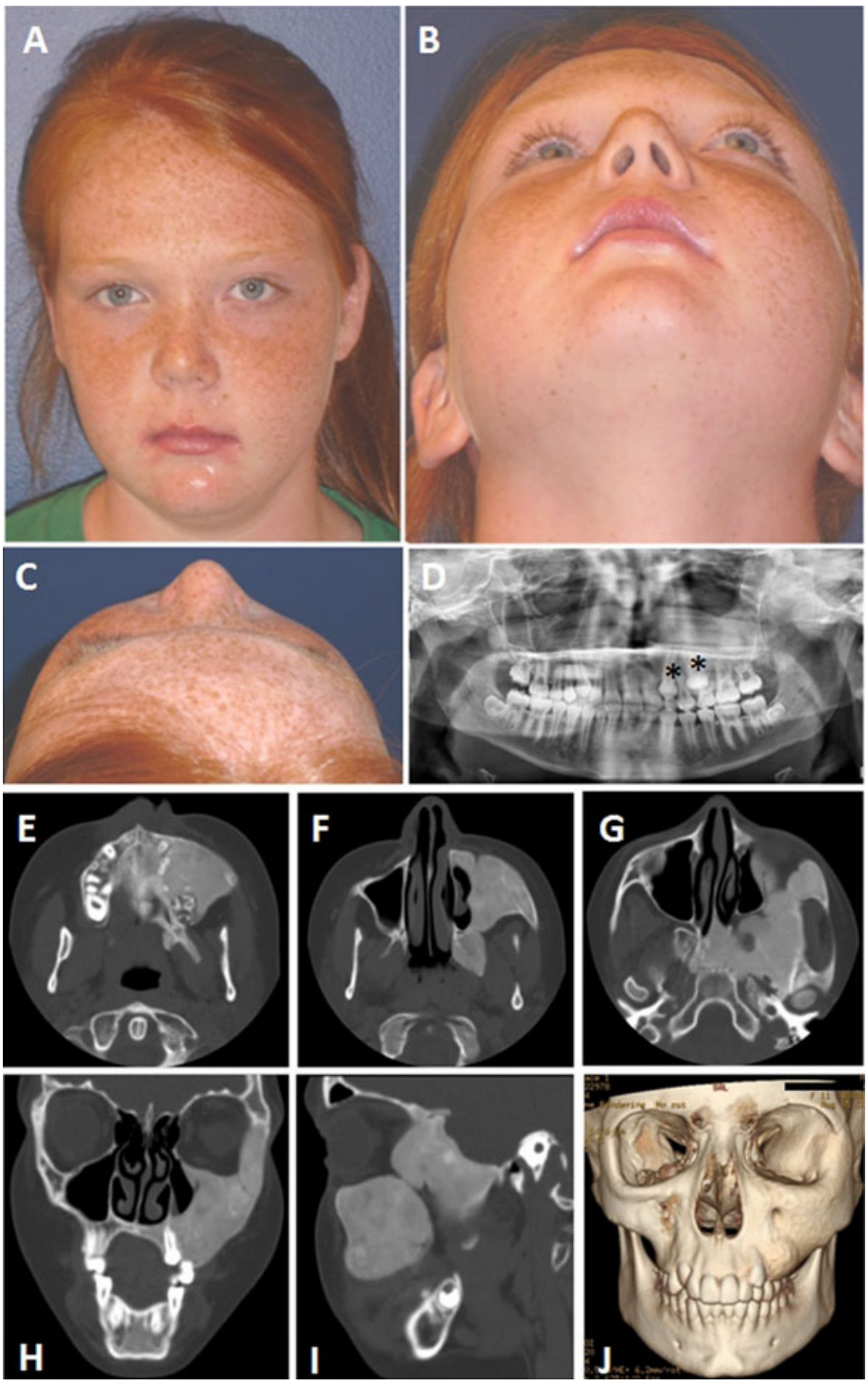

Figure 1 An 11-year old female with monostotic fibrous dysplasia of the left zygomatic-maxillary region. A-C) Clinical photographs demonstrating the appearance. The lesion was quiescent and asymptomatic. It had grown slowly over a period of years. D) Her dentist noted delayed eruption of her teeth (*) on that side as well as mild facial asymmetry and obtained the panorex that identified the lesion. E-I) CT images demonstrate the pathognomonic appearance of FD for her age, a homogenous, "ground-glass" lesion. J) The reconstructed CT image gives a sense of the three dimensional shape of the lesion that accounts for the clinical appearance.

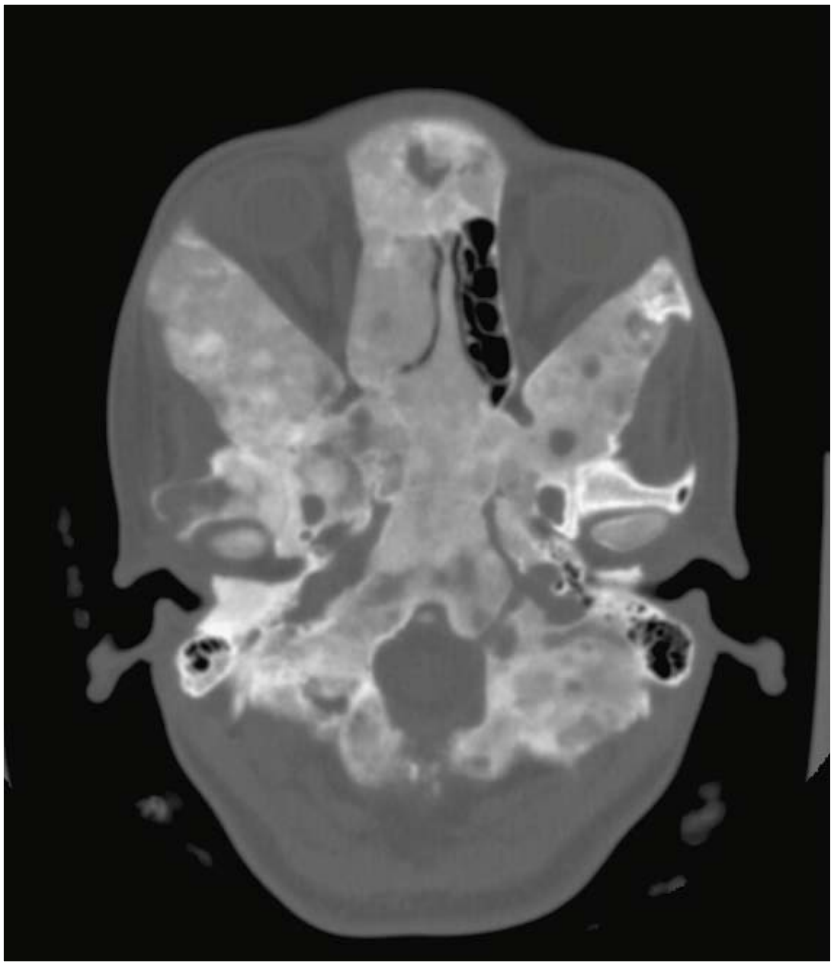

Figure 2 Extensive fibrous dysplasia involvement of the cranial base in a patient with MAS. In patients with PFD or MAS, the anterior cranial base is involved in 95% of the cases as seen in this CT image.

Natural progression and clinical behavior

FD most commonly behaves as a slow and indolent growing mass lesion. The facial deformity and distortion of adjacent structures such as optic nerve, eye/globe, nasal airway, cranial nerve VII, middle ear ossicles, and teeth are gradual and insidious. Uncommonly, in young children and pre-pubertal adolescents, the lesions may demonstrate rapid growth, cortical bone expansion and displacement of adjacent structures such as the eye and the teeth. In some patients, rapid growth is associated with other pathological lesions such as aneurysmal bone cysts (ABC) or mucoceles (Figure 3) [13-15], or more rarely with malignant transformation. Malignant change to osteosarcoma or other forms of sarcoma has been reported to occur in less than 1% of cases of FD [16-22].

When rapid enlargement occurs, adjacent vital structures, such as the optic nerve, globe and auditory canal/structures and nasal airway may be invaded or compressed, resulting in functional deficits. For these reasons, some authors have advocated aggressive surgical resection to avoid potential blindness or hearing loss [23-26]. Rapid enlargement of FD in the nasal bones, maxilla or mandibular symphysis may result in airway obstruction by obliteration of the nasal cavity or by posterior displacement of the tongue. However, it has recently been demonstrated that such aggressive behavior with rapid expansion is the exception and that a conservative expectant approach is more prudent [13,14,27].

In MFD and PFD, progression of the lesions appears to taper off as the patients approach puberty (defined as skeletal maturity throughout this article) and beyond. Although continued active disease and symptoms into adulthood are uncommon, they have been reported [28-30]. In addition, in the NIH Screening and Natural History Study of Fibrous Dysplasia (SNHFD, protocol 98-D-0145) has documented persistent active disease and pain into adulthood in some patients. Based on >25 years of observation at the NIH, it appears that MFD,

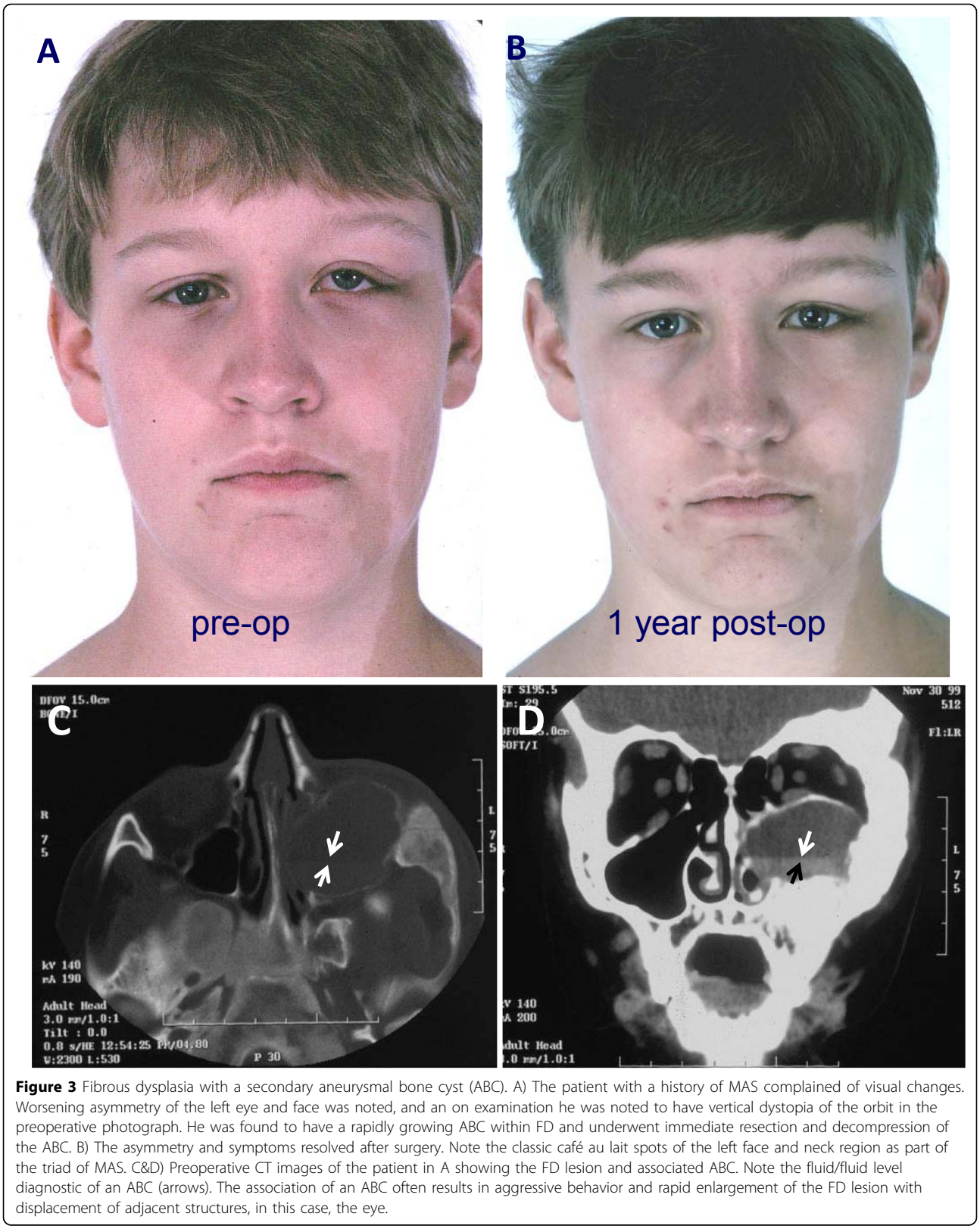

Figure 3 Fibrous dysplasia with a secondary aneurysmal bone cyst (ABC). A) The patient with a history of MAS complained of visual changes. Worsening asymmetry of the left eye and face was noted, and an on examination he was noted to have vertical dystopia of the orbit in the preoperative photograph. He was found to have a rapidly growing ABC within FD and underwent immediate resection and decompression of the ABC. B) The asymmetry and symptoms resolved after surgery. Note the classic café au lait spots of the left face and neck region as part of the triad of MAS. C&D) Preoperative CT images of the patient in A showing the FD lesion and associated ABC. Note the fluid/fluid level diagnostic of an ABC (arrows). The association of an ABC often results in aggressive behavior and rapid enlargement of the FD lesion with displacement of adjacent structures, in this case, the eye.

does not progress to PFD and neither progress to MAS [31].

In MAS, while growth of the lesions may also diminish after puberty, the overall degree of bony enlargement and deformity is often more severe and disfiguring than in patients with PFD. Data in the literature and observations by the NIH SNHFD indicate that the most severe deformities and symptoms occur in patients who have poorly controlled growth hormone excess [32-34]. It is recommended, therefore, that growth hormone excess in patients with PFD and MAS be aggressively managed.

In a retrospective study of 266 serial bone scans from 66 patients followed for up to 32 years in patients with extensive PFD or MAS, Hart et al. demonstrated that 90% of FD lesions, regardless of the site, were present prior to 15 years of age [31]. In the craniofacial region, 90% of all the lesions were detectable by bone scan by age 3.4, and no new lesions in the craniofacial region are very reported beyond the age of 10.

Diagnosis and work-up

Medical history and examination

A thorough history and physical examination are necessary to determine the extent of disease and to determine whether the FD is isolated or one of multiple lesions associated with PFD or MAS. Documentation of the onset and types of symptoms, presence of functional impairments and duration are imperative. Inquiries should include onset of menarche in females (to rule-out precocious puberty), other endocrine abnormalities or pathologies (such as hyperthyroidism, pituitary abnormalities, and renal phosphate wasting), growth abnormalities (review of growth charts), and history of fractures (to rule-out the presence of other FD lesions in the extremities) as well as the presence of skin lesions (café- aulait lesions). These questions are particularly critical in young patients where underlying endocrine abnormalities may not have been detected and aggressive management is warranted. If there are any positive responses to the above inquiries, a referral to an endocrinologist is strongly recommended to rule out PFD or MAS. A skeletal survey or bone scan may be indicated if there is a suspicion of PFD or MAS, particularly in a patient that is not skeletally mature. Additional FD lesions beyond the craniofacial region require further evaluation by an orthopedic surgeon.

If the symptoms include rapid expansion, new onset of pain, visual change or loss, hearing change or loss, evidence of airway obstruction, new onset of paresthesia or numbness, a referral to a surgical specialist should be made immediately. Appropriate specialists that may be consulted include: neurosurgeons, craniofacial surgeons, oral & maxillofacial surgeons, otolaryngologists, neuro-ophthalmologists, audiologists and dentists, depending on the site of involvement or symptoms. In institutions where a craniofacial anomalies team is available, this may be an alternative referral that would assist the patient in further comprehensive evaluation.

Imaging

CT imaging is recommended to define the anatomy of individual lesions and to establish the extent of disease. A standard craniofacial CT, without contrast and with slice thickness no greater than 3.75 mm (from top of the head to the thyroid region), is used to evaluate for the presence of FD in the skull base and facial bones. Historically, plain films of the craniofacial region were used but because of the overlapping of adjacent structures, involvement of the skull base was often underreported. For similar reasons, plain radiographs are not recommended for diagnostic purposes for cranial or facial lesions. Dental radiographs (i.e. panorex and dental films) or a cone-beam CT are appropriate to examine and help manage lesions around the dentition. Depending on the site of involvement, the appropriate referrals should be made for further analysis.

The most common radiographic characteristic of craniofacial FD is a “ground-glass” appearance with a thin cortex and without distinct borders [35]. In an ongoing study at NIH [36], it was demonstrated that the typical characteristics of FD on CT and the natural radiographic progression may vary from a “ground-glass” or homogenous appearance to a mixed radio-dense/radio-lucent lesion as the patient ages (Figure 4). In pre-pubertal patients with PFD or MAS, the lesions most often appear as homogenous, radio-dense lesions on CT. As these patients enter the second decade of life, the FD lesions progress to a mixed appearance, which stabilizes in adulthood but does not resume a homogenous appearance. While the change to a mixed radiographic appearance alone does not require further biopsy or investigation, we recommend careful monitoring and intermittent craniofacial CT during the pubertal phase of the young patient. This period of change in CT appearance coincides with case reports of increased activity of the FD lesions either through rapid growth, worsening facial asymmetry, malignant transformation, or association with other pathologic, radiolucent lesions such as an ABC and accelerated expansion [15]. Additionally, in our collective experience, there have been young patients who have the clinical and histologic diagnosis of a monostotic fibro-osseous lesion that are G_s mutation negative, yet demonstrate a rapidly enlarging and predominantly multi-loculated radiolucent appearance on CT and not the typical indolent growth. The exact pathophysiologic mechanism and its relationship to the variable genotype, i.e. is this a false negative gene test or another entity, has yet to be determined. If the patient is experiencing new onset of symptoms or rapid enlargement at *any* age, an

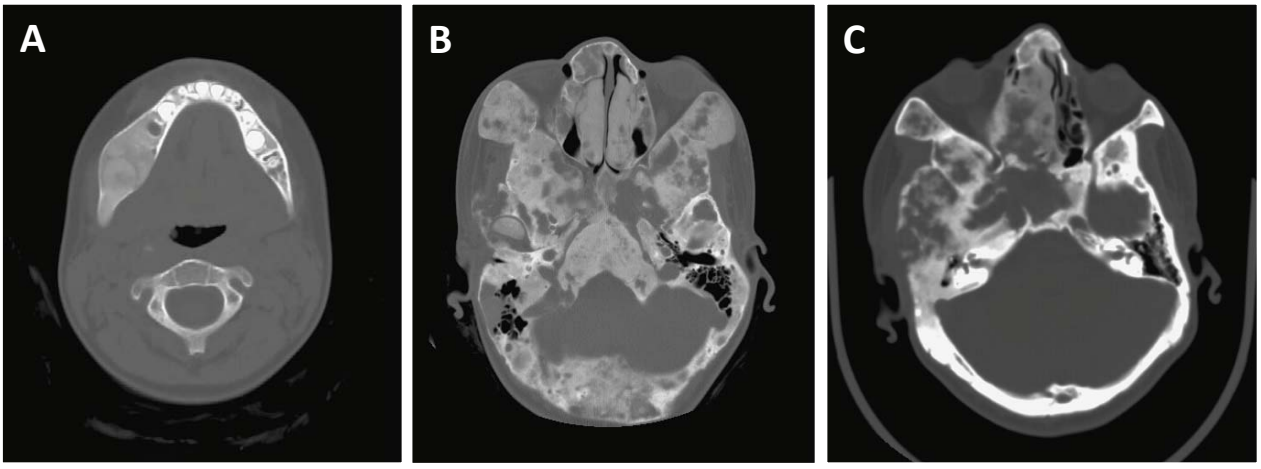

Figure 4 Variations in CT appearance of fibrous dysplasia based on age. A) FD in the young patient most often appears as homogenous, radiodense lesions often described as having a ground glass appearance on CT. B) As these patients enter adolescence, the FD lesions progress to a mixed appearance which stabilizes in adulthood (C) but does not necessarily resume a homogenous appearance. This may explain the numerous radiographic descriptions of FD in the literature such as "ground-glass", "pagetoid", "lytic", and "cystic".

updated CT is recommended as well as an immediate referral to the appropriate specialist for further investigation and management.

Biopsy

A bone biopsy, by the appropriate surgical specialist, should be obtained to confirm the diagnosis of FD, if the site is amenable to biopsy. Unfortunately, the histology does not predict the biological behavior of these lesions [37,38]. Biopsy of FD does not specifically induce growth of the lesion. However FD lesions may be quite vascular and bleeding can be brisk. The surgeon should be prepared to deal with this. If the lesion is quiescent or asymptomatic, and/or in the cranial base, a biopsy may not be possible or necessary. History, clinical examination and the classic radiographic presentation are often adequate to establish the diagnosis of FD.

Management by anatomic site and involvement

Facial bones

Asymmetry and swelling are the most common complaints when FD is found in the bones of the facial skeleton. Secondary deformities due to slow growing FD include vertical dystopia (difference in the vertical position of the eyes), proptosis, frontal bossing, facial and jaw asymmetries or canting. The degree of facial deformity varies, but those with MAS are the most severely affected, particularly when associated with untreated or inadequately treated growth hormone excess (Figure 5 & 6).

The diagnosis and management of facial lesions is at least in part based on the patient's age and stage of skeletal maturity i.e. pediatric versus adult (skeletally mature). In the pediatric population, of all the patients who present for evaluation of facial swelling and asymmetry, more than half of all jaw tumors encountered are of mesenchymal cell lineage, and of these tumors nearly 50% are fibro-osseous lesions, a significant proportion of which are FD [37,39]. Thus, FD must be high on the differential diagnosis for children with facial swelling and asymmetry. The management of FD in young and older patients is dictated by the clinical and biological behavior of the lesion, as the histology does not provide reliable prognostic or predictive information. There are currently no biomarkers to predict the behavior of these fibro-osseous lesions [37]. This is particularly concerning in pediatric patients because of the potential for active growth, malignant transformation and association with other tumors.

The FD lesions of the face may be described as quiescent (stable with no growth), non-aggressive (slow growing), or aggressive (rapid growth +/- pain, paresthesia, pathologic fracture, malignant transformation, association with a secondary lesion). In the case of a quiescent FD lesion in which the patient does not complain of facial deformity, observation and monitoring for changes is an acceptable treatment modality. Annual evaluations may be adequate. The patient's concerns and symptoms, clinical assessment including sensory nerve testing in the region of involvement, photographs, and facial CT should be obtained at each visit. An annual CT may be necessary for the first 2 years; however, the interval may be lengthened based on the clinical findings. Surgical contouring by a maxillofacial or craniofacial surgeon is indicated if the patient is bothered by facial disfigurement. While complete resection may be possible in monostotic lesions, it is unlikely to be possible in PFD or MAS), and

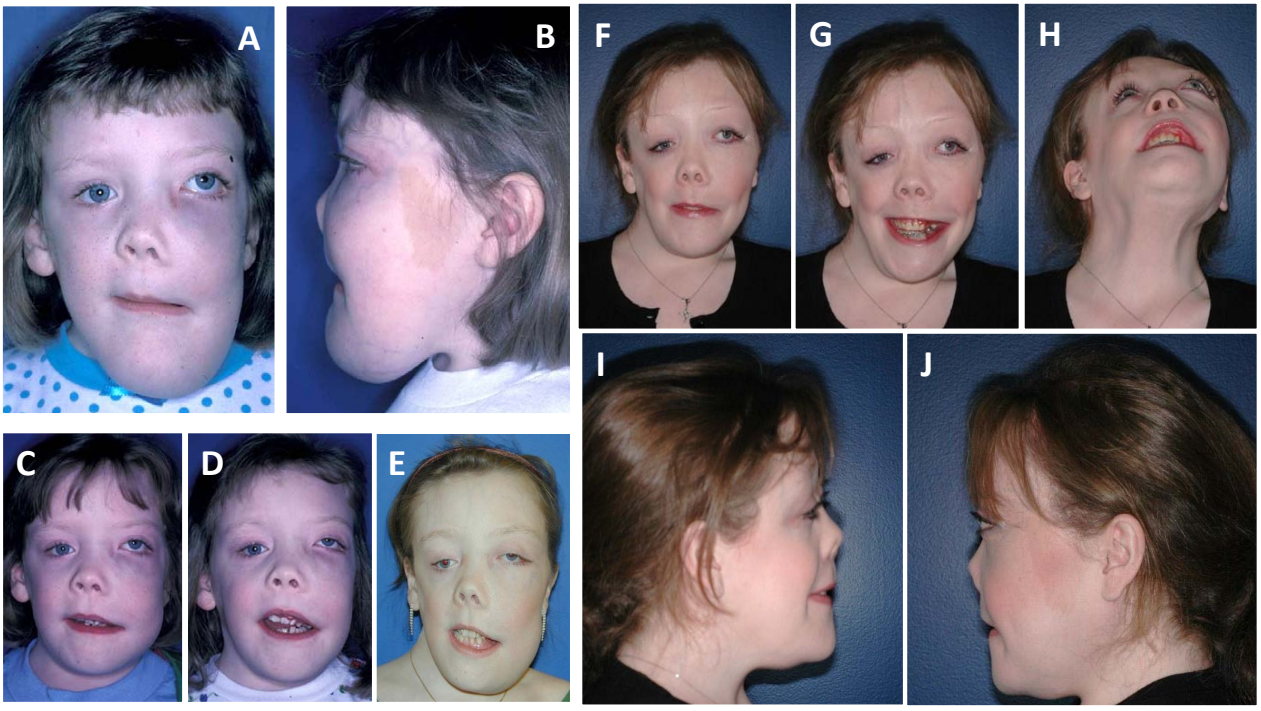

Figure 5 Serial images of a woman who presented at 9-year old with MAS and extensive fibrous dysplasia complicated by growth hormone excess. A&B) At presentation, she had a history of failure to thrive, airway obstruction, and was blind in the left eye at the time of presentation. Due to the airway obstruction in the nose and displacement of the tongue by the mandibular lesions, she underwent extensive contouring of the nasal bones, maxilla, and mandible with excellent results and patent airway. C-E) Over time, this patient's lesions continued to grow but eventually stabilized by age 17 years. F-J) The patient 5 years after the second surgery. She has improved facial contours and symmetry though she continues to have pronounced orbital asymmetry. Her airway remains stable. She graduated magna cum laude from college.F) The 3D model of the patient demonstrates the enlargement of the maxilla, mandible, and blockage of the nasal cavity by the FD at age 17 years. G) The left mandible was significantly contoured to more normal proportions. H) Aggressive contouring of the left maxilla as well as the opening of the occluded nasal cavity. I) The nasal trumpet (green) was necessary to maintain a patent passageway while healing from surgery. J&K) Intraoperative view of the surgically removed fibrous dysplastic bone.

the surgeon must weigh the reconstruction options that will provide the patient with the best outcome as well as preserve the function of adjacent nerves and structures. These patients may also require orthognathic surgery to correct a concurrent malocclusion or facial/dental canting [40]. There is no documented contraindication for orthognathic surgery so long as the lesions are quiescent. Bone healing appears to be normal with conventional rigid fixation [40]. Regular follow-up with the surgeon is necessary to determine that there is no recurrence and further deformity.

In patients with non-aggressive but active FD, it is ideal to wait until the lesion becomes quiescent and the patient has reached skeletal maturity before performing an operation. However, in cases where the patient's psychosocial development may be impaired due to the facial deformity, surgical contouring and/or resection may be warranted. The patient and family must be aware of the potential for regrowth if the lesion cannot be resected completely, which is often the case. In cases of PFD or MAS where the disease is extensive, the lesions are often not resectable. Repeat surgical contouring and extensive debulking may be necessary to achieve acceptable facial proportions [41]. In the future, improvement in CT imaging and software will allow for accurate surgical simulation and intraoperative navigational tools may guide the surgeon throughout the contouring. Advanced CT software is useful for superimposition of pre- and post-operative images. These can then be compared to follow-up CT scans to determine stability of the result or the presence of regrowth. Despite these new imaging technologies, there is no therapy or technology that can predict and/or prevent regrowth.

Patients with aggressive and rapidly expanding FD, occasionally complain of new onset pain or paresthesia/anesthesia [15]. Based on the site of involvement, the patient may also report visual disturbances, epiphora, impaired hearing, nasal congestion or obstruction, sinus congestion and pain and malocclusion. We recommend immediate evaluation by a maxillofacial surgeon, ENT, or craniofacial surgeon and CT imaging. The etiology of this change in behavior may not be readily identified but

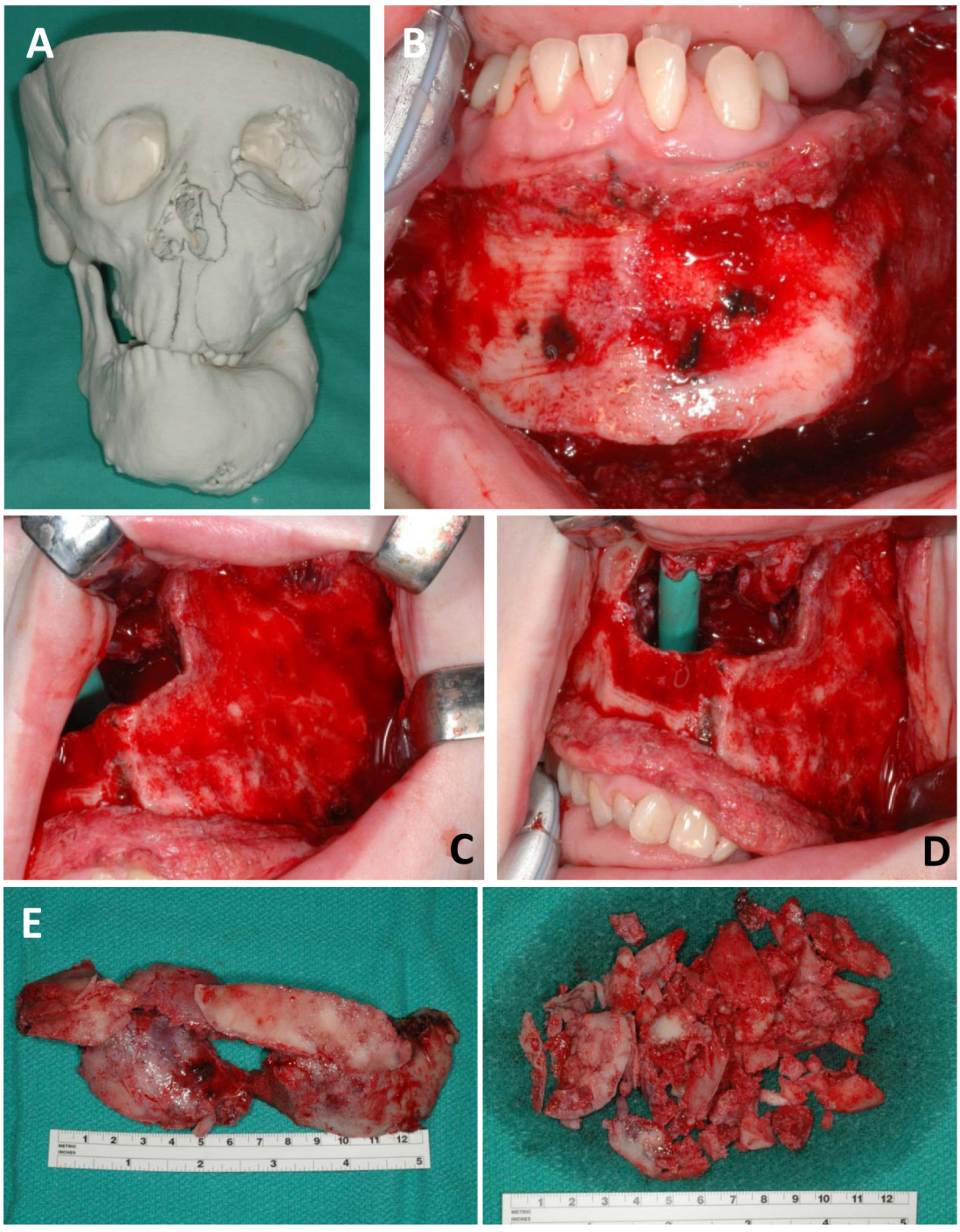

Figure 6 Serial images of the surgical approach to the woman from Figure 5 who presented at 9-year old with MAS and extensive fibrous dysplasia complicated by growth hormone excess. A) The 3D model of the patient demonstrates the enlargement of the maxilla, mandible, and blockage of the nasal cavity by the FD at age 17 years. B) The left mandible was significantly contoured to more normal proportions. C) Aggressive contouring of the left maxilla as well as the opening of the occluded nasal cavity. D) The nasal trumpet (green) was necessary to maintain a patent passageway while healing from surgery. E&F) Intraoperative view of the surgically removed fibrous dysplastic bone.

documented causes include: associated expansile lesions such as ABC or mucocele, malignant transformation, and osteomyelitis. A biopsy of the area of growth is necessary prior to surgical management. Treatment may range from contour resection to en bloc resection depending on the diagnosis.

In cases of an associated lesion, the management is based on that associated lesion e.g. an ABC with FD would warrant curettage of the ABC and contouring of the underlying FD.

Malignant transformation of FD has been reported in less than 1% of cases of FD [16-22]. Typically the malignancy is a sarcomatous lesion, most often osteosarcoma but fibrosarcoma, chondrosarcoma, and malignant fibrohistiocytoma have also been reported [16,20,28,42-45]. The diagnosis may be difficult, particularly in cases of low-grade osteosarcoma [46,47]. In such cases, immunohistochemical analysis with MDM2 and CDK4 may assist in distinguishing FD from a malignancy as a malignancies will often express MDM2 or CDK4 while FD will not [48,49]. The treatment is based on the management of the malignancy and resection with adequate margins is necessary.

Osteomyelitis must be treated with prolonged antibiotic therapy and consultation with an infectious disease specialist. The limited literature and our collective experience indicate that osteomyelitis in the setting of FD is difficult to diagnose and to successfully treat [50-54]. We have managed patients that developed osteomyelitis of the jaws after attempts at exposure and orthodontic movement of impacted teeth. It may resolve with prolonged antibiotic treatment and pain management, however en bloc resection of the FD lesion may be required for refractory pain and persistent infection.

Sinuses

The sinuses may be affected by FD, with the most frequent site being the sphenoid sinus, followed by the ethmoid and maxillary sinuses (Figure 7) [55]. This is not surprising, as the anterior cranial base is often affected in patients with craniofacial PFD [13]. The entire sinus can be completely obliterated by FD, yet surprisingly the incidence of sinusitis is not greater than the general population in these patients. This may be explained by the loss of air space and Schneiderian membrane in an obliterated sinus and the elimination of a source of infection. Patients typically complain of nasal congestion (>34% of those with symptoms and sinus involvement), headaches or facial pain, recurrent sinusitis, and hyposmia. This appears to be associated with FD in the inferior turbinate and the subsequent hypertrophy. There appears to be a correlation between nasal congestion and hyposmia and the severity of disease, but a history of sinusitis and facial pain/headaches does not correlate with the amount of

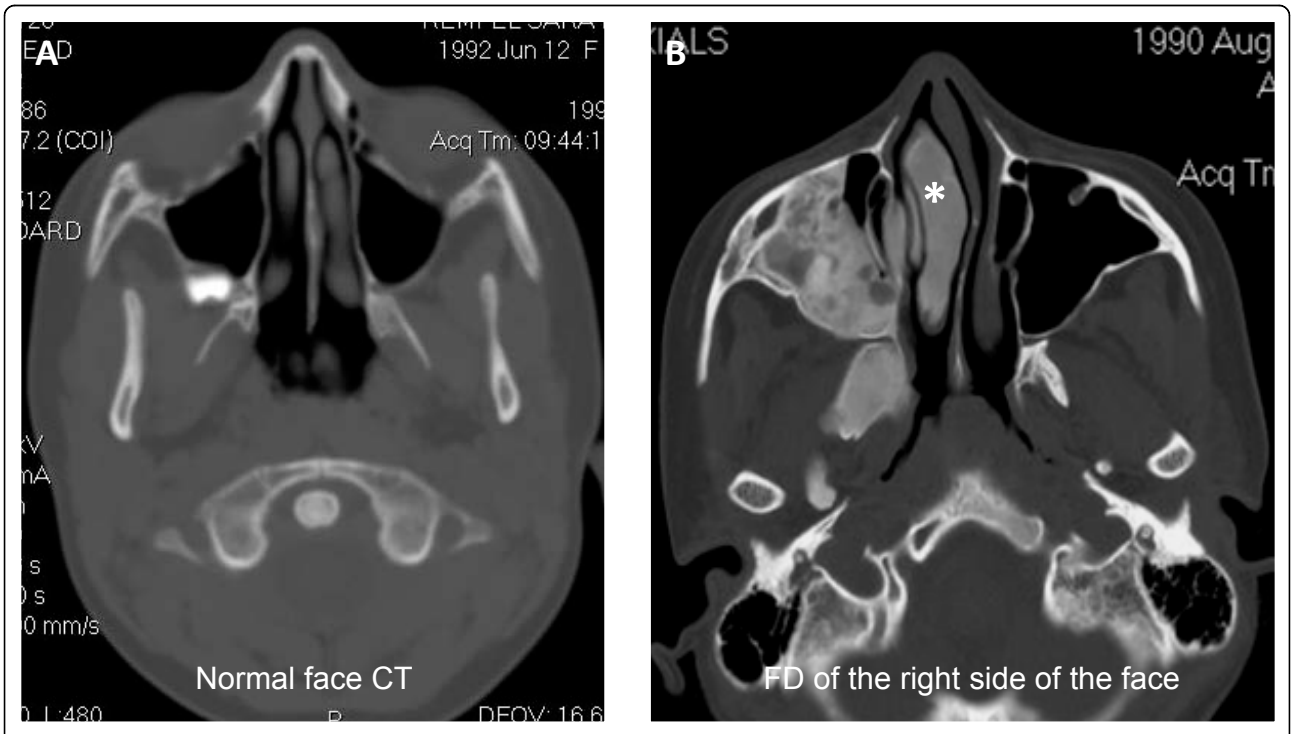

Figure 7 Fibrous dysplasia involving the right maxillary sinus and turbinate. A) Normal facial CT without any FD for comparison. B) FD in the right maxilla and extension into the maxillary sinus. There is also FD involvement of the right turbinate (*) that may explain the patient's nasal congestion.

craniofacial disease [55]. The findings by DeKlotz and Kim also note that growth hormone excess is associated with more significant involvement of the sinonasal region [55].

The management of sinus and nasal congestion includes nasal saline spray, nasal steroid spray, antihistamines for those with seasonal allergies, and antibiotics for suspected bacterial sinus infections. Consultation with an otolaryngologist may be necessary for persistent congestion and chronic sinus infections. Though there is very little literature on the effectiveness of sinus surgery in patients with FD sinus disease and sinus obliteration, if surgery is indicated, we recommend waiting until the adjacent FD is quiescent and the patient is at least in the late teens and skeletally mature to minimize the possibility of regrowth and necessity for re-treatment. Endoscopic sinus surgery with and without image-guided systems has become a popular approach [56-58], although it may be necessary to combine endoscopy with a traditional external approach [59,60]. The extent of resection should be based on the location of the pathological bone and its proximity to important sinus structures, as radical or complete resection may not be necessary or possible. The effectiveness of endoscopic surgery for FD is undetermined as sinus surgery is not commonly done in patients with FD.

The association of other expansile lesions such as a mucocele or ABC with sinus FD may result in rapid growth of the combined lesion [61,62]. This is particularly concerning in areas adjacent to the skull base and brain such as the sphenoid, ethmoid, and frontal sinuses where access may be limited. The symptoms depend on the adjacent involved structures such as the eye, optic nerve, crista galli, and brain. A referral to a multidisciplinary skull base surgery center is necessary for further evaluation and treatment.

Teeth

The dental variations in FD and the management of dental problems in patients with FD are poorly characterized. Due to the lack of information, the dental community is wary of treating patients with FD or MAS out of concern for potential post-procedure complications and exacerbation of the FD lesions around the teeth [63].

Akintoye et al [64] examined 32 patients with craniofacial FD that were enrolled in the SNHFD Study. Twenty-three patients had PFD/MAS and 9 had monostotic disease; this population reflected the NIH study population with more extensive disease. In this study, 41% of the patients had dental anomalies in general, and 28% of the patients had the dental anomaly within FD bone. The most common anomalies included: tooth rotation,

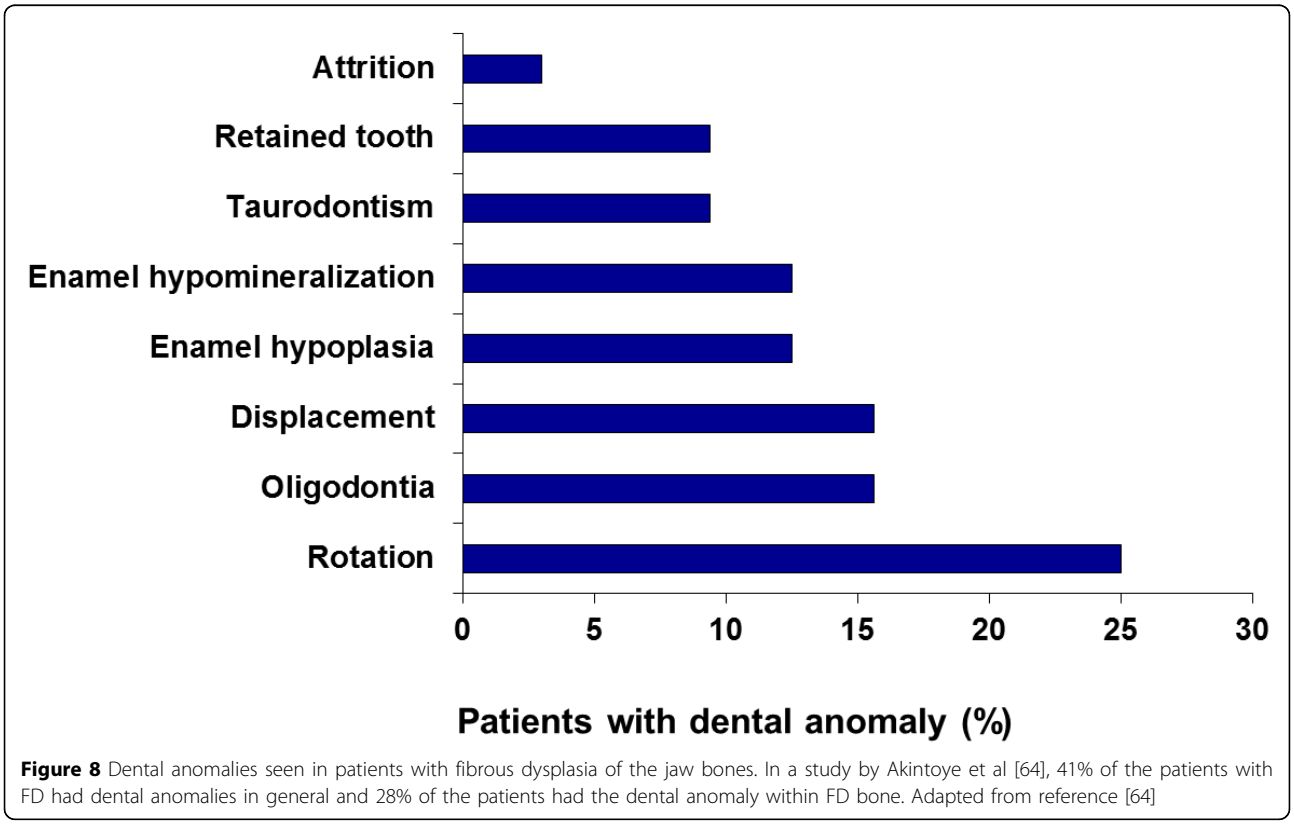

Figure 8 Dental anomalies seen in patients with fibrous dysplasia of the jaw bones. In a study by Akintoye et al [64], 41% of the patients with FD had dental anomalies in general and 28% of the patients had the dental anomaly within FD bone. Adapted from reference [64]

oligodontia, displacement, enamel hypoplasia, enamel hypomineralization, taurodontism, retained deciduous teeth, and attrition (Figure 8). There was no correlation between any endocrine dysfunction or renal phosphate wasting and enamel hypoplasia or hypomineralization, attrition, or any of the other tooth anomalies. However, taurodontism, a condition noted on dental radiographs characterized by enlargement of the pulp chamber in multi-rooted teeth, has been described in patients with syndromes including growth hormone excess [65,66] but never in FD/MAS. Taurodontism was noted only in the FD patients that had 1 or more endocrinopathies. While taurodontism does not require special dental care, it may be an indicator of an underlying endocrinopathy associated with MAS.

The caries index scores were higher among FD patients (Table 1). This may be attributed to the increased enamel hypoplasia and hypomineralization or the limited dental care these patients receive. There were no histological abnormalities in the extracted wisdom teeth that may explain the increased caries index scores. We recommend more frequent dental visits, every 3-4 months. Additionally, no patients reported any complications or exacerbation of their FD lesions after dental restorations, tooth extractions, orthodontic therapy, odontoma removal, maxillary cyst removal, or biopsy of the jaws. Among the 10 patients that received orthodontic therapy, the duration of treatment appeared somewhat longer than conventional cases (2-4 years in duration), the results were less than satisfactory, and there was relapse. We recommend careful monitoring of the post-orthodontic results in patients with FD. Despite the extensive disease in and around the dentition in some of the patients, the arch form was predominantly maintained without significant displacement of the teeth as compared to other benign growths.

While this may describe the natural progression of most FD, there is clearly a subset of patients that have the clinical and histologic diagnosis of FD that have rapid growth of the facial lesions, radiolucent changes on CT, and the displacement of teeth from the natural arch form. While some of these lesions have tested $G_s\alpha$ mutation negative, many patients in this subset have not been genetically characterized to determine if the absence of the $G_s\alpha$ mutation in the presence of a fibro-osseous lesion increases the risk of aggressive behavior and aberrant growth. Further studies are necessary to discern the implications of the mutation or lack of the mutation.

Table 1

	Caries Index	
	Fibrous dysplasia DFT scores	Normal DMFT values*
4-17 years	2.9	1.7
≥18 years	9.6	6.6

*W.H.O country oral health profile-USA DMFT

For patients with missing teeth, dental endosseous implants may be considered [67]. Bone healing and integration of the implants occurs, though it may be slower and the quality of bone is consistent with grade 3 or 4 bone as the cortex is often thin or nonexistent. In a reported case of a 32-year old female with MAS, successful integration and loading of dental implants in the maxilla and mandible occurred. The maxillomandibular lesions had been quiescent for 3 years. The dental implants were at least 15 mm in length and were functional after 5 years. The literature is limited, and it is unclear whether there is an increased risk of implant failure. There is also the concern that osteomyelitis may occur in the setting of a failed implant. If implant treatment is considered, we recommend that the implant be placed once growth of the FD lesion has subsided. Additionally, we would recommend following the principles of implant placement and place the dental implants after a young patient has completed growth to avoid submerged implants and revision of the prosthesis [68].

Skull base disease

Orbit/optic nerve/sphenoid bone

Common findings associated with PFD around the eye include proptosis, dystopia, and hypertelorism due to the involvement of the frontal, sphenoid, and ethmoid regions [30,69]. Less common findings include: optic neuropathy, strabismus, lid closure problems, nasolacrimal duct obstruction and tearing, trigeminal neuralgia and muscle palsy with skull base involvement [70,71] (FitzGibbon, unpublished data). There has been significant controversy regarding the management of FD of the sphenoid bones that encase the optic nerve, particularly in patients whose vision is normal (Figure 9). Clinicians have assumed that such encasement seen on CT will cause blindness because of the proximity and compression of the optic nerve by FD, and because of reported cases of acute loss of vision. In one study it was reported that vision loss was the most common neurologic complication in this disease [72]. With such concerns in mind, prophylactic decompression of the optic nerve ("unroofing") has been recommended by many surgeons [23-26]. Unfortunately, decompression may result in no improvement of vision (reported in 5-33% of cases), or worse postoperative blindness. In addition the abnormal bone tends to grow back in most cases. The first case-control study was conducted by Lee et al [13] to evaluate a cohort of patients with extensive cranial base FD, and determined that observation with regular ophthalmologic examinations in patients with asymptomatic encasement was a reasonable treatment option and optic nerve decompression was not warranted. Though there was statistically significant narrowing of the optic

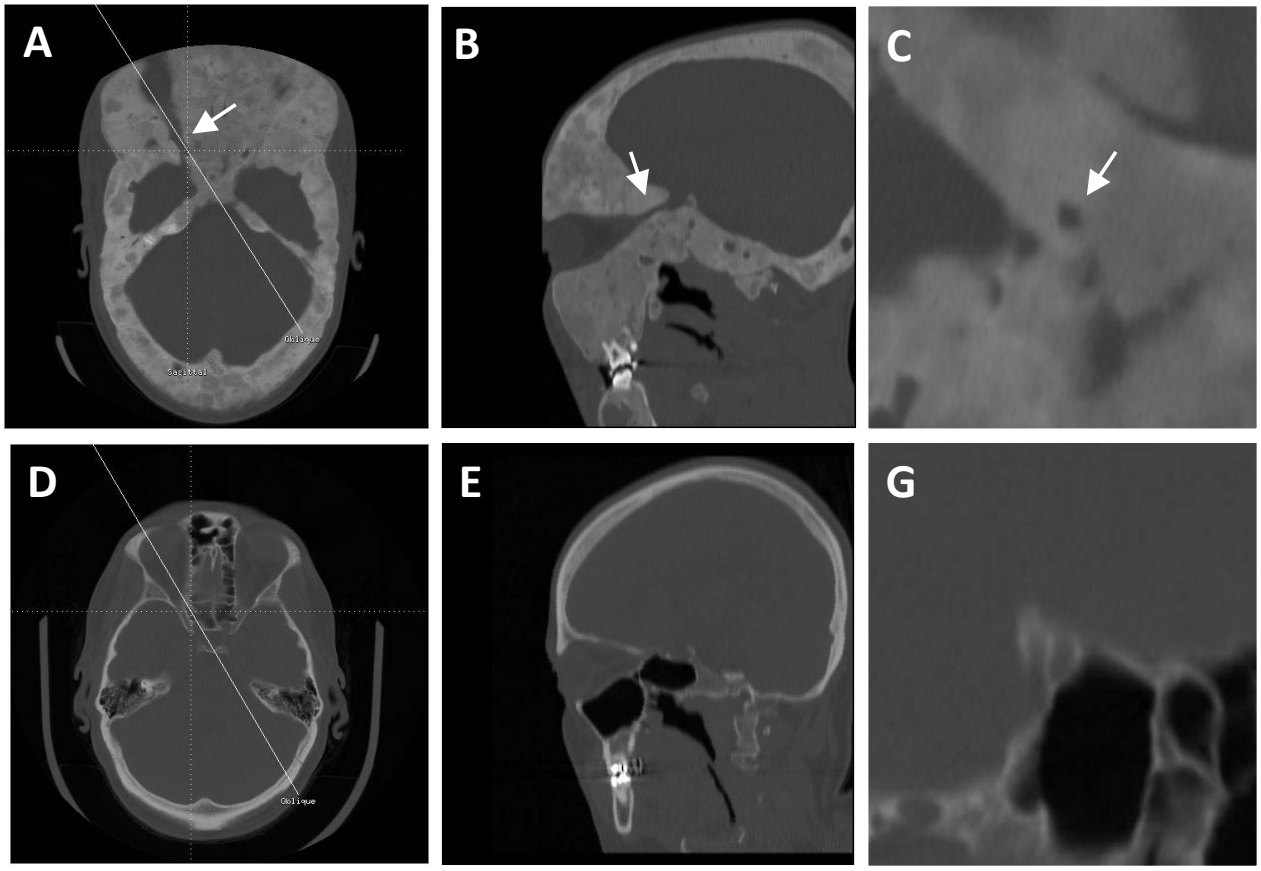

Figure 9 Fibrous dysplasia encasing the optic nerve compared to a normal optic canal. A-C) A patient with extensive fibrous dysplasia (FD). The arrow indicates the optic canal. D-G) CT of a normal and uninvolved optic canal. Several CT slices through the optic canal are shown: A&D) axial, B&E) oblique, and C&G) coronal. A case-control study by Lee et al [13] demonstrated that statistically significant narrowing of the optic canal by FD did not result in vision loss. Thus, observation with regular ophthalmologic examinations in patients with asymptomatic encasement was a reasonable treatment option and optic nerve decompression was not warranted. Adapted from reference [13]

canal in patients with FD, this did not result in increased vision loss and there was no correlation between the findings on the CT and the neuro-ophthalmologic exam. These findings were confirmed by Cutler et al. in a study that included an analysis of the same group of subjects after longer follow-up together with an initial analysis of additional subjects [33]. A recent meta-analysis that included, in addition to the most recent analysis of the NIH SNHFD cohort, an analysis of all the published cases of optic nerve decompression surgery, came to the same conclusions [73]. Based on these results, we recommend that FD in the skull base around vital structures, including the optic nerve, should be managed according to the clinical examination and regular diagnostic imaging and observation is appropriate in asymptomatic patients [13,27,33,73,74].

Once it is determined that there is FD surrounding the optic nerve(s) and orbit, a comprehensive neuro-ophthalmologic examination should be done to establish the baseline. This should be followed by comprehensive annual exams. The exam should concentrate on assessing for optic neuropathy and include visual acuity, visual-field exam, contrast sensitivity, color vision, and dilated fundus exam. Additional examination should include pupillary examination for afferent pupil, extraocular movements, proptosis measurement with exophthalmometry, lid closure, hypertelorism, and tear duct and puncta exam. The diagnosis of optic neuropathy should be reserved for those with a visual field defect or if 2 of the 3 exams (contrast sensitivity, color vision, and fundus/disc exam) are abnormal. A new diagnostic modality, optical coherence tomography (OCT), uses high resolution cross-sections of the optic nerve to determine the thickness of the retinal nerve fiber layer (RNFL) [75-79]. A thin RNFL correlates with visual field changes and evidence of optic neuropathy. This modality may be useful for examining patients that cannot undergo a visual field exam (such as children) or may predict visual recovery after surgery. In the case where the RNFL may be thin prior to surgery, it is unlikely that surgery will improve vision while a patient with a normal RNFL may have some

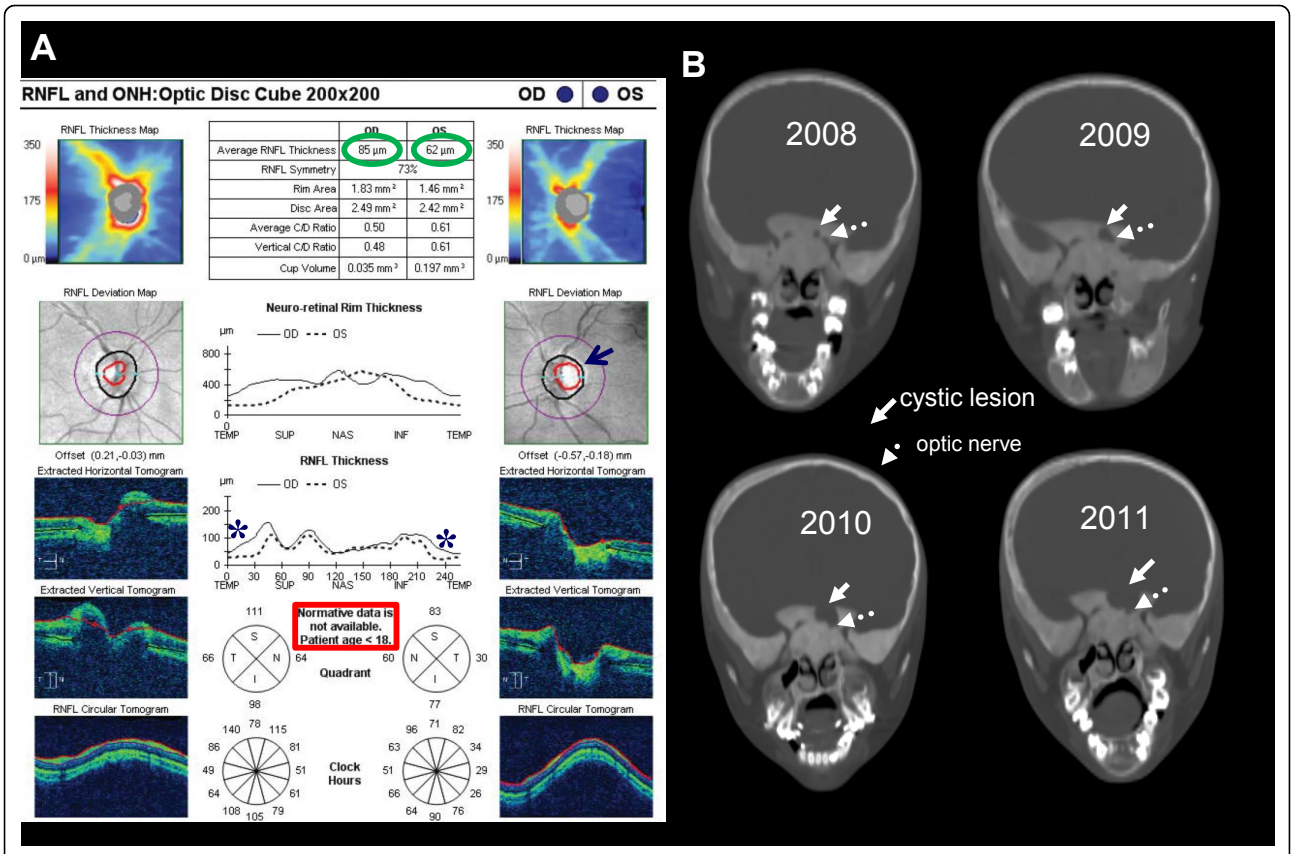

Figure 10 A representative Cirrus™ optical coherence tomography (OCT) optic disc cube study (A) and serial CT scans (B) of a 9-year-old girl with subtle left optic neuropathy and a very slowly expanding cystic lesion abutting the left optic canal. A) The numbers in the two green circles in the RNFL (retinal nerve fiber layer) represent the single number comparison between the two eyes. Generally, the nerve fiber layer is considered thin when it is less than about 70 microns. Note that in the RNFL Deviation Map panels the optic cup (the area within the red circle) on the left (OS) (black arrow) is a bit larger than on the right (OD), also suggestive of axon loss. In the RNFL Thickness graph, note the differences between the left (dashed line) and the right (solid line) in the temporal (TEMP) region (asterisk), indicating that in this region retinal nerve fibers are thinner on the left. For children under 18 normative data for the Extracted Vertical Tomogram and the RNFL Tomogram are not available. B) Serial coronal plane CT images at approximately the same region are shown. The expansile cystic lesion is indicated with the solid white arrow, and the optic nerve by the dashed arrow. The findings indicate the presence of a slowly expanding lesion, the cystic, fluid-filled nature of which was confirmed on MRI. On clinical examination, there were subtle findings of left optic neuropathy in that she performed slightly worse on the Ishihara color test and the Pelli Robson test of contrast sensitivity in her left eye. There was no evidence of an afferent pupil defect. Photos also demonstrated subtle temporal pallor of her left optic disc. There were no objective changes in visual acuity. She has been followed clinically with neuro-ophthalmologic examination approximately every three months to assess for any significant progression, which would be an indication for surgical intervention. The findings on the OCT study confirm the clinical impression of a left optic neuropathy and are particularly useful when visual fields are not obtainable or particularly reliable (usually due to age-related inability to perform the test), as well as an objective measure for longitudinal follow-up. The nerve fiber layer findings on OCT can also be used to predict what visual outcome one might expect after a successful decompression surgery. If one were to find a field defect on examination, but the corresponding optic nerve retinal nerve fiber layer was preserved on OCT testing, it would be reasonable to expect full recovery of vision after surgery. However, if there were nerve fiber layer loss, recovery of vision would be unlikely as the findings most likely represent axons that have died back.

improvement after surgical treatment (either decompression or proptosis correction). A representative case of the utility of the combination of OCT, clinical examination, and imaging is shown in Figure 10.

The etiology of the visual changes and vision loss in patients with craniofacial FD remains unclear. However, patients with abnormal findings are more likely to have an associated endocrinopathy, most commonly growth hormone excess, which typically results in gradual loss of vision, if vision loss is observed. In the cases of other lesions such as an aneurysmal bone cyst or mucocele, vision loss can be much more rapid. A study by Cutler et al [33] demonstrated that 12% of patients with relatively severe craniofacial PFD had evidence of optic neuropathy, that patients with GH excess had a higher relative risk for complete encasement of the optic nerve (4.1 fold), and had a higher relative risk for optic neuropathy (3.8 fold) compared to patients without GH

excess. Preliminary findings by Glover et al demonstrated that patients with an early diagnosis and treatment of GH excess had no optic neuropathy (0 of 14 patients that were diagnosed and treated by age 18) while 4 of 7 patients diagnosed and treated for growth hormone excess after age 18 had optic neuropathy [80]. We strongly recommend that patients with craniofacial PFD are evaluated for growth hormone excess or MAS and that if endocrinopathies are present they be aggressively managed.

Patients with acute visual change or vision loss should undergo a CT of the cranial base and immediate referral to a neurosurgeon or craniofacial surgeon and neuro-ophthalmologist. Several case reports have noted the association of a new, expansile lesion near the optic nerve, typically an aneurysmal bone cyst, and high dose glucocorticoids with immediate decompression and resection is indicated [15]. Unfortunately, the success of surgical treatment is unknown due to the limited cases of acute vision loss.

Auditory canal/temporal bone/cranial nerves

The temporal bone is frequently involved (>70%) in patients with craniofacial PFD or MAS [81], while temporal bone involvement is uncommon in monostotic disease [82,83]. In a recent analysis by DeKlotz et al., despite the high incidence of disease of the temporal bone in PFD, nearly 85% of patients had normal or near-normal hearing; 10% had conductive hearing loss due to PFD, approximately 4% had sensorineural or mixed hearing loss (both conductive and sensorineural), and the remainder had hearing loss due to other, non-PFD related causes. In most cases, the degree of hearing loss was mild (77%) and did not correlate to the amount of disease involvement of the temporal bone. The common causes of hearing loss appeared to be narrowing of the external auditory canal due to the surrounding FD (Figure 11) and fixation of the ossicles within the epitympanum from adjacent involved bone (Figure 12). The narrowing of the external auditory canal may result in significant cerumen buildup. Therefore, it is recommended that regular otolaryngology exams are performed to maintain patency in patients in whom the external auditory canal is particularly narrowed. A rare but potentially concerning complication is the development of a cholesteatoma, an obstruction of the canal with cerumen and desquamated skin [83,84]. This complication typically requires surgical intervention to relieve the obstruction and chronic infection [82,85]. In the case of PFD or MAS, there is concern that contouring and excision of the surrounding FD may exacerbate regrowth of the lesion. However, only case reports have been documented noting this possibility.

We recommend a comprehensive audiology examination and ear evaluation once the temporal bone is found to be involved with FD. Annual hearing/audiology exams are recommended during the active bone growth. For external auditory canal stenosis, regular exams under microscopy are usually required by the otolaryngologist. Surgery for the external auditory canal is recommended for complications such as cholesteatoma or near total ear canal stenosis; however it may be beneficial to wait until growth has slowed and the patient has progressed beyond puberty.

Temporal bone involvement may also result in facial nerve weakness or paralysis as the CN VII exits the cranium through the petrous temporal bone. This finding is quite rare and is likely caused by the compression of the cranial nerve within the Fallopian canal and/or the internal auditory canal [71,83,86,87]. Unfortunately, the location of the compression may be extremely difficult to access. In case of sudden facial weakness, a high resolution cranial base or temporal bone CT is indicated. If an expanding mass within the FD is noted, a referral to a skull base surgeon is warranted for consideration of surgical decompression.

Nonsurgical and adjuvant management of craniofacial FD

While pain is common among FD patients, [88], there are very few studies with a detailed assessment of the symptoms and there is a need for more data relating pain to the location and activity of disease and the effectiveness of various treatment modalities. Kelly et al [11] examined 78 patients (35 children and 43 adults) and found 67% complained of pain. It was not uncommon for the pain to be undertreated; some patients required NSAIDs with and without narcotic treatment, and others were treated with bisphosphonates. Interestingly, the pain scores did not correlate with the disease burden, and adults were more likely to have pain and have more severe pain than children, suggesting there is an age-related increase in the prevalence of pain in FD. They also noted that, despite the high prevalence of craniofacial FD, less than 50% had pain in the craniofacial region, in contrast to at least 50% of patients with lower extremity disease, another high prevalence site, complained of pain. In the same study, approximately 20% of the patients were managed with bisphosphonates and nearly 75% reported pain relief or improvement with this class of drugs.

The use of bisphosphonates such as alendronate, pamidronate, or zoledronic acid for craniofacial FD has been considered for pain reduction and to reduce the rate of growth of the lesion. In general, the clinical studies have demonstrated mixed results on the efficacy of bisphosphonates and FD-related pain with small sample sizes and with most studies examining all skeletal regions, not just the craniofacial sites. Plotkin et al [89] examined 18

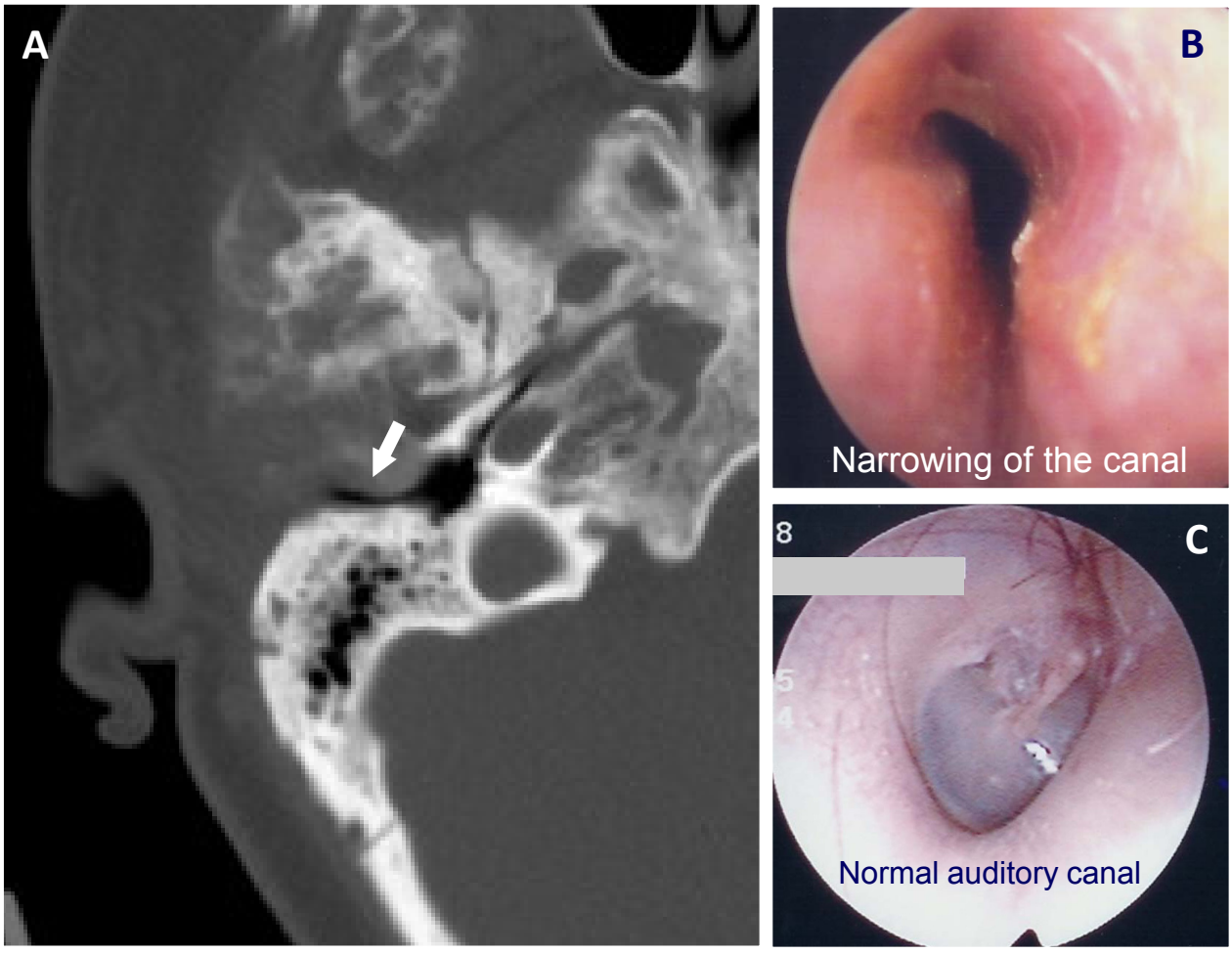

Figure 11 Narrowing of the external auditory canal due to fibrous dysplasia (FD). A) A CT image of a coronal slice through the temporal bone shows a narrowed external auditory canal (arrow) B) Narrowing of the canal is shown and can be compared to a normal canal in (C). The arrow on the CT image (A) demonstrates narrowing of the canal. This has resulted in hearing loss. The clinical images on the right compare a canal narrowed by FD to a normal external auditory canal.

children and adolescents with PFD or MAS and initiated IV pamidronate therapy. They found that pain seemed to decrease (not quantified) and serum alkaline phosphatase and urinary N-telopeptides decreased. There were no serious side effects from the bisphosphonate use however they noted no radiographic or histomorphometric change or improvement of the FD lesions. Matarazzo et al [90] reported on 13 patients with MAS who were treated with pamidronate for 2-6 years, and found a decrease in long bone pain, lowered fracture rate and bone turnover markers, and an increase in bone density on DEXA scan. Chan et al [91] followed 3 children with MAS for 8-10.5 years who were age 2.5-5 years at the start of treatment with pamidronate for MAS. They too noted a decrease in long bone pain and fracture rate however the long bone lesions continued to expand and grow while the facial lesions did not expand; there was no encroachment on the optic nerve throughout the follow-up. Chao et al [92] noted that oral alendronate over a 6-month course reduced intractable headaches and relieved the 3 patients from analgesic dependence. They reported no tumor progression, however the 3 patients were adults and may not have shown progression without the bisphosphonate treatment. Further studies are necessary to determine the efficacy osteoclast inhibitor therapies such as bisphosphonates or denosumab in slowing the growth of craniofacial FD and reducing intractable craniofacial FD pain. The variation in response between children and adults with FD and the safety of prolonged bisphosphonate use in children also require more investigation. New therapies are emerging that include RANK ligand inhibition (i.e. denosumab) however at this time their role in the treatment of FD-related pain or reduction in growth remains to be determined [93].

Figure 12 Fibrous dysplasia of the epitympanum compressing the ossicles. The arrows point to the ossicles in a normal epitympanum (A) and in a FD-involved epitympanum (B). The crowding in the right image has resulted in hearing loss.

Conclusion

We have provided the current understanding of the biologic and clinical characteristics of FD and recommendations for the clinical management in the craniofacial region. Most importantly, each patient may present with variable symptoms and clinical findings, thus the care of these patients must be customized to their needs and sites of involvement.

Recommendations

1. Aggressively screen for and manage endocrinopathies (particularly growth hormone excess).

2. Active disease (rapid growth, new onset of pain or paresthesia, visual or hearing changes) warrants an immediate surgical referral and evaluation.

3. A bone biopsy should be obtained if there is any doubt about the diagnosis. If the lesion is in a site that cannot be biopsied due to unacceptable risks, history, clinical examination and radiographic diagnosis may be adequate for diagnosis.

4. Postpone surgical treatment of lesions until after skeletal maturity when the lesion is quiescent.

5. Surgical resection or contouring may be warranted prior to skeletal maturity if there are symptoms or rapid change in the lesion, however, patients must be aware of the risk of regrowth.

6. Potential use of adjuvant therapy such as bisphosphonates may be considered for refractory pain at the FD site.

7. Management of patients with FD, particularly PFD and MAS, requires a comprehensive evaluation and multidisciplinary involvement for optimal care.

Research questions

1. What are the mechanisms for changes in FD that occur as patients age?

2. What is the mechanism and effect of growth hormone excess on the growth rate and activity of FD?

3. What are potential targeted therapies and mechanisms that can be used to treat FD?

4. What biomarkers might be useful to predict biological behavior and growth of FD lesions?

5. What potential biomarkers or predictors of transformation and associated pathologies can be developed?

6. What combined therapies will prevent recurrence and regrowth (e.g. an operation with adjuvant bisphosphonates, interferon)?

7. What pharmacologic or molecular therapies may reverse the effects of the abnormal gene products in FD?

8. Does the detectability of a G_s mutation in a fibro-osseous lesion predict clinical behavior?

9. Is mutation testing a necessary component of FD evaluation?

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Competing interests

The authors declare that they have no competing interests

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The surgical management of fibrous dysplasia of bone

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Abstract

The surgical management of Polyostotic Fibrous Dysplasia (FD) of bone is technically demanding. The most effective methods to manage the associated bone deformity remain unclear. The marked variation in the degree and pattern of bone involvement has made it difficult to acquire data to guide the surgeon's approach to these patients. In light of the paucity of data, but need for guidance, recognized experts in the management of these patients came together at the National Institutes of Health in Bethesda, Maryland as part of an International meeting to address issues related to fibrous dysplasia of bone to discuss and refine their recommendations regarding the surgical indications and preferred methods for the management of these challenging patients. The specific challenges, recommended approaches, and "lessons learned" are presented in hopes that surgeons faced with typical deformities can be guided in the surgical reconstruction of both children and adults with FD.

The initial evaluation of an adult patient with fibrous dysplasia

In the majority of the patients with fibrous dysplasia (FD) in whom the diagnosed is made in adulthood, FD is an incidental finding. Typically a bone lesion is detected on radiographs that were performed to evaluate a common injury, such as a sprain. Occasionally, the adult patient may present with dull, aching pain and subsequent radiographs may detect a bone lesion. As a first step in the evaluation, a full-body ^{99}Tc-methylene diphosphonate (MDP) bone scan is recommended to not only evaluate the biologic activity of the index lesion, but to detect any additional lesions that may exist throughout the skeleton. If the radiographic appearance is typical (thinning of the cortex without periosteal reaction with a matrix appearance that has been characterized as resembling "ground glass"), most often the diagnosis may be rendered without additional imaging studies (i.e. computed tomography (CT), or magnetic resonance imaging (MRI)). Biopsy is indicated for histologic confirmation only in cases that do not present a typical radiographic appearance.

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Management of adult monostotic disease

Treatment decisions for adult patients with monostotic disease depend entirely on the presence of symptoms. The typical lesion, which is identified incidentally and remains asymptomatic, should be treated with observation and serial radiographs at an interval determined by consensus between the patient and the surgeon until they are satisfied that the lesion is biologically inactive and mechanically insignificant. When surgical intervention is indicated, monostotic lesions are typically treated with conventional surgical procedures [1]. In the absence of clinical symptoms, typical monostotic disease may be observed without specific intervention. In select patients, surgical management may be indicated for a variety of reasons. In some patients, the fear of malignant disease may be so profound that the surgeon is unable to adequately reassure the patient of the benign nature of the process. In other patients, the lesion may cause a true mechanical deficit that has led to bone pain or fracture and therefore intervention may be indicated. Typical orthopedic procedures to remove the lesion and to graft the defect may be used in these cases. The use of internal fixation should be considered in most cases to aid in immediate weight bearing and to augment the strength

of the bone. If recurrent FD results in the resorption of the graft, generally accepted principles of orthopedic tumor surgery are followed. In MFD in adults, one can expect low levels of tumor recurrence.

The initial evaluation of a child with fibrous dysplasia

Typically a child with FD will consult the orthopedic surgeon for complaints of pain, limp, or management of a pathologic fracture through an area of FD. If the child also has café-au-lait macules, the diagnosis of McCune-Albright Syndrome (MAS) is easily made. The classic diagnostic criteria for MAS had been FD, café-au-lait macules, and precocious puberty [2,3], but better understanding of the molecular and developmental etiology of FD/MAS has led the acceptance of the fact that any combination of one or more of the typical features of MAS (FD, café-au-lait macules, and/or hyperfunctioning endocrinopathies such as gonadotropin-independent precocious puberty, hyperthyroidism, growth hormone excess, etc.) warrants the diagnosis of MAS. In fact, given that the molecular etiology of even monostotic FD (MFD) is the same activating mutation in $G_s\alpha$ as is found in full spectrum MAS [4], MFD can be considered a *forme fruste* of MAS.

The consensus of the authors is that the initial evaluation of the child should begin with a ^{99}Tc-MDP bone scan to assess for the presence and/or extent of polyostotic FD (PFD). Before age six, and especially before the age of three, the bone scan may not show all areas that will ultimately be involved with FD, as small foci of FD may not be detected by the bone scan. After age six, affected areas of FD are usually detectable, and the family can be reassured that it is very unlikely that any "new" areas of FD, and certainly no new areas of clinical significance beyond what is already seen, will subsequently appear [5]. However, parents should also be informed that affected areas identified at a young age may progress. All young patients diagnosed with FD, and especially those with PFD require an evaluation by an endocrinologist, even in the absence of history or clinical findings suggestive of endocrine dysfunction. In addition, older patients with MFD, who have any history or clinical findings suggestive of endocrine dysfunction, should be referred for an endocrine evaluation. Patients whose bone scan shows cranial or facial involvement will require an evaluation by a craniofacial specialist. While CT imaging is often necessary to evaluate craniofacial FD, the consensus of the authors is that CT and/or MRI evaluation of long bone and spinal lesions are rarely indicated. Biopsy and/or molecular diagnosis (gene testing for mutations in *GNAS*) is rarely indicated in polyostotic disease, as the diagnosis can be rendered confidently on the basis of the history, physical examination and radiographs. When surgical procedures are required material may be obtained for histologic and/or molecular diagnostic confirmation or research purposes.

Management and follow-up of pediatric polyostotic fibrous dysplasia

Treatment of PFD in children during the growing years is often very challenging. Patients may present across a broad spectrum of clinical involvement. The initial presenting extent of bone involvement is often misleading, especially in the young child. Small areas of involvement may escape detection by the initial bone scan if the child is less than six years of age, and most areas will expand in size subsequent to the initial detection in the young child. Most patients will develop fractures and long bone deformity in the absence of surgical intervention. In the absence of a fracture or symptoms, the follow-up for a child with FD consists of twice yearly clinical evaluations with special attention to limited range of motion, obvious angular deformity and limb length discrepancy. The appendicular skeleton can often be evaluated without radiographs, with the exception of the proximal femur, where deformity may be progressive with little visible deformity until the angulation is severe (Fig. 1). Therefore, when disease is present in the proximal femur, radiographs should be obtained periodically. Limb length discrepancy can be an early sign of progressive deformity. Radiographs are used selectively to monitor the progression of lesions initially identified using the bone scan. Radiation exposure should be minimized; therefore the routine use of skeletal surveys is discouraged. Whenever available, single exposure, full-length standing radiographs of the entire lower extremities are the best way to assess for progressive disease, deformity, and limb length discrepancy (Fig. 2). Individual films of bones with suspected "insufficiency fractures" are obtained as needed.

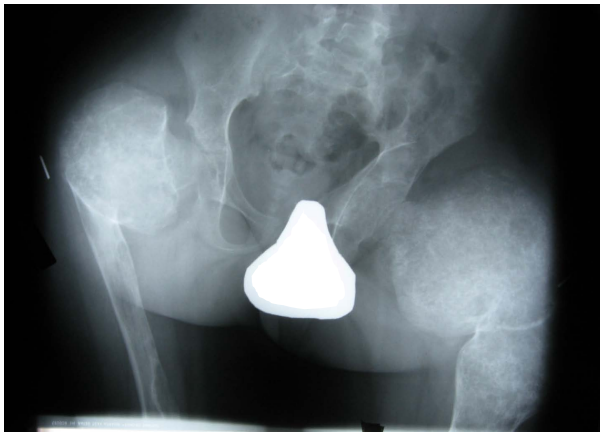

Figure 1 Fibrous dysplasia of the proximal femur. The radiograph demonstrates severe femoral involvement with deformity, and a typical ground glass appearance in both proximal femora.

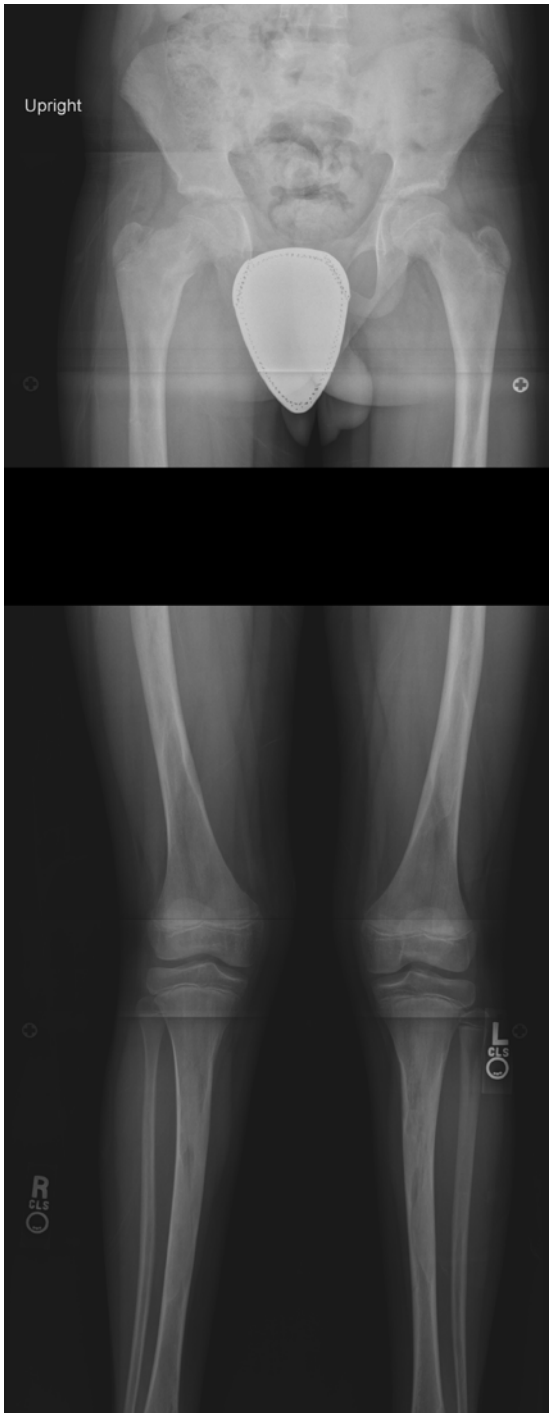

Figure 2 Long standing anterior/posterior (A/P) radiograph. This single view A/P film of both extremities with the patient standing allows for assessment of the extent of FD in both legs, hip angulation, and for potential limb length discrepancy. This radiograph demonstrates involvement of both femurs, both tibias, and early deformity of the upper right femur with decreasing neck-shaft angle.

After the initial diagnostic bone scan, "follow-up" bone scans in the absence of a specific indication are not indicated.

Scoliosis

Scoliosis is common in FD and may lead to significant deformity and even rarely to death, if untreated [6,7]. In most patients it may be evaluated by clinical exam alone. However, radiographs are appropriate when the patient shows signs of increasing deformity on physical examination. Presently, there is no peer-reviewed published literature to guide the use of scoliosis bracing in FD. Bracing in typical adolescent idiopathic scoliosis modifies the alignment of the spine using indirect pressure on the spine through pressure on the ribs. As many of the patients with FD significant enough to have progressive scoliosis have rib involvement, management by bracing management is likely to be problematic and ineffecitve. For patients with significant and progressive scoliosis, surgical fusion and instrumentation is indicated (Fig. 3). Computed tomography is helpful in detecting the degree of FD in each individual vertebral segment that is to be included in the fusion. Fixation devices (hooks, screws, wires, etc.) cannot be used safely in vertebral segments with FD. Fixation should be placed in adjacent vertebral segments that are not involved in order to provide stability and correction of deformity. Standard instrumentation and fusion has been used successful in the small number of cases with which the authors have experience, and somewhat surprisingly the results of a single operation have shown excellent long-term durability.

Fracture and deformity management

Standard closed management is often appropriate for selected upper extremity fractures. However the fractures should not be allowed to heal with residual angulation, as remodeling and correction of residual angulation does not typically occur as quickly and as reliably in FD as it would in normal bone. With that in mind, the use of internal fixation for upper extremity fractures may be considered, especially in older children. The entire child must be considered when making a decision regarding the management of upper extremity involvement. For example, in children requiring chronic use of supportive devices (i.e. crutches or canes) due to lower extremity issues, correction of deformity and internal fixation of selected upper extremity deformities is appropriate, as the upper extremities of those individuals are weight bearing (Fig. 4).

Lower extremity fractures will almost always require the use of internal fixation, although selected non-displaced tibia fractures may be managed with casts. Non-weight-bearing management should be avoided

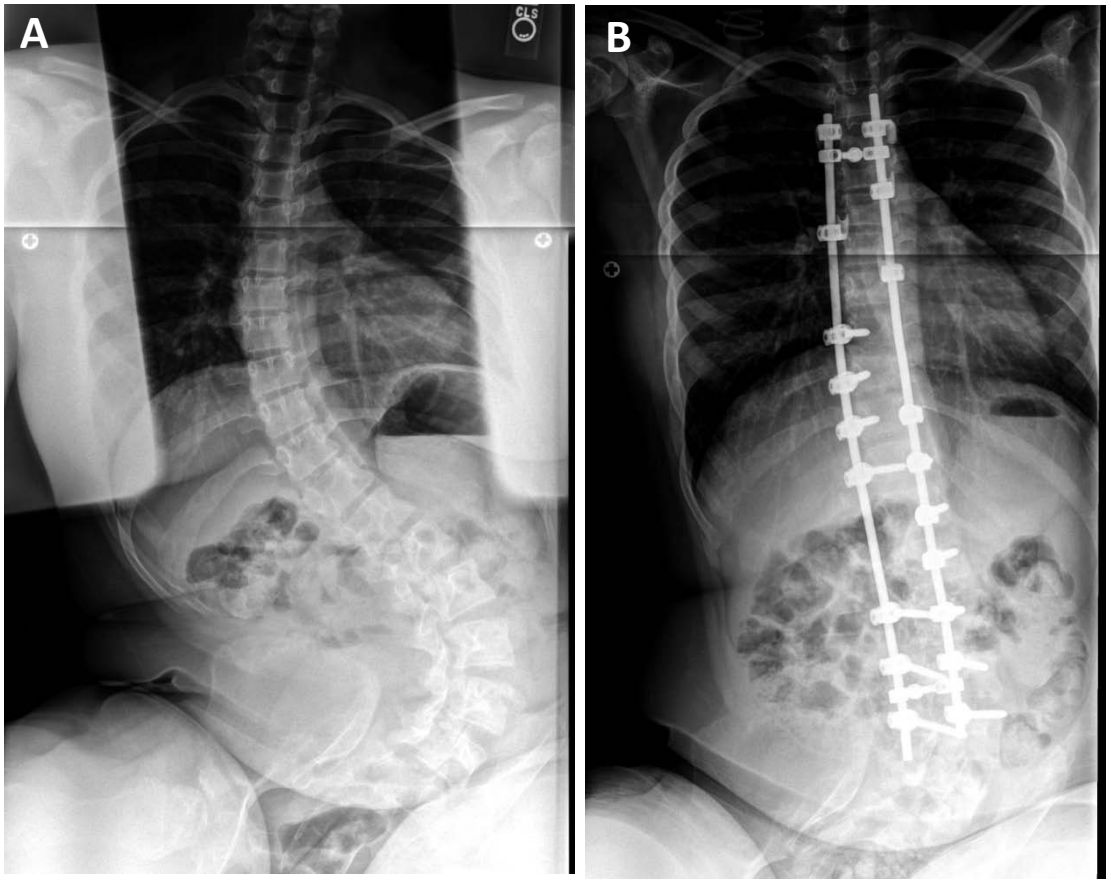

Figure 3 Surgical management of progressive scoliosis in a patient with fibrous dysplasia. Pre-treatment radiograph shows extensive scoliosis with both a thoracic and lumbar curve (A). The same patient is shown after posterior spinal fusion (B).

whenever possible. Patients with FD frequently have underlying bone fragility due to a combination of FD in other parts of the skeleton, metabolic issues, and diminished activity. Prolonged non-weight-bearing treatment following surgery will only aggravate the preexisting bone weakness. The use of internal fixation devices may allow early weight-bearing and should be considered when feasible. As with the upper extremity, remodeling of angulation may not occur.

Ideally, deformity should be avoided, and when present corrected. The new bone formed after fractures and corrective osteotomies is dysplastic, thus recurrent fractures and deformity should be expected. In virtually all cases, the cortex of the femur and tibia is severely compromised, and therefore the use of typical plate and screw devices is discouraged, unless screws can be placed outside the FD lesions obtaining purchase in normal cortical bone. Screw failure is extremely likely if the screws are placed into FD bone and should be used with caution only in selected patients with adequate cortical bone. When screws are used, augmentation with external devices (cast or brace) may be indicated (Fig. 5). Bracing as a prophylactic treatment for deformity is ineffective. Likewise, there is no indication for prophylactic use of internal fixation devices in the absence of fracture, deformity, or chronic weight-bearing bone pain.

The use of intramedullary (IM) devices is strongly suggested for all lower extremity fractures and reconstructions [8-10] (Fig. 6). A variety of devices are available, however, few are designed specifically to address the unique challenges of reconstruction of the proximal femur in children. The proximal femur is very commonly involved in this disease and presents the most unique reconstruction challenges. Once varus deformity occurs in the femur, realignment becomes extremely challenging. Varus below a neck-shaft angle of 130 degrees is very concerning and varus below 120 degrees may constitute an indication for surgical intervention, even in the absence of a fracture or weight-bearing bone pain [9,10]. A decline in the neck-shaft angle on sequential radiographs warrants consideration of surgical intervention. In cases where the neck-shaft angle has become severely deformed, single-staged correction may not be feasible. In selected cases, staged procedures using

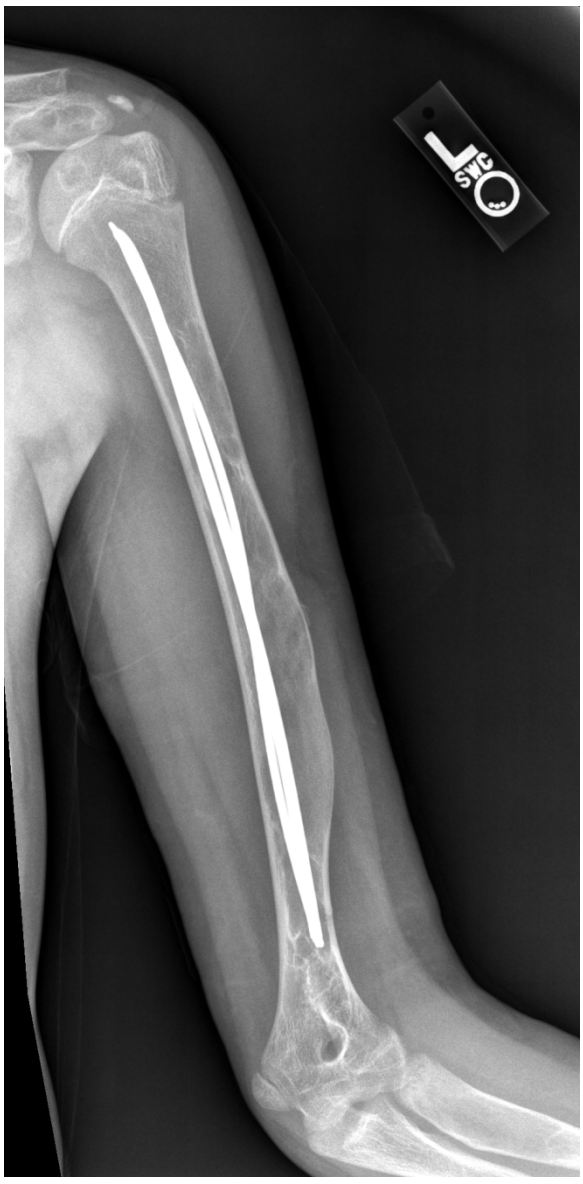

Figure 4 Intramedullary rods of the humerus in fibrous dysplasia. Demonstrated are flexible intramedullary rods in the humerus for the treatment of chronic upper arm pain in a patient who needed to weight bear through using their arms.

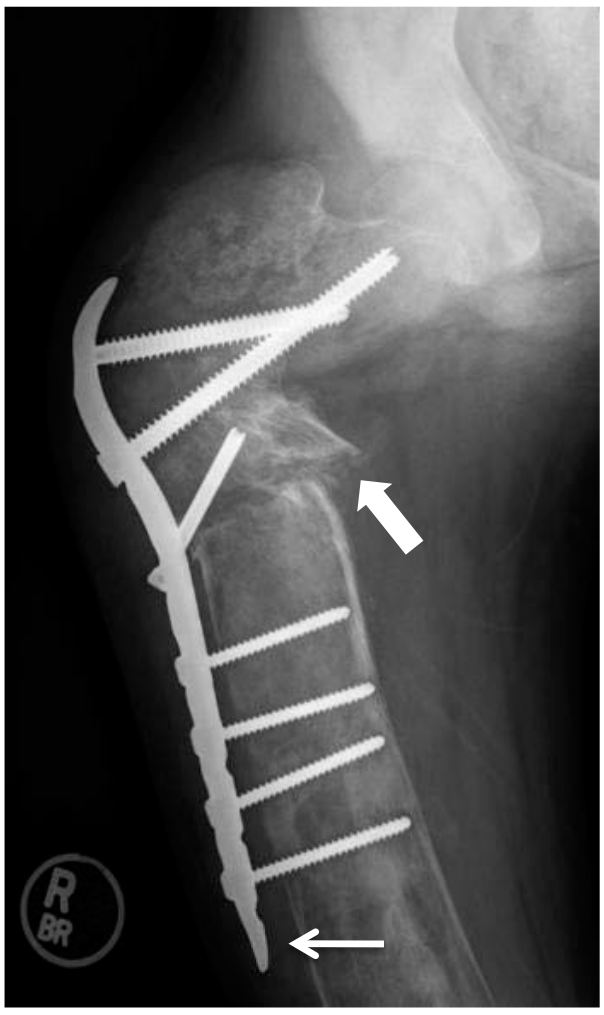

Figure 5 Screw and plate device in upper femur. This radiograph demonstrates the first stage reconstruction in a patient with severe deformity using a plate and screw device. The weak bone cortex results in poor fixation and eventual failure. Plate and screw constructs should be avoided if possible, or used only for temporary fixation until intramedullary fixation is possible. The thin white arrow demonstrates a problem typically encountered when fixation screws are inserted in to bone affected with FD, i.e. the plate has pulled away from the bone due to loss of screw fixation.

blade-plate or screw-plate devices to achieve partial correction may be used and later converted to IM devices when the desired correction is achieved.

Over-correction into valgus alignment in the upper femur should be considered when possible. Although this introduces a theoretical risk of abductor muscle weakness, the practical results have shown near-normal function and less frequent need for revision surgery. A study of the neck-shaft angle in children with PFD shows a correlation between normal neck-shaft angle and improved functional outcomes (5). Fixation devices designed for use in the upper extremity of adults may be adapted for use in the pediatric lower extremity on a case-by-case basis (Fig. 7). Until recently, smaller IM devices suitable for use in the upper femur were not available, however, more devices are now being manufactured and may be suitable for these reconstructions. Even when suitably sized devices are available, they are typically designed to reproduce normal childhood alignment and therefore may be difficult to use when attempting to produce a valgus alignment.

Internal fixation devices may be used in non-deformed bone to treat frequent fractures or chronic weight-

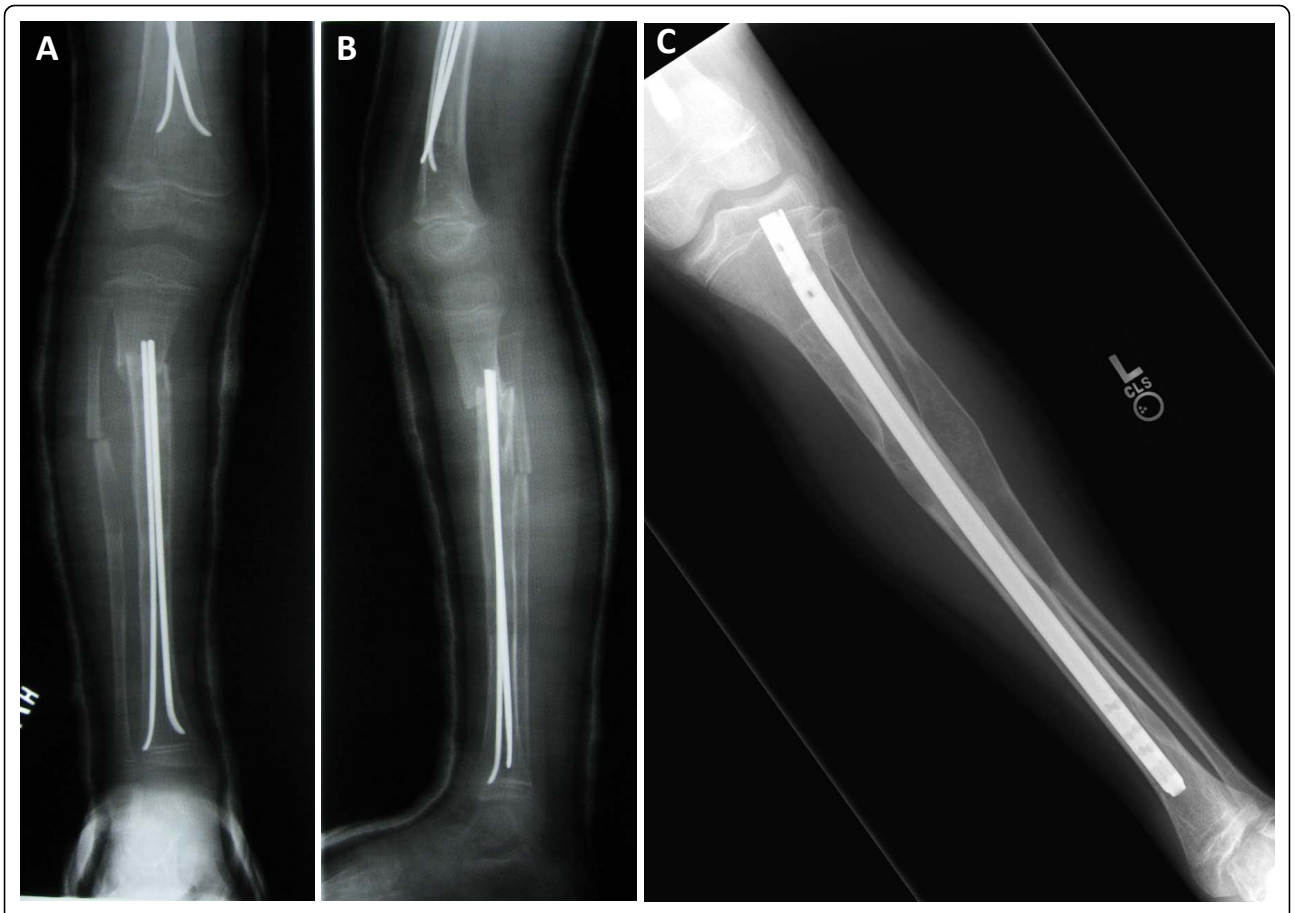

Figure 6 Intramedullary rods in fibrous dysplasia. The use of flexible intramedullary rods in both the femur and tibia in a small child following corrective osteotomy (A&B). A fixed intramedullary rod used in an older child is also shown (C).

bearing bone pain (Fig.8). Fixation for bone pain should be delayed until the medical management has been optimized by the patient's endocrinologist. The importance of proper pharmacologic management of the endocrine and metabolic aspects of this condition cannot be overemphasized, as the associated endocrinopathies (i.e. hyperthyroidism, phosphate wasting) often lead to decreased bone strength both within the FD bone and in the surrounding "unaffected" bone [11]. The use of bisphosphonates has been effective in reducing the incidence of significant weight-bearing bone pain [12,13], but has not been shown to decrease progressive deformity or to decrease the rate of fracture or surgery [14]. It is very important to counsel the parents and patients regarding the need for repeated surgical procedures to control the progressive nature of the bone deformities. This is especially problematic in young children with significant disease. As the skeleton is growing, the soft tissues exert very strong forces which will often exceed the strength of the bone that is affected with FD. Recurrent deformity will require repeated surgical procedures that become less frequent as the child reaches adult height.

Limb length discrepancy is common in PFD and is more likely to occur in patients with severe disease, requiring multiple corrective procedures. Attempts to surgically lengthen bone with FD will result in the formation of more dysplastic bone. Mechanical devices, such as circular frames with thin wire fixation, are not likely to hold in FD bone. Lengthening may be considered if there are bones or bone segments that are of good quality and not involved with FD. Epiphyseodesis of the longer limb at the appropriate time may be considered; however, many FD patients are destined to be of short stature and may not accept a procedure that reduces adult height. A patient and family that have undergone multiple major surgical procedures may prefer to accept the need to wear a permanent shoe lift as a means to deal with a limb length discrepancy, rather than accept another surgical procedure.

Transformation of fibrous dysplasia

Over time, fibrodysplastic bone may undergo transformation into either benign or malignant tumors. Transformation into aneurysmal bone cysts (ABC) may occur in any bone with FD, but has been reported most often in the

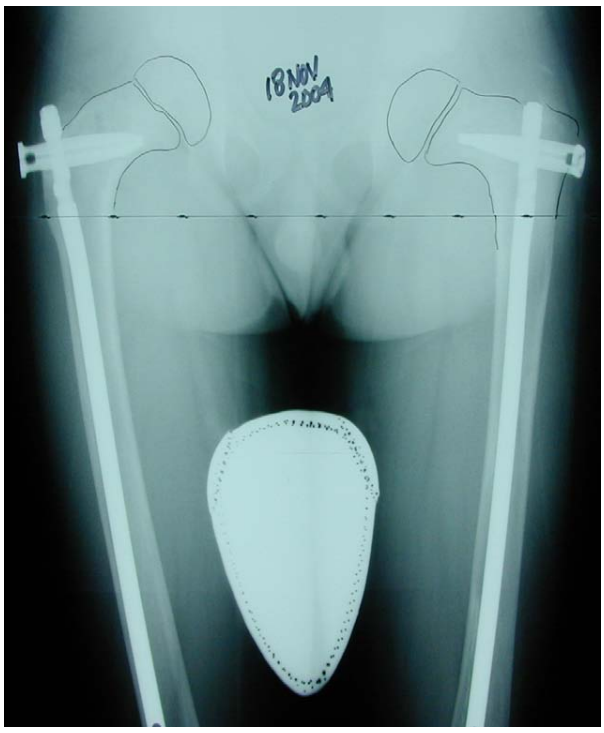

Figure 7 Upper extremity devices in a small femur. Demonstrated is the adaptation of rods created for use in the upper extremity in the bilateral femora of a child with FD.

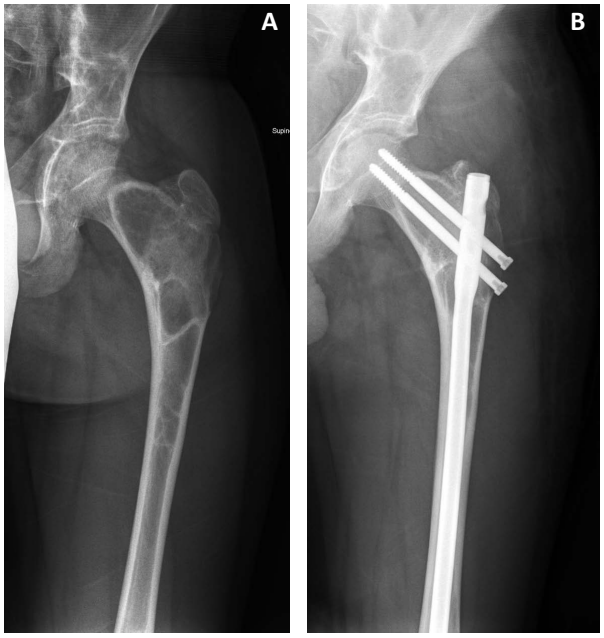

Figure 8 The use of a standard adult device in an adult with fibrous dysplasia. Demonstrated is the use of a standard intramedullary rod in a mature patient with fibrous dysplasia with chronic weight-bearing pain before (A) and after surgery (B).

skull. Aneurysmal bone cysts can also occur in many pre-existing benign bone tumors. When ABC's form in FD bone, the already soft and dysplastic bone deteriorates into an enlarging cyst that is filled with blood. The cyst typically expands much more rapidly than FD would, leading to increasing bone pain and fracture. Unfortunately, the radiographic appearance of ABC is very similar to FD and thus is often not recognized without the use of more sophisticated studies such as MRI (Fig. 9). Surgical management is required in cases of ABC formation.

Malignant transformation in FD is very rare and most reported cases appeared to be associated with radiation therapy, which was commonly used to treat FD lesions in the past [15]. At this time, there is no indication for the use of radiation therapy in the management of FD of bone.

Bone grafting

Bone grafting may be indicated for selected adult patients with monostotic disease [16]. Allograft is preferred to autograft to eliminate donor site morbidity. Bone grafting for patients with PFD is not useful. Attempts to completely remove polyostotic disease with curettage and bone grafting are rarely successful. Such surgery results in significant blood loss, and the FD lesions typically remodel the grafts with FD over time. There may be a limited indication for the use of allograft in conjunction with internal fixation for selected cases where the graft material provides temporary augmentation for the internal fixation. Large whole bone allographs may be used in adult patients as composite reconstructions in association with artificial joint replacement surgery in selected cases. There are always exceptions to any rule, and occasionally the small bones of the hands and fingers may suffer repeated fractures that warrants the use of grafting. These bones can often be treated effectively with curettage and bone grafting without fixation.

Bone infection and blood loss

The majority of FD lesions are richly supplied with blood vessels, and extensive bleeding may be anticipated for patients in whom a lengthy reconstruction is planned. The presence of an ABC in the lesion can also increase the blood loss during surgery. This may become significant, especially for reconstructions where multiple corrective osteotomies are required and where the medullary canal must be reconstituted with drilling and/or reaming prior to the insertion of an IM device. Blood transfusion may be necessary if multiple sites of deformity correction are attempted at one episode of surgery. Therefore we recommend that the surgeon advocate early intervention before the development of significant bone deformity. Bone infection following surgery for FD is uncommon and perhaps less frequent than in similar surgical

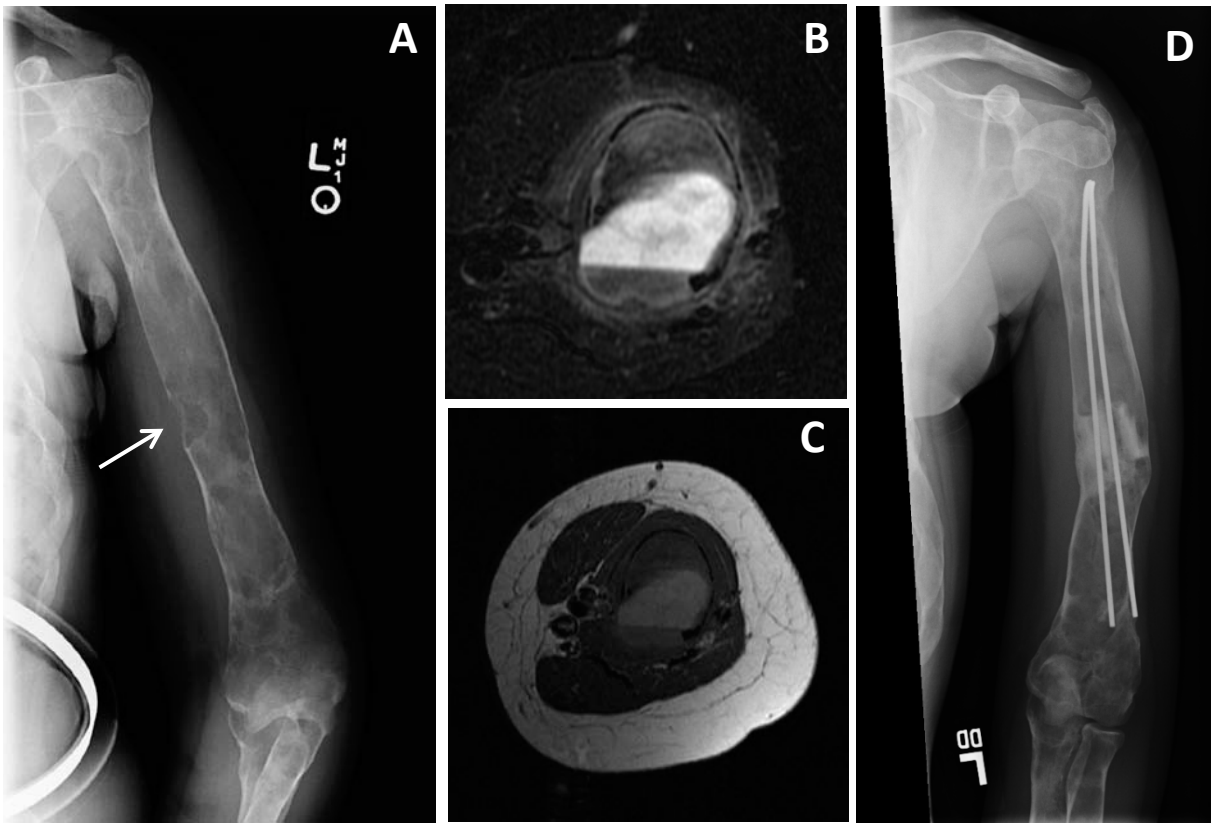

Figure 9 Aneurysmal bone cyst (ABC) of the upper extremity in fibrous dysplasia. This 16 year-old girl with McCune-Albright syndrome developed pain in the left humerus. A radiograph revealed a new lytic lesion that breeched the cortex (A, arrow). MRI revealed a fluid/fluid level within the lesion consistent with an ABC (B&C). The post-surgery radiograph shows a good result with the use of grafting material and flexible intramedullary rods (D).

procedures performed in otherwise normal bone. The rich blood supply of the FD tissue may provide some degree of protection from infection in these patients. The authors have limited experience with infection in FD surgery and suggest that standard orthopedic principles of management be utilized.

Summary

In summary, PFD is an extremely complex condition causing fractures and deformity in children. Although relatively standard procedures are effective in adults with MFD, children with PFD require aggressive and innovative intervention if severe deformity is to be avoided. Bone grafting is seldom indicated. The use of intramedullary internal fixation devices is preferred over plate and screw devices whenever possible. The management of each patient must be individualized. The expectations of the parents must be prospectively managed and the patient and parent must be prepared for multiple episodes of reconstructive surgery throughout the growing years.

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Competing interests

The authors declare that they have no competing interests.

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Bone-Grafting in Polyostotic Fibrous Dysplasia

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Background: Polyostotic fibrous dysplasia is a skeletal disease that results from somatic activating mutations in the gene GNAS in skeletal stem cells, leading to proliferation of immature osteogenic cells with replacement of normal marrow and bone with fibro-osseous tissue. Lesions may cause bone deformity or fracture. In the surgical care of polyostotic fibrous dysplasia, the role of grafting and the optimal grafting material are not clear. The purpose of this study was to evaluate the long-term survival of bone-grafting procedures in subjects with polyostotic fibrous dysplasia over time.

Methods: The operative reports and radiographs of a cohort of subjects with polyostotic fibrous dysplasia followed in a natural history study were reviewed. Twenty-three subjects (mean age at the time of enrollment, thirteen years [range, two to forty years]) with fifty-two bone-grafting procedures had a mean follow-up time of 19.6 years (range, twenty-nine months to forty-seven years). Kaplan-Meier life table estimates, Cox proportional hazard models, and t tests comparing means were performed to assess various aspects of graft survival.

Results: Kaplan-Meier curves showed a 50% estimate of survival of 14.5 years. Cox proportional hazards models showed no advantage comparing allograft with autograft or structural with nonstructural graft materials. The mean age of the patients was significantly greater ($p < 0.001$) in the subgroup of subjects in whom grafts were maintained over time (20.9 years) compared with the subgroup of patients whose grafts were resorbed over time (9.8 years).

Conclusions: Bone-grafting, including both allograft and autograft, is of limited value in ablating the lesions of fibrous dysplasia. The expectations of patients and surgeons should include the high probability of graft resorption over time with return of bone characteristics of fibrous dysplasia, particularly in younger patients. This suggests the maintenance of normal bone mechanics with implant support should be the priority of any surgical intervention.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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Fibrous dysplasia is a rare disorder of bone resulting in fracture, deformity, and pain. It is caused by somatic activating mutations of the $G_s\alpha$ protein encoded by the gene GNAS[1-3]. Skeletal stem cells that harbor this mutation have an impaired ability to differentiate into mature osteoblasts and instead retain a fibroblast-like phenotype[4,5]. Mutated cells proliferate and replace normal bone and marrow with a generally undermineralized and structurally unsound fibro-osseous tissue[6,7]. Disease is a mosaic with a broad spectrum of clinical severity[8]. Fibrous dysplasia may be monostotic or polyostotic. Any area of the skeleton may be involved; however, the skull base and proximal parts of the femur are most commonly affected, with femoral lesions resulting in the most functional impairment[9,10]. Lesions may occur in isolation or may be associated with café-au-lait skin pigmentation and/or hyperfunctioning endocrinopathies, termed the McCune-Albright syndrome[11,12].

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Orthopaedic treatment of polyostotic fibrous dysplasia is challenging, particularly with multiple lesions or major deformity. Surgical management of the proximal part of the femur, given its structural importance and propensity for extensive involvement, often presents the greatest challenge[13-17]. Bone-grafting for ablation of fibrous dysplasia lesions was first popularized by Enneking and Gearen[13]. In 1986, this group of researchers reported good outcomes using allograft fibular strut grafts for stabilization of lesions of fibrous dysplasia in the proximal part of the femur[13]. However, none of the patients reported in that study had mechanical deformity, and the majority of the patients had monostotic fibrous dysplasia and were older than eighteen years of age[13]. The lack of deformity and monostotic disease suggests that these patients had what would be considered mild disease. The exuberance for bone-grafting following that landmark study[13] was tempered by subsequent reports. In 1987, Stephenson et al. reported on a relatively large series of forty-three patients with fibrous dysplasia (nineteen with polyostotic fibrous dysplasia) who had a total of twenty-four grafting procedures and were followed for a mean time of 10.4 years[18]. In that series, there was a distinct difference between what was reported as a satisfactory outcome between the groups of patients who were younger than eighteen years and those who were eighteen years of age or older. Although details on grafting materials and the length of time that graft was retained are lacking, the outcome for grafting was reported as satisfactory in only one of fourteen procedures in patients younger than eighteen years of age. A retrospective study from the DuPont Institute that included twenty-two subjects, all of whom were younger than eighteen years of age at presentation, found that curettage and bone-grafting using either morselized allograft or autograft did not improve the surgical results beyond what was achieved by mechanical fixation[15]. Additional reports of bone-grafting in fibrous dysplasia have included case reports and small series with short follow-up and sometimes included bone diseases other than fibrous dysplasia in the analysis[17-24]. Important factors in comparing the outcomes in these studies are the extent of fibrous dysplasia (monostotic fibrous dysplasia or polyostotic fibrous dysplasia), the age of the subjects, and the presence or absence of concomitant endocrine dysfunction as part of the McCune-Albright syndrome. Based on clinical observations in patients with polyostotic fibrous dysplasia, we hypothesized that bone-grafting in this population has a high rate of resorption and is ineffective for long-term management. To test this hypothesis, we performed a retrospective analysis to determine the outcomes of bone-graft survival in a relatively large, longstanding cohort of subjects with polyostotic fibrous dysplasia.

Materials and Methods

The database of a cohort of subjects enrolled in an ongoing, long-term study of the natural history of fibrous dysplasia or the McCune-Albright syndrome at the National Institutes of Health (NIH) was accessed. The current study was performed utilizing data collected from 1998 to 2010, including retrospective data from previous surgical procedures. All subjects had the diagnosis of fibrous dysplasia confirmed by either mutation testing or the presence of additional features of the McCune-Albright syndrome. The study was approved by the institutional review board, and informed consent or assent was obtained from all subjects and guardians.

All subjects enrolled in the study underwent evaluation for skeletal disease and endocrinopathies. Subjects with bone-grafting were identified from surgical histories and skeletal radiographs. Operative reports and serial radiographs were reviewed. Additional information was obtained by contacting patients and/or their treating surgeons.

Bone grafts were evaluated by examination of radiographs. If a subsequent grafting procedure was required at the same location, it was assumed that the previous graft had failed. Grafts were characterized as maintained if they were still visible on radiographs and appeared to have incorporated into bone (Fig. 1), partially resorbed if radiographs showed

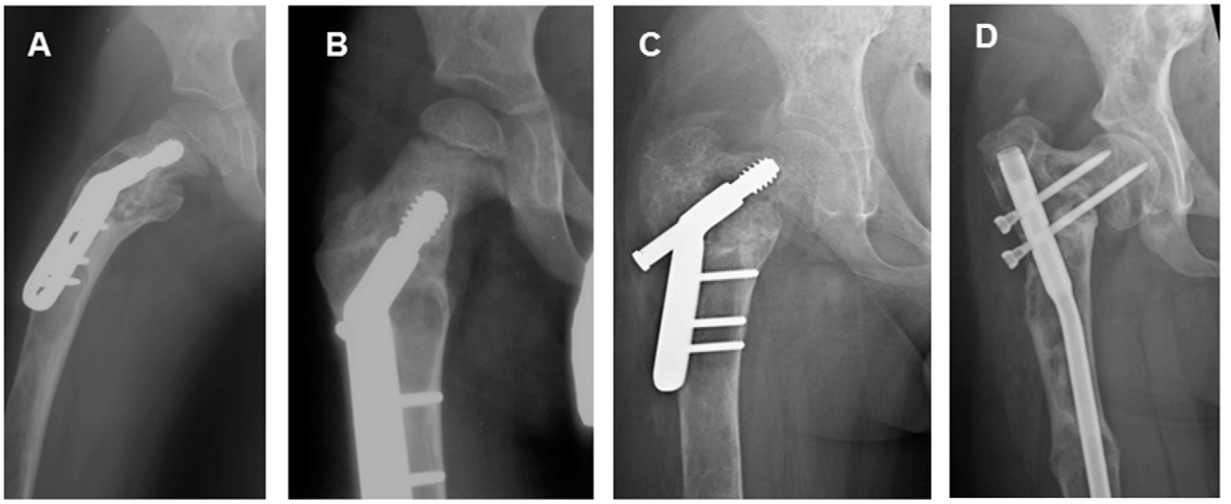

Fig. 1

Graft and implant evolution demonstrating a typical approach to restore the neck-shaft angle in proximal femoral disease using different grafting materials and devices. Grafting materials included allograft and Grafton (**Fig. 1-A**) and allograft chips (**Fig. 1-B**). Grafting material was minimally resorbed (**Fig. 1-C**), and eventually support was attempted with an intramedullary rod (**Fig. 1-D**).

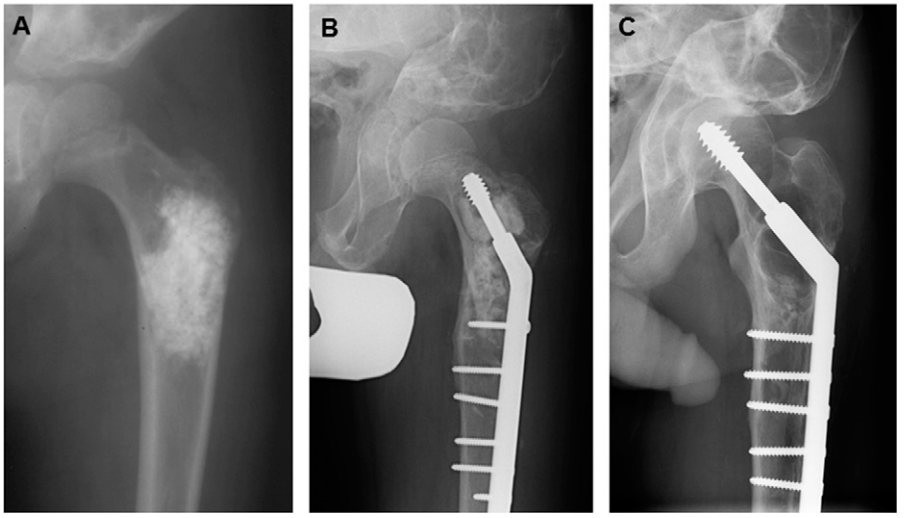

Fig. 2

Partially resorbed graft. **Fig. 2-A** The initial approach included curettage and bone-grafting with coral and iliac crest graft. **Fig. 2-B** Five years later, a hip screw and side plate as well as bone-grafting with an allograft strut and allograft chips were used. **Fig. 2-C** Eight years later, implant revision alone was performed with the lytic lesion of fibrous dysplasia visible again; the grafting material had been resorbed.

loss of the graft over time but some graft remaining (Figs. 2-A and 2-B), and completely resorbed if there was no radiographic sign of the graft (Fig. 2-C).

Survival analyses were performed using Kaplan-Meier life table estimates and Cox proportional hazard models. Student t tests were used to compare means. Significance was set at $p < 0.05$. All analyses were performed using SAS (version 9.2; SAS Institute).

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Results

Twenty-five subjects with polyostotic fibrous dysplasia were studied. The subjects underwent fifty-four bone-grafting procedures. In two patients with one graft each, documentation and imaging were insufficient to determine both graft type and graft fate, and these grafts were eliminated from the analyses. Thus, there were a total of twenty-three patients with fifty-two total grafts included in the analyses. Of these fifty-two grafts, autograft was used in sixteen procedures, allograft was used in twenty-five procedures, and both were used in five procedures; in six cases, the specific details of the materials were not in the operative report. Allograft materials included Grafton (BioHorizons), AlloMatrix (Wright), boplant, and coral, as well as human demineralized bone cubes, chips, and struts. Structural grafts were defined as those that offer support to the implanted devices and ultimately become mechanically efficient structures once incorporated into surrounding bone. The list of specific grafts is included in Table I. The bone grafts had structural properties in eighteen cases and were morselized to fill space in thirty-four cases. The mean subject age at the time of the surgical procedure was thirteen years (range, two to forty years). Forty (74%) of the grafting procedures were performed in subjects younger than eighteen years of age, and fourteen (26%) were performed in subjects eighteen years of age and older. Fifteen patients were male and ten patients were female. Endocrinopathies were present in twenty-three subjects, including eighteen with FGF23 (fibroblast growth factor 23)-mediated phosphate

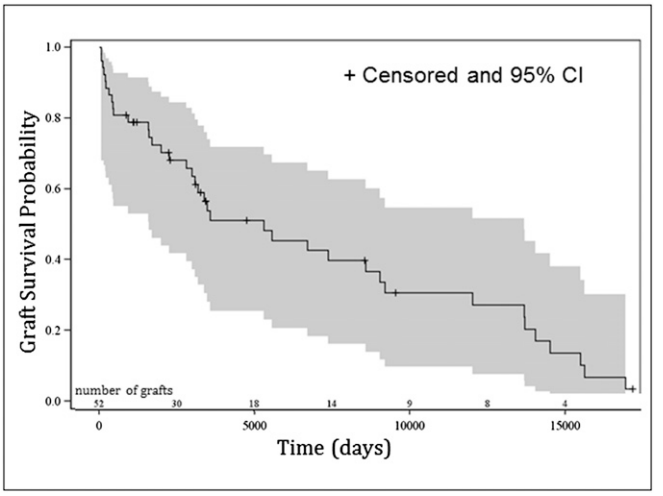

Fig. 3

Graft survival for all materials. The Kaplan-Meier survival curve for the entire population and for all materials is shown. The number of surviving grafts at specific intervals is indicated above the x axis. The time points at which data censoring took place are indicated by the plus signs. 95% CI = 95% confidence interval.

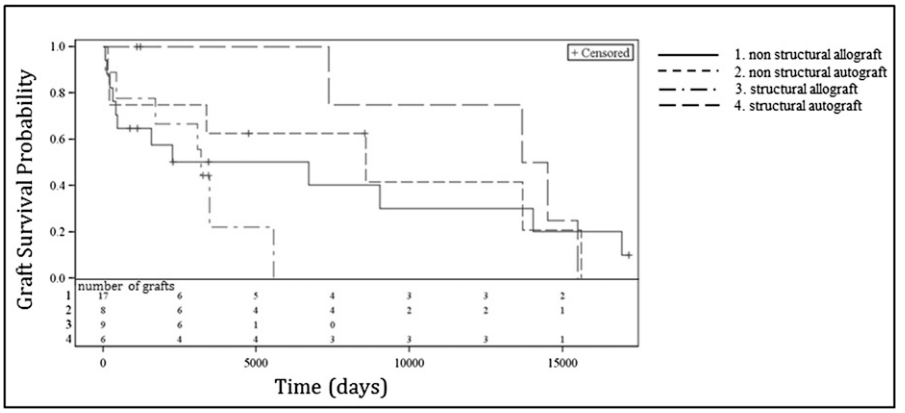

Fig. 4

Graft survival by material. The Kaplan-Meier survival curves were stratified into four groups consisting of nonstructural allograft (solid line), nonstructural autograft (small dashed line), structural allograft (dashed and dotted line), and structural autograft (large dashed line), as indicated. There was no significant difference between any of the curves, indicating no selective advantage of one type of graft over another. The number of each type of graft surviving at fixed intervals is indicated in the lower section of the panel above the x axis. The time points at which data censoring took place are indicated by the plus signs.

wasting, ten with precocious puberty, eleven with hyperthyroidism, and four with growth hormone excess. The majority of lesions were located in the proximal part of the femur (twenty-one), the tibia (three), and the proximal part of the humerus (one). Four (16%) of twenty-five subjects had had treatment with bisphosphonates prior to the surgical procedure with the intent to treat bone pain and/or to decrease the size of the fibrous dysplasia lesion. The mean alkaline phosphatase (and standard deviation) was 503 ± 413 IU/L (normal, 44 to 147 IU/L), indicating substantial disease activity. Grafts were assessed by evaluating radiographs. All but one graft was located intraosseously. Graft fate was determined in fifty-two grafts. Of these, thirty-nine (75%) were resorbed over time (included in this group were two grafts that were noted to have partial resorption), and thirteen (25%) survived and seemed to be incorporated. The mean length of follow-up was 19.6 years, with a median of 14.5 years (range, 2.4 to 47.0 years).

Kaplan-Meier survival curves for the grafts were constructed, showing an overall median survival estimate of 5302 days (approximately 14.5 years) (Fig. 3). Separate curves for different graft materials showed no significant advantage ($p > 0.05$) of any particular grafting material (Fig. 4). Furthermore, Cox proportional hazard models, used to analyze survival and the effect of covariates, assessed various clinical characteristics and graft materials and did not show any patient demographic characteristic (including the presence of any endocrinopathy and/or bisphosphonate treatment) that significantly affected graft survival ($p > 0.05$), nor was any grafting material significantly more advantageous ($p > 0.05$). However, when subjects were analyzed as the group in which the graft survived compared with the group with graft resorption, there was a significant difference ($p < 0.001$) between the groups in the age at which the grafting procedure was performed (Fig. 5). According to the t test, subjects in whom the graft was resorbed were significantly younger ($p < 0.001$) than those in whom the graft survived; the mean age was 9.8 ± 6.3 years for the patients in whom the graft was resorbed and 20.9 ± 9.6 years for the patients in whom the graft survived. Analyses of structural compared with nonstructural allografts in patients younger than eighteen years of age and in patients eighteen years of age or older showed no significant differences ($p > 0.05$) (data not shown).

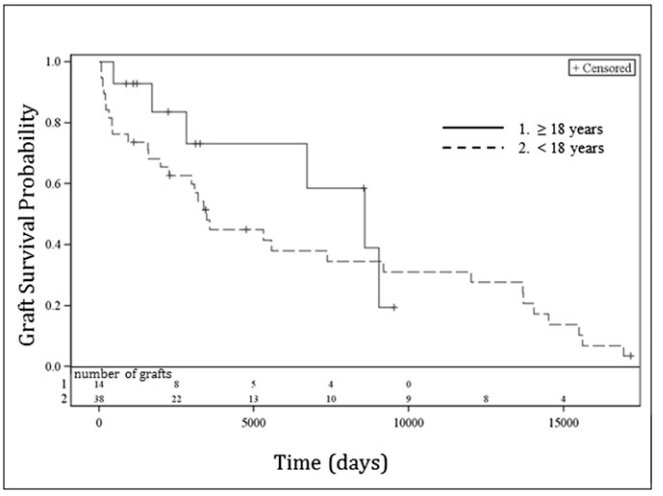

Fig. 5

Graft survival by age. Kaplan-Meier survival curves for all grafts grouped according to age at which a graft was used. The length of survival of the grafting material in subjects who received grafting at eighteen years of age or older are shown by the solid line, and survival of the grafting material for those who were younger than eighteen years of age at the time of grafting is shown by the dashed line. Time points at which data censoring took place are indicated by the plus signs.

TABLE I Summary of Patient and Graft Characteristics

Patient	Sex	Age (yr)	Site	Graft Type	Structural or Nonstructural	Concurrent Instrumentation*	Graft Fate	Length of Follow-up (yr)
1	F	7	Right femur	Morselized portion of femur	Nonstructural	Howmedica screw and sideplate with Ender nail	Resorbed	9.3
2	M	8	Left femur	Femoral allograft	Nonstructural	4.5 cortical compression screws	Maintained	9.4
		8	Right femur	Unknown	Structural	NA	Maintained	9.4
3	M	3	Left femur	Bone bank chips from femoral head	Nonstructural	NA	Resorbed	46.3
		4	Right femur	Bone chips	Nonstructural	NA	Resorbed	45.9
		6	Left femur	Cortical strips of tibia bone	Structural	NA	Resorbed	43.8
		7	Right femur	Cortical bone	Structural	NA	Resorbed	42.4
4	F	14	Left tibia	Fibular wedge	Structural	NA	Resorbed	20.2
5	M	2	Right femur	Fibular strut	Structural	Small threaded Steinmann pin	Resorbed	4.7
		2	Left femur	Fibular strut	Structural	Small threaded Steinmann pin	Resorbed	4.7
6	M	3	Right femur	Bone bank ribs	Nonstructural	NA	Resorbed	44.8
		4	Right femur	Iliac bone	Nonstructural	NA	Resorbed	43.7
		5	Right femur	Iliac bone	Nonstructural	NA	Resorbed	43.3
		5	Right femur	Cancellous bone	Nonstructural	Blount plate	Resorbed	42.8
		23	Right humerus	Freeze-dried rib, cancellous bone chips	Nonstructural	Cerclage wire	Resorbed	24.8
7	F	7	Left femur	Struts	Structural	NA	Resorbed	8.8
8	M	7	Right femur	Fibular strut, bone chips	Both	Anterior 6-0 dynamic compression plate	Resorbed	14.5
9	F	13	Right femur	Freeze-dried cortical strut	Structural	65-mm 5-hole 130° blade plate	Resorbed	9.7
		13	Right femur	Freeze-dried cortical bone	Unknown	70-mm 5-hole 95° condylar plate	Resorbed	9.5
10	M	12	Left femur	Bone bank rib	Nonstructural	NA	Maintained	47.0
11	F	18	Left femur	Crushed cancellous bone chips	Nonstructural	Zickel nail, tri-fin nail	Resorbed	19.7
		19	Left femur	Morselized freeze-dried bone bank bone	Nonstructural	Lukey wire	Resorbed	18.3
12	M	13	Right femur	Iliac crest bone	Nonstructural	NA	Maintained	21.7
		26	Right femur	Fibular strut	Structural	NA	Maintained	8.7
		29	Right femur	Fibular strut	Structural	NA	Maintained	5.7
		32	Right femur	Cancellous cubes	Nonstructural	Locking screws	Maintained	2.4
13	F	19	Left femur	Tibial strut	Structural	Blade plate	Resorbed	4.7
14	F	28	Right femur	Morselized cancellous iliac bone, reconstituted coral, bone matrix gel	Nonstructural	38-cm Richards intramedullary hip screw, 115-mm femoral head and neck screw	Resorbed	7.8

continued

TABLE I (*continued*)

Patient	Sex	Age *(yr)*	Site	Graft Type	Structural or Nonstructural	Concurrent Instrumentation*	Graft Fate	Length of Follow-up *(yr)*
15	M	4	Right femur	Unknown	Unknown	NA	Resorbed	9.8
16	M	7	Right femur	Unknown	Unknown	NA	Resorbed	8.2
		7	Right femur	Bone chips, Grafton	Nonstructural	3-hole 130° plate with 45-mm screw	Resorbed	7.7
		7	Left femur	Cancellous bone chips	Nonstructural	Lateral nail	Resorbed	7.6
		7	Right femur	Cancellous bone chips	Nonstructural	4-hole plate	Resorbed	7.3
		8	Left femur	Allomatrix	Nonstructural	Nancy nail	Resorbed	7.0
		9	Left femur	Allomatrix	Nonstructural	NA	Resorbed	6.2
17	F	15	Left femur	Bone bank bone	Nonstructural	NA	Maintained	3.0
		15	Left humerus	Unknown	NA	NA	Partially resorbed	3.0
18	M	21	Left femur	Unknown	Unknown	Kuntscher nail	Maintained	26.1
19	M	5	Right femur	Fibular strut	Structural	NA	Resorbed	8.6
		6	Right femur	Intercalary cortical bone, Grafton crunch, cancellous cubes	Nonstructural	NA	Resorbed	6.9
		9	Right femur	Freeze-dried corticocancellous fibular strut, cancellous cubes	Both	NA	Resorbed	4.3
20	M	10	Left femur	Fragmented bone bank rib	Nonstructural	NA	Resorbed	38.4
		10	Right femur	Ground cancellous boplant (soaked in thrombin)	Nonstructural	NA	Resorbed	38.3
		15	Right femur	Unknown	Unknown	NA	Resorbed	34.1
		16	Right tibia	Cortical tibia bone, fragmented bone bank rib	Both	Compression plate	Resorbed	32.8
		40	Right femur	Cortical strut	Structural	NA	Maintained	8.9
21	F	23	Left femur	Corticocancellous iliac crest bone	Nonstructural	Zickel nail	Resorbed	23.5
		23	Right femur	Corticocancellous iliac crest bone	Nonstructural	Zickel nail	Resorbed	23.4
22	M	24	Right femur	Unknown	Unknown	NA	Resorbed	14.6
		32	Right femur	Unknown	Unknown	NA	Maintained	6.1
23	M	11	Left femur	Cortical cancellous bone	Structural	Richards intermediate hip screw	Resorbed	13.8
		15	Left femur	Iliac crest, Interpore-500 coral	Nonstructural	NA	Resorbed	8.4

*NA = not applicable.

Discussion

These data demonstrate that in relatively young subjects with polyostotic fibrous dysplasia, the majority of bone grafts failed to incorporate, and the lesions eventually returned to a dysplastic state. Within a time frame of just more than fourteen years, half of the patients had complete loss of the graft. This suggests that bone-grafting is of limited value in younger patients with polyostotic fibrous dysplasia and not likely to induce a reliable or durable biological response. Surgical planning should look more toward restoration of the mechanical axes and support of the bone with appropriate implant fixation.

The work of Enneking and Gearen, which is widely cited and popularized the use of fibular allograft struts in patients with fibrous dysplasia, examined a population of mostly skeletally mature patients, the majority of whom had monostotic fibrous dysplasia (ten with monostotic fibrous dysplasia and five with polyostotic fibrous dysplasia)[13]. Yet even in that study, fibular grafts failed in two of five subjects with polyostotic fibrous dysplasia. Our study included a larger proportion of younger subjects, all of whom had polyostotic fibrous dysplasia, and found that allograft and autograft bone disappeared, with no selective advantage to either material. Thus, given these data, the application of the principles that appeared to be effective in older subjects with monostotic fibrous dysplasia to younger patients with polyostotic fibrous dysplasia or the McCune-Albright syndrome is not warranted.

Although the length of graft survival was significantly less in subjects younger than eighteen years of age, the presence of an endocrinopathy did not independently contribute to graft loss. A greater degree of graft loss in younger subjects may be because fibrous dysplasia lesions are typically more active in younger patients. Fibrous dysplasia lesions have long been reported to burn out with age. This concept is supported by recent evidence demonstrating that, in fibrous dysplasia, there are proportionally more active mutation-bearing bone cells in younger patients and that the drop-out of mutation-bearing cells can be accompanied by the emergence of microscopic areas of normal-appearing bone[25]. This effect presumably results from apoptosis of mutant skeletal progenitor cells, while adjacent normal progenitor cells self-renew and enable formation of a normal skeletal structure. The radiographic correlate of this finding is the observation that fibrous dysplasia lesions tend to become more sclerotic with age. Thus, in younger patients, the effect that fibrous dysplasia has on adjacent normal bone, in terms of erosion and destruction of adjacent normal structures, seems to be mimicked by the effect of fibrous dysplasia cells on bone graft material. Although the goal of curettage, which precedes bone-grafting, is to clear the lesion of these diseased, mutation-bearing cells, the fact that grafting material is eroded suggests that, in practice, removing all of the mutant cells is not possible and is not advisable to attempt. An approach to increase the likelihood of clearing the lesions of mutation-bearing cells so as to enhance graft incorporation is the addition of cryoablative techniques. Although two series studying this technique have included subjects with fibrous dysplasia[21,26], neither suggested that this technique improved the outcome in younger patients with polyostotic fibrous dysplasia, the group most in need of ablation of residual mutation-bearing cells. Therefore, in deciding which surgical approach to take, surgeons must determine which set of data is more applicable to the patient under consideration: for an older patient with monostotic fibrous dysplasia, or for a younger patient with polyostotic fibrous dysplasia. The recent assertion offered in surgical series and expert opinion reports that bone-grafting should be abandoned in younger patients with polyostotic fibrous dysplasia[17,27-29] is supported by the current study.

Optimal surgical management of femoral fibrous dysplasia has not been determined. The age of the patient and the location, size, and biological behavior of the lesions all influence the selection of the type of intervention. The poor physical qualities of the dysplastic bone make conventional internal fixation devices such as plates and screws less effective. Stable fixation is a technique with the potential to allow early weight-bearing, to decrease chronic bone pain at rest and with weight-bearing, and to improve function. Our current recommended practice (albeit without peer-reviewed evidence of its effectiveness) is to utilize intramedullary nailing in the surgical procedure for severe fibrous dysplasia involvement of weight-bearing long bones. Intramedullary nailing provides long-term stabilization of widely affected femora, preventing fractures and major progressive deformities. It may be used acutely for fracture treatment or in elective surgical procedures. Interlocking intramedullary nailing with neck cross-pinning to control rotation may improve functional results and prevent deformity by stabilizing mechanical alignment and sharing load to allow early rehabilitation. The newly available small-diameter pediatric interlocking intramedullary nails provide new treatment options for young patients.

The strengths of this study included a relatively large cohort and a robust follow-up period. Subjects were well characterized with regard to endocrine dysfunction and were heterogeneous in both age and grafting material. The subject numbers were necessarily limited given the disease rarity; however, the population provided sufficient power for analyses of the primary outcomes of interest, including the effect of age on graft survival. The subject numbers and the variability in the length of follow-up limited the ability to perform additional subanalyses examining the effects of other subject characteristics on graft outcomes. It is therefore possible (but unlikely) that if the subgroups of subjects with various types of grafting material, surgical techniques, or specific aspects of endocrine dysfunction were larger, differences between the survivals of various materials may have been demonstrated. The use of bisphosphonates by four subjects is a potential confounding variable. Although the effects of bisphosphonates on fibrous dysplasia have not been definitively determined, available data suggest that these medications do not improve fibrous dysplasia appearance or bone quality and would thus not be expected to have an impact on graft survival[30].

The limitations of this study included the inability to accurately determine the specific indications for the initial or

repeat operation(s) or to directly assess pathological fractures in relationship to bone-grafting. This is because the orthopaedic care was not performed at the NIH, and those data were collected retrospectively as part of a natural history study. The data collection tool did not capture data of sufficient detail to answer these questions. The evaluation of graft fate was also limited to the assessment of radiographs. Important potential confounders include the inherent bias of retrospective design and referral bias at the NIH, which may reflect a more severely affected population. Studies in diseases with broad clinical phenotypes such as fibrous dysplasia or the McCune-Albright syndrome are frequently confounded by heterogeneity in patient cohorts, which may limit generalizability of results. As is typical in fibrous dysplasia or the McCune-Albright syndrome, there was clinical heterogeneity among the subjects in this analysis with regard to disease severity and presence of endocrinopathies. The impact of specific endocrinopathies on graft fate and other clinical outcomes in fibrous dysplasia is unknown and requires additional, larger studies to determine.

In summary, bone-grafting in young patients with polyostotic fibrous dysplasia is of very limited value. Further research is needed to determine the role of additional techniques such as metallic implant support in surgical management of fibrous dysplasia lesions, particularly in younger patients with higher disease burden. ■

NOTE: This article is dedicated to the memory of the first author, the late Dr. Arabella Leet (1965-2013), who died suddenly and tragically during the preparation of the manuscript.

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ORIGINAL ARTICLE

JBMR®

Scoliosis in Fibrous Dysplasia/McCune-Albright Syndrome: Factors Associated With Curve Progression and Effects of Bisphosphonates

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ABSTRACT

Scoliosis is a complication of fibrous dysplasia/McCune-Albright syndrome (FD/MAS); however, risk factors and long-term outcomes are unknown. Bisphosphonates are commonly used; however, it is unknown whether their use decrease the risk of progressive scoliosis. Clinical data from the National Institutes of Health (NIH) cohort study was reviewed. Cobb angles were measured, and variables associated with scoliosis progression were identified. Of 138 subjects with available radiographs, 84 (61%) had scoliosis, including 55 (65%) classified as mild (Cobb angle >10 to ≤30 degrees), 11 (13%) as moderate (>30 to ≤45 degrees), and 18 (22%) as severe (>45 degrees). Total skeletal disease burden was highly associated with scoliosis severity ($p < 0.0001$). Endocrinopathies associated with scoliosis included fibroblast growth factor 23 (FGF23)-mediated hypophosphatemia ($p < 0.001$) and hyperthyroidism ($p < 0.001$). Bone turnover markers, including osteocalcin and NTX-telopeptides, were associated with severe scoliosis ($p < 0.01$). Associations were identified between Cobb angle and functional metrics, including leg length discrepancy ($p < 0.01$), hip range of motion ($p < 0.05$), and strength of the gluteus medius and maximus ($p < 0.01$). Longitudinal analyses were conducted in 69 subjects who had serial radiographs over a median 4.9-year period (range, 0.9 to 14.7 years). Twenty-two subjects were treated with bisphosphonates; there was no difference in Cobb angle progression compared to untreated subjects (0.10 versus 0.53 degrees/year, $p = 0.36$). Longitudinal data was available for 10 of 12 subjects treated with spinal fusion; one had instrumentation failure, but in nine subjects Cobb angles were stable with 6.1 years of follow-up (range, 0.9 to 14.7 years). Two fatalities from scoliosis-associated restrictive lung disease occurred in subjects managed non-operatively. Scoliosis occurs frequently in patients with polyostotic FD, and may be potentially fatal. The primary risk factor for progressive scoliosis is total skeletal disease burden. Treatable features that contribute to scoliosis progression include leg length discrepancy, FGF23-mediated hypophosphatemia, and hyperthyroidism. Current data do not support routine use of bisphosphonates to prevent progression of spinal curvature. Spinal fusion is frequently effective in providing long-term stability, and may be lifesaving. Published 2018. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: ANTIRESORPTIVES; THERAPEUTICS; IMPLANTS; ORTHOPAEDICS; PRIMARY TUMORS OF BONE AND CARTILAGE; CANCER

Introduction

Fibrous dysplasia (FD) is a mosaic disorder arising from somatic activating mutations in $G\alpha_s$, resulting in the replacement of bone and marrow with fibro-osseous tissue.[1,2] Discrete, expansile bone lesions lead to fractures, deformity, functional impairment, and pain.[3] FD can involve one bone (monostotic) or multiple bones (polyostotic), and can affect any part or combination of the skeleton.[3] FD may occur in isolation, or in association with café au lait skin macules and hyperfunctioning endocrinopathies, including hyperthyroidism, precocious puberty, growth hormone excess, hypercortisolism, and fibroblast growth factor 23 (FGF23)-mediated

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hypophosphatemia. The combination of FD and one or more extraskeletal features is termed McCune-Albright syndrome (MAS).[3,4]

Scoliosis is common in FD/MAS, and when severe can result in significant morbidity, including pain, functional impairment, and respiratory compromise.[5,6] Risk factors for the development and progression of scoliosis in FD have not been determined, and long-term clinical outcomes are unknown. Bisphosphonates have been advocated as a potential treatment to decrease bone turnover and pain in FD patients[7,8]; however, there is little data associating bisphosphonate treatment with skeletal outcomes such as progression of scoliosis.

The purpose of this investigation was to define the spectrum and natural history of scoliosis in a large cohort of patients with FD/MAS, to identify clinical factors that contribute to progressive scoliosis, and to evaluate the effect of bisphosphonate treatment on the rate of scoliosis progression.

Subjects and Methods

Subjects

Subjects were evaluated at the National Institutes of Health (NIH) Clinical Center as part of a longstanding cohort study in FD/MAS (http://clinicaltrials.gov/show/NCT00001727). The study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research (NIDCR), and all subjects gave informed consent/assent. The diagnosis of FD/MAS was established on clinical grounds with molecular diagnosis as needed, according to previously reported guidelines.[3] Spinal radiographs were obtained in subjects with significant involvement of the axial skeleton as assessed on bone scan, or those in whom scoliosis was suspected based on physical examination. All subjects with spinal radiographs available for Cobb angle measurement were included in the analyses.

Radiographic evaluation

Cobb angles were measured using a digital picture archiving and communication system (PACS) platform by a single reader (SHT). When multiple curves were present, the largest angle was utilized. Scoliosis severity was categorized into three groups: mild ($>$10 to $\leq$30 degrees), moderate ($>$30 to $\leq$45 degrees), and severe ($>$45 degrees).

The skeletal disease burden score (SDBS) is a quantitative measure of total skeletal FD involvement validated to predict clinical outcomes.[9] SDBS was determined for all subjects from ^{99}Tc- methylene diphosphonate bone scintigraphy using previously reported methodology.[9] These bone scans were also evaluated to identify FD in the cervical, thoracic, and lumbar spine.

Functional metrics

Subjects underwent physiatric evaluation, including assessment of leg length, hip range of motion, and muscle strength based on manual muscle testing. Age- and sex-adjusted *Z*-scores were determined for range of motion based upon previously established normative data.[10]

Bisphosphonate treatment

Information was collected regarding bisphosphonate treatment, including formulation, dose, and dates administered.

Statistical analysis

Statistical analyses performed with GraphPad Prism (version 7.01; GraphPad Software, Inc., La Jolla, CA, USA) included Fisher exact tests, chi-square analyses, Mann-Whitney tests, Kruskal-Wallis tests, linear regressions, and Spearman correlations as appropriate. SPSS (version 23; IBM Corp., Armonk, NY, USA) was used to perform multiple linear regression analysis. Mediation analyses between variables was performed using Baron and Kenny's joint significance test.[11] Statistical significance was predetermined for p values <0.05. Numerically continuous variables are reported as median (interquartile range [IQR]; range).

Results

Subject characteristics

Of 198 total subjects in the NIH FD/MAS cohort, 138 had spinal radiographs available for Cobb angle measurement, and 84 (61%) of these subjects had some degree of scoliosis. Fifty-five subjects (65%) were classified as having mild scoliosis ($>$10 to $\leq$30 degrees), 11 subjects (13%) as moderate ($>$30 to $\leq$45 degrees), and 18 subjects (22%) as severe ($>$45 degrees). The primary curve was thoracolumbar in 39 subjects (46%), thoracic in 31 subjects (37%), lumbar in nine subjects (11%), and cervicothoracic in five subjects (6%). Curves were C-shaped in 34 subjects (40%), and S-shaped in 50 subjects (60%).

Subject characteristics are included in Table 1. There was no significant difference in the prevalence of scoliosis between male and female subjects. Subjects with scoliosis were younger than those without scoliosis ($p = 0.03$); however, there were no significant differences in age between scoliosis severity groups. A total of 106 subjects (77%) had at least one MAS-associated endocrinopathy. Of these, hypophosphatemia and hyperthyroidism were significantly associated with increased scoliosis severity ($p < 0.001$).

Radiographic evaluation

Skeletal disease burden score (SDBS) was significantly associated with severity of scoliosis ($p < 0.0001$, Table 1). When evaluating Cobb angle as a continuous variable, a significant positive association was identified between scoliosis severity and SDBS ($R^2 = 0.34$, $p < 0.0001$, Fig. 1*A*). Spinal FD was highly significantly associated with both the presence of scoliosis ($p < 0.0001$), and with scoliosis severity ($p < 0.0001$). Of 60 total subjects with an SDBS $\geq$35 (indicating that $\geq$50% of the total skeleton is involved with FD), 50 (83%) had FD involving the spine, and 10 (17%) had no spinal FD involvement. All subjects with an SDBS $\geq$35 had severe scoliosis.

Leg length discrepancy and functional metrics

For all groups with scoliosis (mild, moderate, and severe), there was a significant discrepancy in leg lengths when compared to subjects without scoliosis ($p < 0.05$, Table 1). When analyzing Cobb angle as a continuous variable, a significant positive regression was observed with leg length discrepancy ($R^2 = 0.08$, $p < 0.01$, Fig. 1*B*).

Negative associations were found between Cobb angle and manual muscle testing at the level of the hips bilaterally in both the gluteus medius and maximus (left gluteus medius: $R = -0.34$, $p = 0.0006$; right gluteus medius: $R = -0.41$, $p < 0.0001$; left gluteus maximus: $R = -0.29$, $p = 0.0039$; right gluteus maximus: $R = -0.03$, $p = 0.002$). There was no significant correlation

Table 1. Subject Characteristics

Characteristic	No scoliosis ($n = 54$)	Mild scoliosis (>10 to ≤30 degrees) ($n = 55$)	Moderate scoliosis (>30 to ≤45 degrees) ($n = 11$)	Severe scoliosis (>45 degrees) ($n = 18$)	p
Age at last follow-up (years), median (range)	14 (2–53)[bcd]	22 (3–80)[a]	28 (10–59)[a]	22.5 (3–50)[a]	0.03
Male, *n* (%)	26 (48)	25 (45)	3 (27)	6 (33)	NS
Endocrinopathies, *n* (%)					
Precocious puberty	28 (52)	25 (45)[c]	9 (82)[b]	13 (72)	0.06
Hyperthyroidism	11 (20)[d]	17 (31)[d]	5 (45)	14 (78)[ab]	<0.0001
Hypophosphatemia	6 (11)[bd]	17 (31)[ad]	4 (36)	11 (61)[ab]	0.0004
Growth hormone excess	11 (20)	12 (22)	4 (36)	6 (33)	NS
Hypercortisolism	4 (7)	1 (2)	0 (0)	6 (33)	N/A
Skeletal disease burden score, median (range)	12.2 (0.4–29.8)[bd]	34.6 (15.5–44.8)[ad]	40.2 (11.3–63.7)	64.4 (45.7–73.2)[ab]	<0.0001
Leg length discrepancy (cm), median (range)	0.5 (0.0–1.0)[bd]	1.5 (0.5–2.5)[a]	1.3 (1.0–3.0)[a]	2.0 (1.0–3.5)[a]	0.0002
Bone turnover markers, median (range)					
Alkaline phosphatase (U/L)	303 (164–422)[d]	351 (193–613)[d]	521 (233–883)	663 (481.5–1356)[ab]	0.0001
Osteocalcin (ng/mL)	100 (43–164)[d]	104 (47–184)[d]	96 (77–180)	229 (123–330)[ab]	0.0027
NTX-telopeptide (nmol/mmol)	495 (147–893)[d]	413 (119–1043)[d]	661 (270–1347)	1225 (885–3463)[ab]	0.0008

Values of p represent the overall significance of difference between scoliosis types as calculated by ANOVA or chi-square analyses.
NS = not significant, N/A = non-applicable.
[a]Significant difference from normal.
[b]Significant difference from mild.
[c]Significant difference from moderate.
[d]Significant difference from severe.

between iliopsoas strength and Cobb angle (left: $R = -0.17$, $p = 0.09$; right: $R = -0.14$, $p = 0.18$).

Negative correlations were observed between Cobb angle and hip range of motion *Z*-scores bilaterally with flexion (left: $R = -0.34$, $p = 0.0007$; right: $R = -0.38$, $p < 0.0001$), extension (left: $R = -0.38$, $p < 0.0001$; right: $R = -0.22$, $p = 0.03$), internal rotation (left: $R = -0.23$, $p = 0.02$; right $R = -0.32$, $p = 0.001$), and abduction (left: $R = -0.33$, $p = 0.001$; right: $R = -0.38$, $p = 0.0001$). Insignificant correlation was observed in hip external rotation (left: $R = -0.05$, $p = 0.59$; right: $R = 0.02$, $p = 0.86$).

Impaired ambulation was defined as the regular use of assistive ambulation devices (cane, crutches, walker, and/or wheelchair). The presence of impaired ambulation was highly associated with scoliosis ($p = 0.0009$).

Bone turnover markers

Serum bone turnover markers included alkaline phosphatase and osteocalcin, reflecting bone formation, and N-terminal telopeptides, reflecting bone resorption. By categorical analysis, bone turnover markers correlated only with severe scoliosis ($p < 0.001$, Table 1). Linear regression analysis of Cobb angle as a continuous variable was positively associated with bone turnover markers (alkaline phosphatase $R^2 = 0.074$, $p = 0.0001$, osteocalcin $R^2 = 0.086$, $p = 0.0007$, and N-terminal telopeptides $R^2 = 0.093$, $p = 0.0003$) (Fig. 1*C*, *D*).

Spinal fusion procedures

Twelve subjects underwent posterior spinal arthrodesis. Procedures were performed outside of NIH between 1978 to 2011. Instrumentation systems included Luque rods alone (1/12), Moss-Miami (1/12), Wisconsin segmental with Luque and Harrington rods (1/12), Unit rods (1/12), Zimmer rods (1/12), and dual rods with pedicle screws and hooks (1/12). Two subjects had anterior spinal decompression procedures performed prior to posterior fusions, one utilized Harm's interbody cages. Fusion was performed from as superiorly as T_1 to as inferiorly as the pelvis. Postoperative complications included one case of right upper lobar atelectasis, one case of pneumonia, and one case of retained surgical sponge requiring retrieval.

Only one case of instrumentation failure was reported. This patient was implanted with dual rods with pedicle screws, and hooks from T_3 to L_4. Three months postoperatively an upper claw and upgoing hook had loosened and were no longer stable. The patient developed pain at the location of the unstable instrumentation, after which the instrumentation was removed.

Longitudinal analyses

Sixty-nine subjects (50% of the cohort) had serial films available for longitudinal analysis of scoliosis progression. The median length of time between the initial and most recent radiograph was 4.9 years (IQR, 6.5 years; range, 0.9 to 14.7. years).

Bisphosphonate treatment

Twenty-two subjects were treated with bisphosphonates during the longitudinal observation period. Subjects were treated on clinical grounds, primarily outside of NIH by local clinicians. Regimens were therefore individualized and varied for each

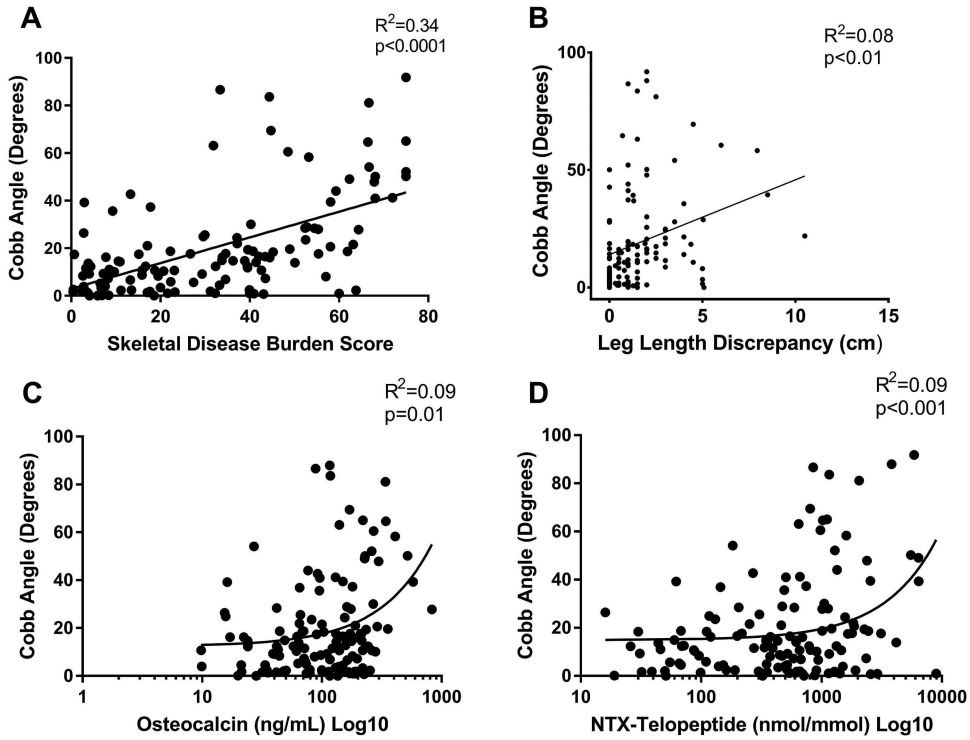

Fig. 1. Clinical and biochemical factors associated with scoliosis severity. (*A*) Skeletal disease burden score, a quantitative measure of overall fibrous dysplasia burden (see Collins and colleagues[9]). (*B*) Leg length discrepancy. (*C*) Osteocalcin, a bone formation marker. (*D*) NTX (a bone resorption marker) were all significantly associated with the severity of scoliosis, as measured by Cobb angle. NTX = N-terminal telopeptide.

patient. Although some subjects received fixed dosing intervals, others were infused at variable intervals, as needed to control bone pain. Table 2 shows the cumulative dose of bisphosphonates received for each subject during the observation period.

Thirty-one subjects in the longitudinal cohort never received bisphosphonates. Seven subjects received bisphosphonates prior to but not during the observation period, and were eliminated from the analyses. One bisphosphonate-treated subject was eliminated from the analyses because the dosing regimen could not be verified. For subjects treated with spinal fusion, only preoperative serial films were included in the analyses. Eight subjects were eliminated from the analyses because they did not have preoperative serial films available for review.

There was no significant difference in the change/year in Cobb angle for the 22 bisphosphonate-treated subjects compared to the 31 subjects who never received bisphosphonates: median (IQR; range) 0.10 degrees/year (IQR, 1.83 degrees; range, −14.90 to 5.67 degrees) versus 0.53 degrees/year (IQR, 2.17 degrees; range, −3.53 to 22.31 degrees) ($p = 0.36$) (Fig. 2*A*). No significant differences in clinical features were identified between the groups of bisphosphonate-treated and untreated subjects, including age (22 years [IQR, 29 years; range, 6 to 75 years] versus 16 [IQR, 12 years; range, 2 to 58 years]; $p = 0.09$), length of follow-up (4.9 years [IQR, 6.6 years; range, 0.9 to 13.5 years] versus 4.6 years [IQR, 6.5 years; range, 0.9 to 13.8 years]; $p = 0.93$), baseline Cobb angle (15.82 degrees (IQR, 27.42 degrees; range, 0 to 63.87 degrees] versus 12.16 degrees [IQR, 19.62 degrees; range, 0 to 66.15 degrees]; $p = 0.31$), SDBS (46.1 [IQR, 45.5; range, 7.8 to 68.1] versus 33.3 [IQR, 32.6; range, 2.4 to 68.1]; $p = 0.06$), and leg length discrepancy (1.3 cm [IQR, 2.9 cm; range, 0 to 8.5 cm] versus 1.0 [IQR, 2.08 cm; range, 0 to 10.5 cm]; $p = 0.63$). There were no significant differences in the prevalence of MAS-associated endocrinopathies between groups (data not shown).

Surgical management

Longitudinal data was available for 10 of the 12 subjects treated with spinal fusion. Therefore, in the cohort of subjects evaluated longitudinally, 59 (86%) were managed non-operatively, while 10 (14%) underwent spinal fusion. The median follow-up for non-operative subjects was 4.3 years (IQR, 6.5 years; range, 0.9 to 13.8 years), and 6.1 years (IQR, 7.9 years; range, 0.9 to 14.7 years) for those treated with spinal fusion ($p = 0.05$). The median change/year in Cobb angle in the non-operative group was 0.59 degrees/year (IQR, 1.9 degrees/year; range, −14.9 to 22.3 degrees/year), whereas there was essentially no progression in the operative group (−0.25 degrees/year [IQR, 1.4 degrees/year; range, −14.3 to 1.78 degrees/year]; $p = 0.03$) (Fig 2*B*). For the purposes of the analyses, clinically significant progression was defined as an increase in Cobb angle of >10 degrees. Eighteen of the 59 non-operative subjects (31%) had clinically significant progression, with a median change in Cobb angle of 18.3 degrees (range, 10.7 to 66.9 degrees). Within the non-operative group, subjects with clinically significant progression had a significantly greater median SDBS compared to non-progressors (44.6 [IQR, 33.9; range, 29.4 to 63.4] versus 31.2 [IQR, 32.3; range, 10.7 to 43.0]; $p = 0.02$). Only one of the 10 operative subjects with serial films met criteria for clinically significant progression (10.5 degrees). Representative radiographs for non-operative and operative subjects are shown in Figs. 3*A-D* and 4*A-C*.

Table 2. Characteristics of Subjects Treated With Bisphosphonates

Sex/age (years)	Observation and treatment period (years)	Cumulative bisphosphonate dose
F/39	13.3	Zoledronate 40 mg
M/16	5.4	Zoledronate 48 mg
M/17	9.0	Zoledronate 84 mg
M/14	8.8	Zoledronate 28 mg
F/22	2.5	Zoledronate 4 mg
M/32	9.8	Pamidronate 150 mg, zoledronate 53 mg
F/28	2.5	Zoledronate 5 mg
M/44	13.3	Zoledronate 18 mg
F/41	4.9	Risedronate 10,950 mg
F/32	2.0	Alendronate 14,600 mg
M/14	3.0	Alendronate 14,600 mg
M/8	8.3	Pamidronate 160 mg
M/36	13.5	Alendronate 29,200 mg
F/4	2.7	Pamidronate 360 mg
M/9	3.1	Alendronate 7,300 mg
M/49	1.0	Alendronate 3,640 mg
F/7	6.2	Pamidronate 240 mg
M/8	6.4	Pamidronate 75 mg, zoledronate 2 mg
M/9	1.0	Pamidronate 40 mg, zoledronate 2 mg
F/3	4.3	Pamidronate 100 mg
M/17	1.2	Zoledronate 10 mg
F/12	2.0	Zoledronate 20 mg

F = female; M = male.

Fatalities

Two fatalities occurred from scoliosis-associated complications of restrictive lung disease in subjects with progressive scoliosis. Both subjects were managed non-operatively. A 19-year-old woman expired from multi-organ failure and disseminated intravascular coagulation due to pneumonia. Her Cobb angle at the time of death was 91.8 degrees. A 41-year-old man succumbed to respiratory failure and acidosis, with a Cobb angle of 121.4 degrees at time of death.

Multiple linear regression analyses

Multiple linear regression analyses were conducted to identify potential relationships between the clinical variables associated with scoliosis. After controlling for demographics (age and sex), SDBS remained significantly associated with Cobb angle ($p = 0.03$). When additional variables (including MAS endocrinopathies, leg length discrepancy, and bone turnover markers) were incorporated into a statistical model that controlled for both demographics and SDBS, no statistically significant associations with Cobb angle were identified (see Supplementary Table 1). Based on our observations that these variables may be clinically relevant, we tested for the possibility that the effects of these variables were mediated through the effects of SDBS using the Baron and Kenny's joint significance test (see Supplementary Fig. 1). The results of these analyses showed that relationships between the following variables and Cobb angle were fully mediated by SDBS: leg length discrepancy, alkaline phosphatase, osteocalcin, N-terminal telopeptide, and hypophosphatemia. Additionally, the relationships between Cobb angle and the location of FD in the spine (cervical, thoracic, lumbar), and hyperthyroidism were partially mediated by SDBS.

Discussion

Findings from this large series show that scoliosis occurs frequently in patients with polyostotic FD, and in severe cases may be progressive and potentially lethal. Total skeletal FD involvement was highly correlated not only with the presence and severity of scoliosis, but also with the likelihood of scoliosis progression. This highlights that staging of total disease burden with skeletal imaging (such as scintigraphy) is an important component of evaluation in FD that may inform the risk of developing future complications. Serum bone turnover markers were an additional marker of disease activity that correlated with severe scoliosis; these should be considered as an adjunct to clinical and radiographic assessment.

Statistical analyses indicated that skeletal disease burden was the only significant variable predicting scoliosis progression. However, mediation analyses showed that additional clinical variables may affect scoliosis through their relationship with disease burden. This suggests that these variables are clinically relevant if they are considered in the context of an individual's overall FD burden, and are likely to have a greater impact in

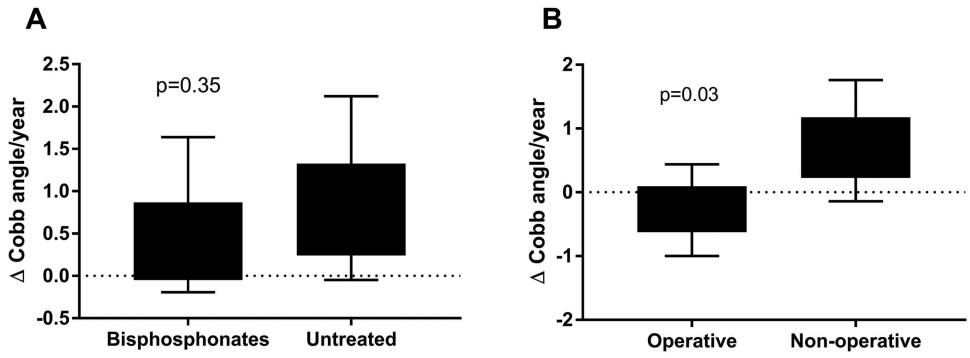

Fig. 2. Progression of scoliosis. (*A*) Change per year in Cobb angle in subjects treated and not treated with bisphosphonates. (*B*) Change per year in Cobb angle for subjects managed non-operatively and with spinal fusion. Boxes show median values, and whiskers show interquartile range.

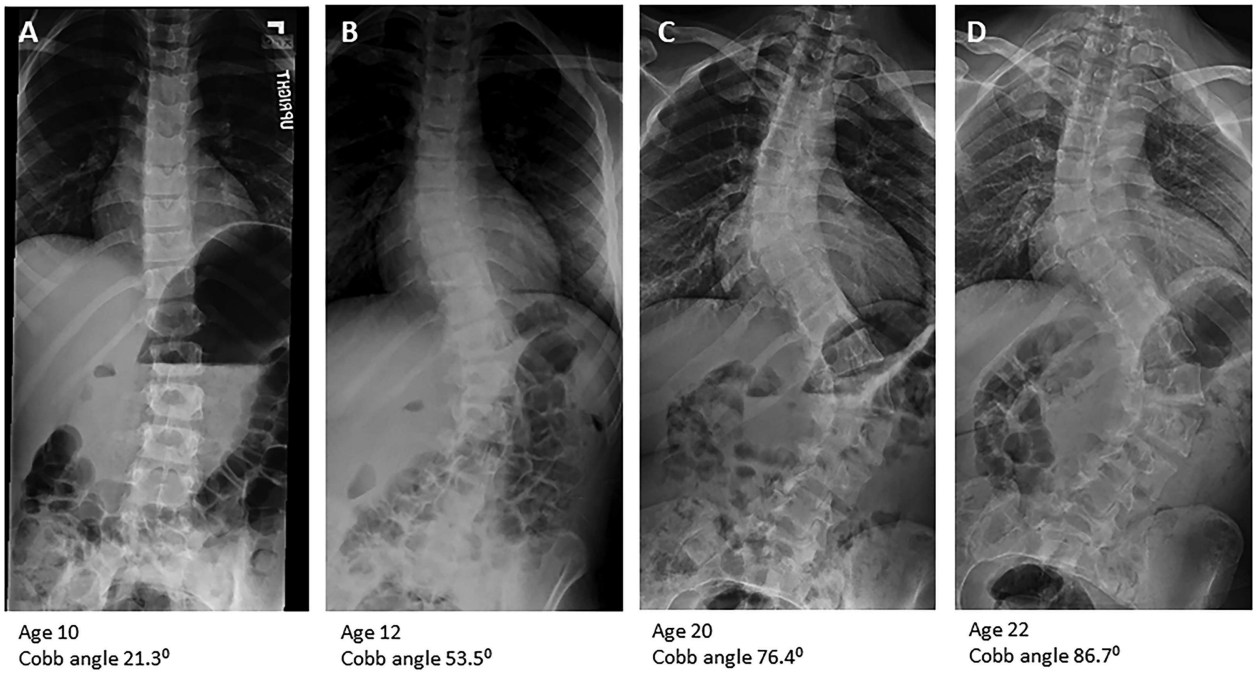

Fig. 3. Serial radiographs demonstrating progressive scoliosis in a subject managed non-operatively. (*A*) Scoliosis is mild at age 10 years, with a Cobb angle of 21.3 degrees. (*B*) By age 12 years, Cobb angle has progressed to 53.5 degrees. (*C*) Further progression of scoliosis, with a Cobb angle of 76.4 degrees at age 20 years. (*D*) By age 22 years, scoliosis is increasingly severe, with a Cobb angle of 86.7 degrees.

patients who have greater amounts of skeletal disease. Leg length discrepancy was one such variable that indirectly impacted Cobb angle, likely through its effects on spinal alignment.[12] Leg length discrepancies are common in FD due to mosaic involvement of the lower limbs. FD lesion growth tends to expand limb length, whereas fractures and deformities decrease limb length, resulting in complex and dynamic malalignment. Impairments in hip mobility and pelvic girdle

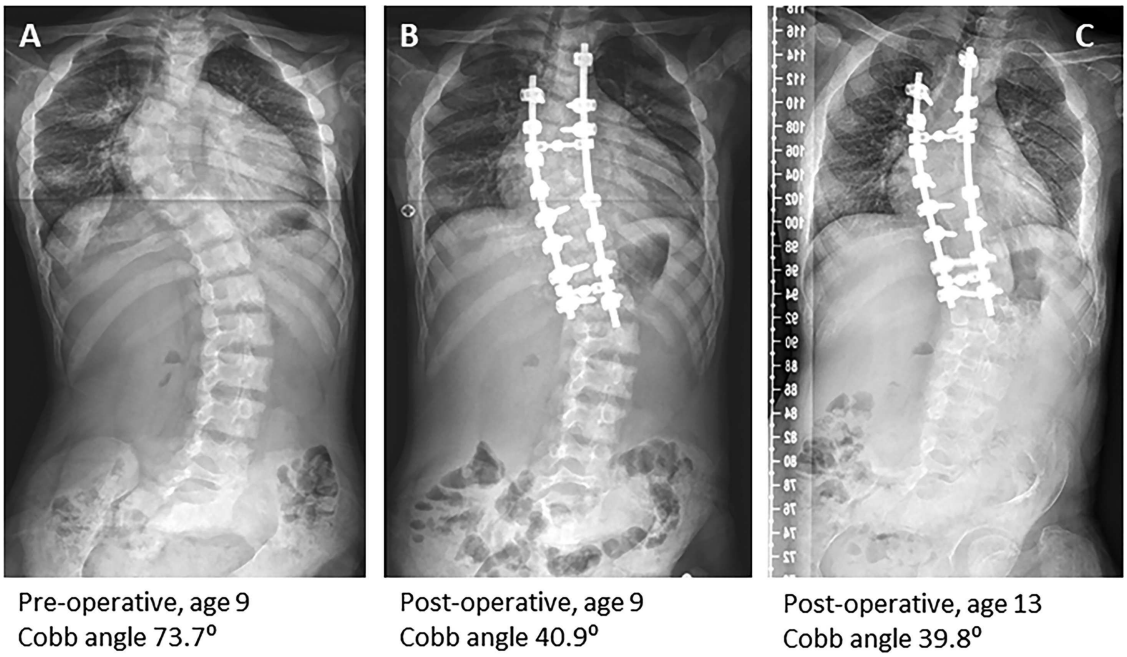

Fig. 4. Stable scoliosis in a subject managed operatively. (*A*) Preoperative radiograph from a 9-year-old girl with severe progressive scoliosis and a thoracic curve of 73.7 degrees. (*B*) Shortly following posterior spinal fusion with placement of pedicle screws, dual rods, and crosslinks, the thoracic curve has improved to 40.9 degrees. (*C*) 3.5 years postoperatively, the now 13-year-old girl has a stable Cobb angle of 39.8 degrees.

strength demonstrate that functional deficits contribute to clinical disease. Similar to other forms of scoliosis, it is unclear whether these muscular impairments directly impact spinal curvature, or arise as secondary effects.[13] However, skeletal disease burden was highly associated with scoliosis even in subjects without spinal FD, suggesting a potential causative role for functional deficits. Of note, leg length discrepancy has been independently associated with decreased hip strength, range-of-motion, and gait efficiency in patients with FD.[14] These findings highlight the critical importance of monitoring for and treating leg length discrepancies as part of routine care. Our current practice includes functional evaluation at least yearly for all patients with FD involving the spine or lower extremities, and more frequently for patients experiencing complications that may alter gait dynamics, such as fractures and surgeries. Management is targeted at correcting pelvic obliquity to balance the forces influencing spinal alignment, with a current threshold for intervention of 0.3 cm (1/8 inch). Conservative management, through introduction of lifts and other orthotic devices, is recommended in combination with targeted physical therapy. Surgical treatments such as epiphysiodesis should be undertaken cautiously given the multiple dynamic factors that may affect leg length discrepancies in FD, which may limit the long-term success of this approach.

Additional features associated with scoliosis included the MAS-associated endocrinopathies FGF23-mediated hypophosphatemia and hyperthyroidism. Hypophosphatemia has previously been associated with increased fractures in patients with FD,[15] and this study is the first to demonstrate an association with bony deformities. Taken together, these findings demonstrate the critical importance of ongoing monitoring of phosphorus levels in patients with FD. Treatment should be initiated in patients who have serum phosphorus levels below the normal range for age, regardless of symptoms, with the goal of preventing skeletal complications. This study is the first to associate MAS-associated hyperthyroidism with negative skeletal outcomes in FD. This is consistent with the known detrimental effects of excess thyroid hormone on bone metabolism,[16,17] and supports an aggressive approach to managing endocrinopathies in patients with MAS.

This study extends the clinical spectrum of FD with the first reported fatalities from progressive scoliosis. The lack of fatalities in subjects managed operatively supports that spinal fusion may be lifesaving in this population.

Bisphosphonate treatment was not associated with decreased progression of spinal curvature in longitudinal analyses. Bisphosphonates are frequently prescribed in patients with FD; however, data linking treatment with skeletal outcomes are lacking. Previous studies have reported reductions in bone turnover, but inconsistent effects on pain and radiographic appearance of FD lesions.[7,18,19] A placebo-controlled trial of alendronate demonstrated improvements in resorption markers and bone density, but no effects on pain.[20] This study is the first to evaluate the effects of bisphosphonates on FD deformity. Interpretation of these findings is limited by the retrospective nature of the study design, which resulted in significant variability in bisphosphonate dosing. Although a variety of formulations and regimens were used, most subjects received a relatively high cumulative exposure. Although the study cohort was large, given the rarity of FD/MAS, it is possible that a larger population may be required to detect therapeutic effects of bisphosphonates. Prospective controlled studies with consistent treatment regimens are needed to definitively determine the role of bisphosphonate therapy in preventing skeletal deformity in FD.

Strengths of this study include extensive follow-up and detailed subject phenotyping that allowed for investigation of associations between scoliosis and specific clinical features. This is the largest series of patients studied to date. Despite the considerable morbidity associated with scoliosis in FD, the current literature on this topic is extremely limited, and findings from this series have the potential to directly impact care for patients. Limitations include the retrospective nature of the study. Because subjects were seen at a tertiary referral center, the cohort may be biased toward more severely affected patients. This may limit the generalizability of the results; however, it also enables the identification of risk factors associated with scoliosis development and progression. In particular, findings from this study may overestimate the prevalence of scoliosis in FD/MAS, because patients with milder forms of the disease may not have been sufficiently represented. This is the largest series to include long-term outcomes from spinal fusion procedures in patients with FD. Somewhat surprisingly, given the generally poor durability of orthopedic operations in FD,[21,22] this study shows that surgical management of scoliosis in FD can be safe and have durable efficacy. However, because of the variety of instrumentation and techniques, these findings are unable to inform specific surgical approaches.

Scoliosis occurs frequently in patients with polyostotic FD, and clinical monitoring as part of a multidisciplinary team should be part of routine care. The primary risk factor for progressive scoliosis in FD is total skeletal disease burden. Treatable features that contribute to scoliosis progression include leg length discrepancy, pelvic girdle weakness, FGF23-mediated hypophosphatemia, and hyperthyroidism. Clinical care for patients with FD should involve systematic evaluation and treatment of these features, which may impact long-term skeletal outcomes. The current data does not support routine use of bisphosphonates to prevent progression of spinal curvature. Spinal fusion is frequently effective in providing long-term stability, and may be potentially lifesaving.

Disclosures

The authors report no disclosures.

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content: RS, SP, LCG, MTC, and AMB. Approving final version of manuscript: JAB, SHT, KT, LK, LCG, SP, RS, MTC, and AMB. AMB takes responsibility for the integrity of the data analysis.

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McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia

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Abstract

Fibrous dysplasia (FD) is sometimes accompanied by extraskeletal manifestations that can include any combination of café-au-lait macules, hyperfunctioning endocrinopathies, such as gonadotropin-independent precocious puberty, hyperthyroidism, growth hormone excess, FGF23-mediated renal phosphate wasting, and/or Cushing syndrome, as well as other less common features. The combination of any of these findings, with or without FD, is known as McCune-Albright syndrome (MAS). The broad spectrum of involved tissues and the unpredictable combination of findings owe to the fact that molecular defect is due to dominant activating mutations in the widely expressed signaling protein, $G_s\alpha$, and the fact these mutations arises sporadically, often times early in development, prior to gastrulation, and can distribute across many or few tissues.

The complexity can be mastered by a systematic screening of potentially involved tissues and cognizance that the pattern of involved tissues is established, to some degree, in utero. Thorough testing allows the clinician to establish, often times at presentation, the full extent of the disease, and importantly as well what tissues are unaffected. Treatment and follow-up can then be focused on affected systems and a meaningful prognosis can be offered to the patient and family. The authors outline screening and treatment strategies that allow for effective management of the extraskeletal manifestations of FD.

Introduction

The original extraskeletal manifestations of fibrous dysplasia (FD) reported by McCune [1] and Albright [2] were café-au-lait spots, precocious puberty, and hyperthyroidism. With time a number of manifestations were added to the spectrum of findings that could be seen in association with FD. These included growth hormone (GH) excess [3], hypercortisolism [4], hypophosphatemia/osteomalacia [5], hepatic involvement [6], cardiac involvement [7], and others [8].

NIH cohort

To evaluate the extraskeletal manifestations observed in patients with FD we reviewed all of the patients seen at the National Institutes of Health over the last 24 years. The evaluation included physical examination, imaging studies (skeletal survey, head CT, nuclear medicine bone scan, ultrasound of the thyroid and gonads, and MRI of the pituitary), biochemical studies of skeletal metabolism and endocrine axes, and when available mutation analysis of affected tissue. There have been 140 patients evaluated at the time of this review. Patients have been followed from <1 – 24 years.

Prevalence of extraskeletal manifestations

The relative prevalence of findings in MAS patients in the NIH cohort are shown in Table 1. While these data probably reflect the relative prevalence of each of these findings, it is also likely that the NIH cohort represents a more severely affected group of patients than is typically found in clinical practice. Therefore the likelihood of an individual patient with FD having a given manifestation is probably lower than shown here.

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Table 1 Prevalence of major findings in the NIH cohort of patients with fibrous dysplasia/McCune-Albright syndrome

Clinical finding	% patients[1]
Fibrous dysplasia	98
Café-au-lait spots	66
Gonadal abnormalities	
Male: (ultrasound)[2]	70
Female: precocious puberty	50
Thyroid abnormalities	
Abnormal ultrasound (U/S)	66
Hyperthyroid + abnormal U/S	28
Renal phosphate wasting	43
Hypophosphatemia	10
Growth hormone excess	21
Cushing's syndrome	4

[1] n = 140; 58 males, 82 females
[2] detected on ultrasound

In addition to the major and more common/classic findings seen in association with FD as part of the McCune-Albright syndrome, we have observed a number of other findings in associated with the disease. These are shown in Table 2.

Timing of appearance of extraskeletal manifestations

An important consideration in terms of patient/family counseling and the ability to give a prognosis for patients with FD/MAS is when are the manifestation of the disease established, and its corollary question, when is it safe to say that a given aspect of the disease will not manifest. The answer to these questions depends upon early and complete screening to establish if a tissue is affected or not. Whether or not a tissue is affected is also important for long term follow-up. In a study by Hart et al., using the combined tools of ^{99}Tc-MDP bone scans, skeletal surveys, and CT scans of the skull, we were able to establish that the majority of skeletal disease, depending on the site, was established roughly between 3 – 10 years of age. Almost all sites of disease that eventually became clinically significant were present by the age of 5 (Table 3). In most cases, this means that almost all clinically significant disease will be present at the time of the first evaluation.

Table 2 Prevalence of less common findings in the NIH cohort of patients with fibrous dysplasia

Other clinical findings	% patients[1]
Gastrointestinal	7
History of hepatitis[2]	4
Reflux[2]	5
Pancreatitis[2]	3
Polyps[3]	5
Cardiac	6
Tachycardia[4]	4
Aortic root dilatation (GH excess)[5]	2
Hematologic	1
Platelet dysfunction	1
Cancer	4
Thyroid[6]	1
Breast[6]	2
Bone[6]	1
Testicular[6]	1
Hyperparathyroid	1
Neuropsychiatric	9

[1]n = 140; 58 males, 82 females, [2]appeared in childhood, common causes excluded, [3]atypical, upper GI tract polyps, myxomatoid pathology more common, [4]unexplained/not associated with hyperthyroidism, [5]only seen in patients with growth hormone excess, [6]all tumors bear $G_s\alpha$ mutation, adjacent normal tissue mutation negative.

While not as well studied, this same pattern of the early establishment of disease is probably true for the extraskeletal manifestations. For example, by ultrasound, the most sensitive tool for the detection of thyroid disease, involvement of the thyroid, or lack thereof, is established at the first evaluation and persists over many years of follow-up. These findings are consistent with our current understanding of the molecular genetics and embryology of the disease. The manifestations of FD/MAS are due to somatic activating mutations in the *GNAS* gene, sometimes referred to as the *gsp* oncogene, which codes for the protein $G_s\alpha$ that is involved in intracellular cAMP production [9,10]. To result in a disease that involves cells derived from all three germ layers (ectoderm – e.g. skin, mesoderm – e.g. bone, and endoderm – e.g. thyroid), the mutation must occur very early in development. Thus the "map" of involved tissues, many of which will not become clinically evident for some time, are determined in utero. With the exception of Cushing's syndrome, phosphaturia, and precocious puberty, in the vast majority of cases once a manifestation is present, it exists throughout life. Figure 1 depicts graphically what one can expect, as far as the age at which clinically significant disease becomes evident.

Café-au-lait spots

When present, the café-au-lait spots that can be seen in MAS are typically the first manifestation of the disease, usually appearing either at or shortly after birth. As such, they can be an early clue to the diagnosis. They have been

Table 3 Age at which FD lesions are established by site

Percent of lesions present	Craniofacial	Axial	Extremity	Total body
50%	NA	7.4	4.9	5.7
75%	NA	11.7	9.6	10.7
90%	3.4	15.5	13.7	15

NA = not applicable

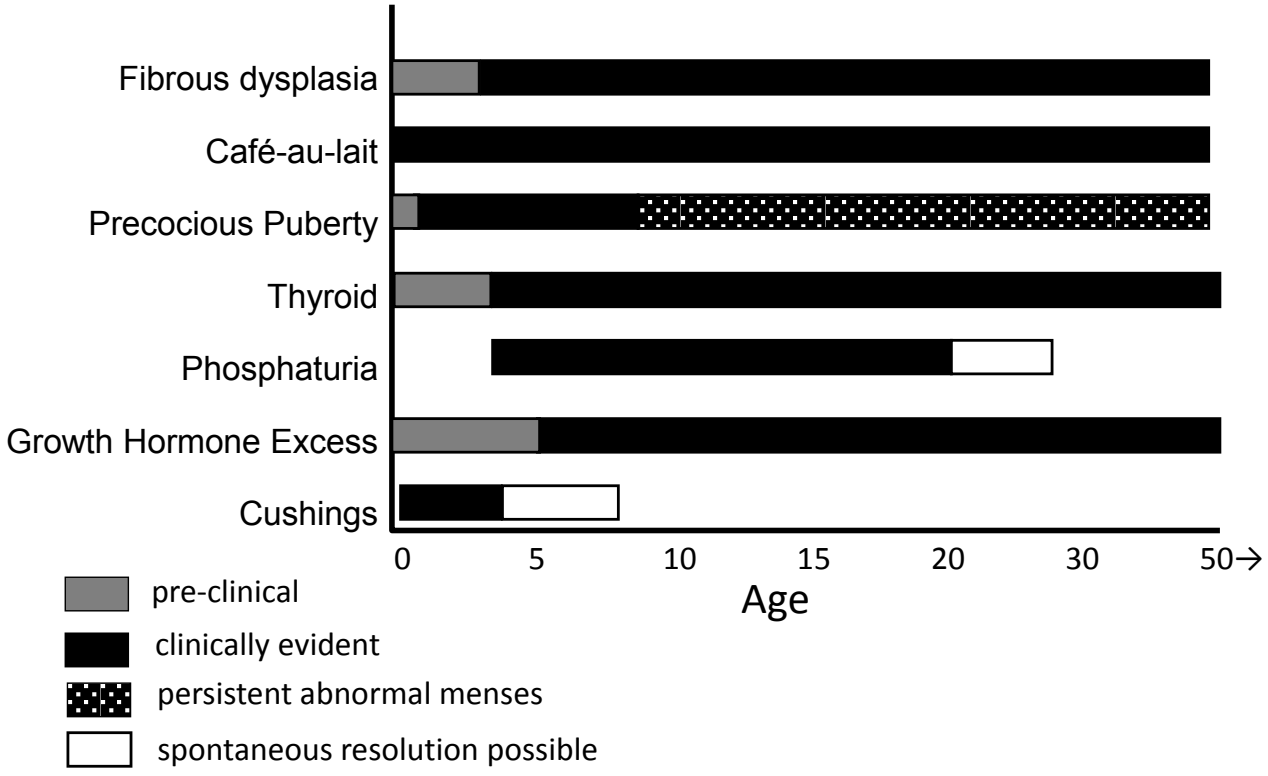

Figure 1 The relative age at which any given aspect of the disease becomes clinically evident is depicted by a solid black bar. Preclinical disease is depicted by gray bars, and ages during which spontaneous resolution is possible for Cushing's disease and phosphaturia are shown in open bars. The period of time during which abnormal menstruation can be expected is depicted by the stippled bar.

classically described as having a "coast of Maine" border, which refers to the jagged appearance of the Maine coastline as it appears on maps. While this is usually the case, it is not always true. Examples of café-au-lait spots seen in MAS that both conform with and defy this dictum are shown in Fig. 2. Likewise, café-au-lait spots found in MAS usually show some association with ("respect") to the midline. Again, while this is often the case, there are frequent exceptions. Examples of these can be seen in Fig. 2 C & E. While these spots do cross the midline, they retain some association to the midline.

Contrary to what has been previously reported, we have not observed a correlation between the size of the spots and the extent of the disease. Nor have we observed a correlation between side of the body on which the spot is found and the side of the body on which the FD is found.

The café-au-lait spots seen in association with FD are the result of *gsp*-bearing melanocytes in which the mutation brings about c-AMP-mediated tyrosinase gene activation and melanin production in mutation-bearing cells [11]. There are no well-defined effective treatments for the hyperpigmentation seen in MAS. Attempts to bleach areas of hyperpigmentation usually leave an area of under pigmentation, which is usually unsatisfying to the patient. A single report of the efficacy of Q-switched ruby laser in the treatment of the café-au-lait spots of MAS has been reported [12], but further evidence of efficacy is necessary before such a treatment can be routinely recommended.

Precocious puberty

Introduction

Precocious puberty is one of the defining manifestations of McCune-Albright syndrome (MAS) (10). It arises due to autonomous *gsp*-mediated gonadal function in cells harboring the *GNAS* activating mutation. Thus, it is characterized as a form of peripheral precocious puberty, in contrast to the early hypothalamic-pituitary-gonadal (HPG) axis activation designated as central precocious puberty. Although it might theoretically be expected to affect girls and boys equally, precocious puberty in children with MAS is far more common in girls, in whom it is typically both the presenting feature as well as the one that ultimately leads to the diagnosis being made. As the clinical characteristics, diagnosis and treatment are distinctly different, precocious puberty in girls will be considered separately from precocious puberty in boys with MAS.

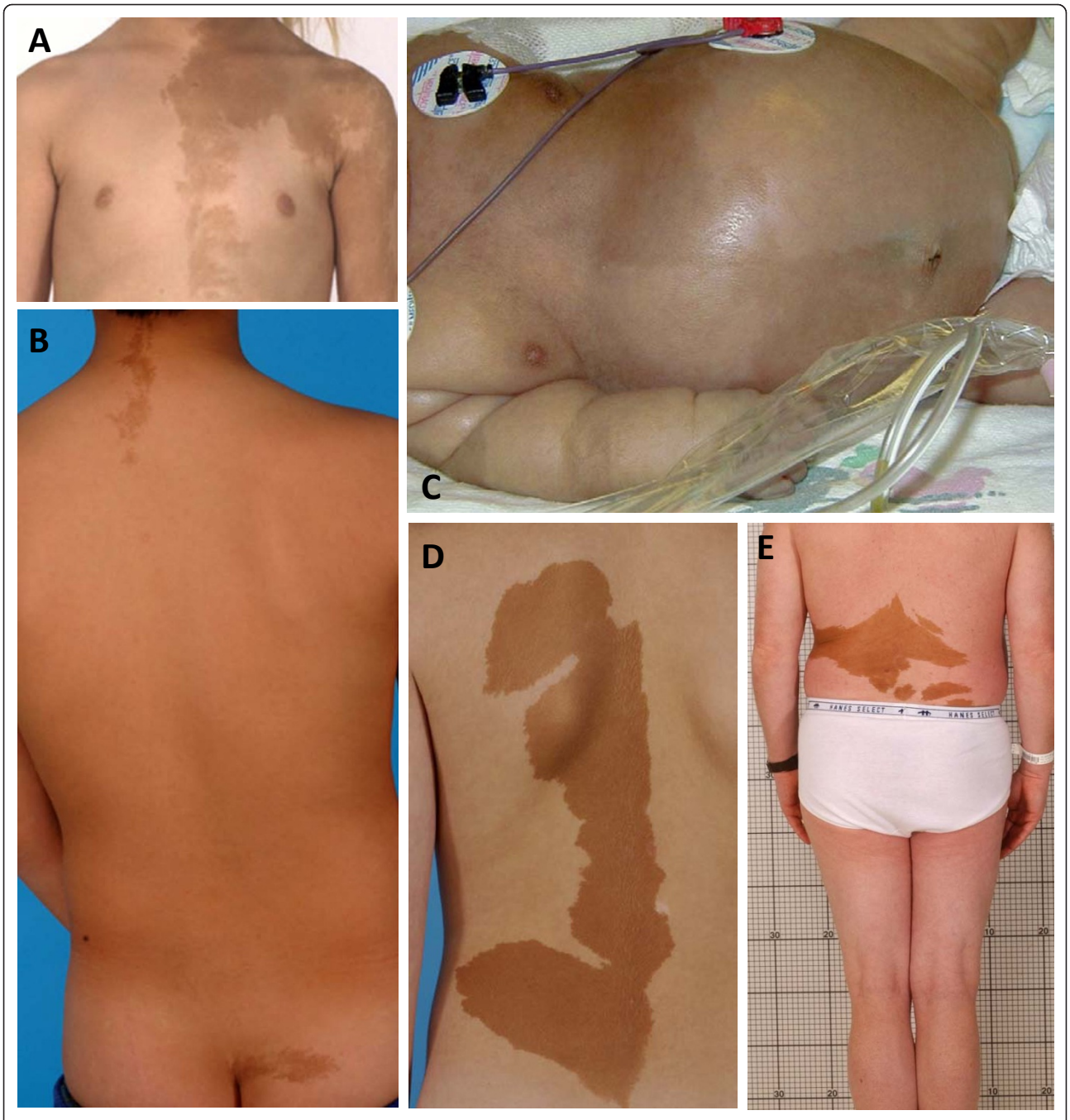

Figure 2 Representative Café-au-lait Spots Seen in McCune-Albright Syndrome. A spectrum of spots is shown; Panels A & B demonstrate "classic" spots that both respect the midline and display "coast of Maine" borders. Panel C shows a very unusual spot seen in a child with MAS and neonatal Cushing syndrome. While the spot respects the midline, the borders are smooth and the spots alternate from left to right in a harlequin pattern. Panel D depicts a very large spot with relatively smooth borders seen in a patient with relatively little FD. Panel E demonstrates a spot that clearly does not respect the midline.

Precocious puberty in girls

The typical presentation of precocious puberty in girls with MAS consists of vaginal bleeding. Typically painless, sometimes profuse, and usually accompanied by the development of breast tissue; this represents withdrawal bleeding following the resolution of large unilateral estrogen-producing ovarian cysts [11]. Since the cysts are usually asymptomatic, their presence often goes unrecognized until the bleeding occurs. On physical exam, most girls are noted to have mild breast enlargement at a Tanner II or III stage of development. If the child does not come to attention until after the

resolution of the initial episode, the breast tissue may have resolved and on casual inspection involuted breast tissue may be missed. Similarly, the finding of obvious and classic café-au-lait macules in girls with MAS is quite variable and, even if present, their significance may go unrecognized. Therefore, it is not unusual for girls to present initially to an emergency department or primary care clinic and have the treating physicians fail to include MAS in the differential diagnosis. As some of the clinical and radiographic findings overlap with those of juvenile granulosa cell tumors, girls with MAS sometimes end up undergoing unnecessary oophorectomy for a presumed ovarian tumor [12]. Ideally, vaginal bleeding in a prepubertal girl should always prompt consultation with a pediatric endocrinologist so that, in the case of MAS, unneeded loss of the ovary can be prevented.

In addition to a history and physical exam, the initial evaluation of precocious puberty in a girl with suspected MAS consists of laboratory and radiographic studies. Classic biochemical findings include elevated estradiol and estrone levels, which are many-fold higher than prepubertal values, in association with suppressed gonadotropins. Pelvic ultrasound typically reveals a large unilateral ovarian cyst which may be hemorrhagic and appear to have mixed cystic and solid elements. As would be predicted, extreme asymmetry in ovarian volumes between the two sides is the norm, in striking contrast to the symmetrical ovarian enlargement emblematic of central precocious puberty [13]. If seen after the initial episode, growth parameters and bone age x-ray are often normal. The diagnosis of MAS is typically made clinically on the basis of classic features, including café-au-lait pigmentation. A bone scan to look for fibrous dysplasia and screening for other MAS-associated endocrinopathies are important elements of the diagnostic work-up. However, isolated precocious puberty without any other identifiable abnormalities may also be seen in girls with MAS [14]. Serial ultrasounds, if indicated, will reveal a gradual resolution of the ovarian cyst over several weeks.

The natural history of precocious puberty in girls with MAS is extremely variable. The first episode can occur as early as during the first few months of life or as late as age 6 or 7 years. Likewise, subsequent episodes are highly unpredictable. While many girls have extended periods of quiescence that last for several years, others have frequent bouts of vaginal bleeding along with progressive breast development followed by the onset of pubic and axillary hair and adult body odor. As is seen with all forms of significant sex steroid exposure during the prepubertal years, linear growth acceleration and advanced skeletal maturation also ensue. Unfortunately, there is no way to predict exactly when the next episode of precocious puberty will occur, which can contribute to the anxiety experienced by parents when this complex disorder is diagnosed. Similarly, the precocious puberty flare-ups themselves vary in severity. In contrast to the typical vaginal bleeding, some girls are noted to simply have periodic waxing and waning of breast enlargement without overt bleeding.

Historically, the prevailing notion was that the HPG axis would override autonomous ovarian function in girls with MAS once physiologic puberty was underway. However, this has given way to the recognition that women with MAS continue to experience intermittent autonomous ovarian function marked by the development of large unilateral ovarian cysts and irregular vaginal bleeding [15]. This has the potential to interfere with normal ovulatory function with subsequent implications in terms of fertility [16]. However, in most cases adults with MAS have been able to have children, even if it may take longer than normal to conceive.

Management

Clinical management of precocious puberty in a girl with MAS consists initially of observation. Girls with only sporadic and infrequent vaginal bleeding often do not need to be treated. In the subset of girls with a progressive form of precocious puberty, pharmacologic intervention is recommended in order to prevent early epiphyseal fusion and augment adult height. However, other than anecdotal case reports, to what extent height is compromised and whether intervention ameliorates this, is not well established. As is the case for all aspects of MAS, both the rarity and heterogeneity of the disease present significant challenges to rigorous investigation.

Current treatment of precocious puberty in girls with MAS revolves around the use of anti-estrogens. Two basic strategies exist. The first relies on interfering with estrogen biosynthesis through the use of an aromatase inhibitor [17], while the second aims to blunt the effects of estrogen at the level of the end-organ through receptor blockade. To date, small uncontrolled trials have been conducted with first, second and third generation aromatase inhibitors. Experience with the first generation agent, testolactone, was ultimately marred by sub-optimal efficacy as well as issues with compliance [18]. Investigation of the second generation aromatase inhibitor, fadrozole, was abandoned following concerns about adrenal suppression [19]. Among the third generation compounds, anastrozole has been deemed ineffective [20]. Letrozole, however, was found to result in a significant decrease in rates of skeletal maturation in a small number of girls treated for 3 years, although mean ovarian volumes were unchanged [21]. Most girls also experienced a decrease or cessation in vaginal bleeding while on letrozole, although one subject who had entered secondary central precocious puberty developed a large cyst with subsequent ovarian torsion. Treatment with the

selective estrogen receptor modulator, tamoxifen, has also been studied in a group of girls with MAS treated for one year. In addition to a significant decrease in vaginal bleeding, tamoxifen resulted in an improvement in growth velocity and bone age advancement [22]. Despite these positive results, the finding of increased uterine and ovarian volumes in the girls treated with tamoxifen represents a potential safety concern that to date remains unresolved. Lastly, preliminary results from a prospective study utilizing the pure estrogen receptor blocker, fulvestrant, are available. A decrease in the median number of vaginal bleeding days as well as in the average rate of skeletal advancement in 30 girls treated for one year was seen [23]. Thus, relatively comparable efficacy has now been observed with several agents used in the treatment of precocious puberty in girls with MAS, although none have been perfect and none have emerged as being clearly superior to the others. Studies comparing available medications in a head to head fashion are needed.

Precocious puberty in boys

There are several important differences between precocious puberty in girls with MAS and its counterpart in boys. One distinction is that precocious puberty is very rare in affected boys, who are diagnosed with MAS far more often due to the finding of bone disease or café-au-lait pigmentation. An additional dissimilarity is that the precocious puberty, when present, is more likely to be subtle and indolent in boys. Lastly, the activating $G_s\alpha$ mutation and resulting gonadal hyperfunction have been reported to be limited to the testicular Sertoli cells in several boys with MAS. This has resulted in either unilateral or bilateral macroorchidism without precocious puberty [24][25][26][27]. Interestingly, many of these cases have also been associated with testicular microlithiasis, which has also been identified in males of all ages with MAS [28][29]. Due to its extreme rarity, only anecdotal case reports detailing treatment options for precocious puberty in boys are available. The most common approach employs combination therapy in the form of an androgen receptor blocker such as spironolactone, flutamide or cyproterone acetate along with a compound that interferes with sex steroid synthesis such as ketoconazole or an aromatase inhibitor [30]. On principle, the same strategies used to treat boys with other forms of peripheral precocious puberty such as familial male precocious puberty, would be efficacious in the setting of MAS. One such example is the combination of bicalutamide, a pure androgen receptor blocker, with the third generation aromatase inhibitor anastrozole [31]. Similar to what has been reported in women with MAS, fifteen year follow-up in a boy with MAS and history of precocious puberty indicated persistent autonomous testicular hyperfunction and suppressed gonadotropins [32]. Although inhibin B was undetectable, active spermatogenesis occurred and was seemingly unaffected.

Thyroid

At the NIH approximately 2/3 of the patients had involvement of the thyroid when assessed by the most sensitive method for assessing thyroid involvement, ultrasound [13]. Only about 1/2 of the patients who had involvement of the thyroid detected on ultrasound had frank hyperthyroidism, as evidenced by a suppressed TSH. As in every aspect of MAS, the thyroid findings exist along a spectrum from an isolated area seen on ultrasound with no clinical findings to patients with obvious goiters, and hyperthyroidism that is unable to be adequately controlled with medications and requires either surgery or ablation. The presence of the *gsp* mutation in thyroid tissue results in ligand-independent activation of the TSH/G-protein/cAMP pathway, which is known to result in both hyperplasia and hyperfunction [14]. Additionally, the *gsp* mutation results in increased thyroxine (T4) to triiodothyronine (T3) conversion, which accounts for the T3-dominant biochemical phenotype of MAS patients with hyperthyroidism [13].

It is important to diagnose hyperthyroidism in MAS, as hyperthyroidism can advance bone age, which may already be a problem in children with precocious puberty, lead to or exacerbate osteoporosis, and cause a plethora of other metabolic derangements. Diagnosis is usually straight forward and involves the measurement of TSH and thyroid hormones, T3 and T4. It is not uncommon to have a normal T4 in the setting of a suppressed TSH. This apparently incongruous finding is clarified when T3 is measured and found to be high. In patients in whom the only abnormality is an abnormal ultrasound, it is important to continue to check TSH and thyroid hormone periodically as the development of frank hyperthyroidism may occur later. The ultrasound findings in MAS are usually a mixture of mostly cystic with some solid lesions (Fig. 3) [13,15].

Hyperthyroidism in MAS usually responds quite well to thionamides. However, since hyperthyroidism is one of the aspects of MAS that persists, it is often desirable for the patient to undergo definitive treatment, which usually means surgery or ablation with radioactive iodine. Surgery may be difficult in very small children, and is therefore recommended to delay surgery in small children.

Hypophosphatemia

While rickets in association with FD was originally reported in 1968 [5], it was not until 2001 that it was evident the cause was a circulating phosphaturic hormone, similar to what is seen in the inherited forms of rickets

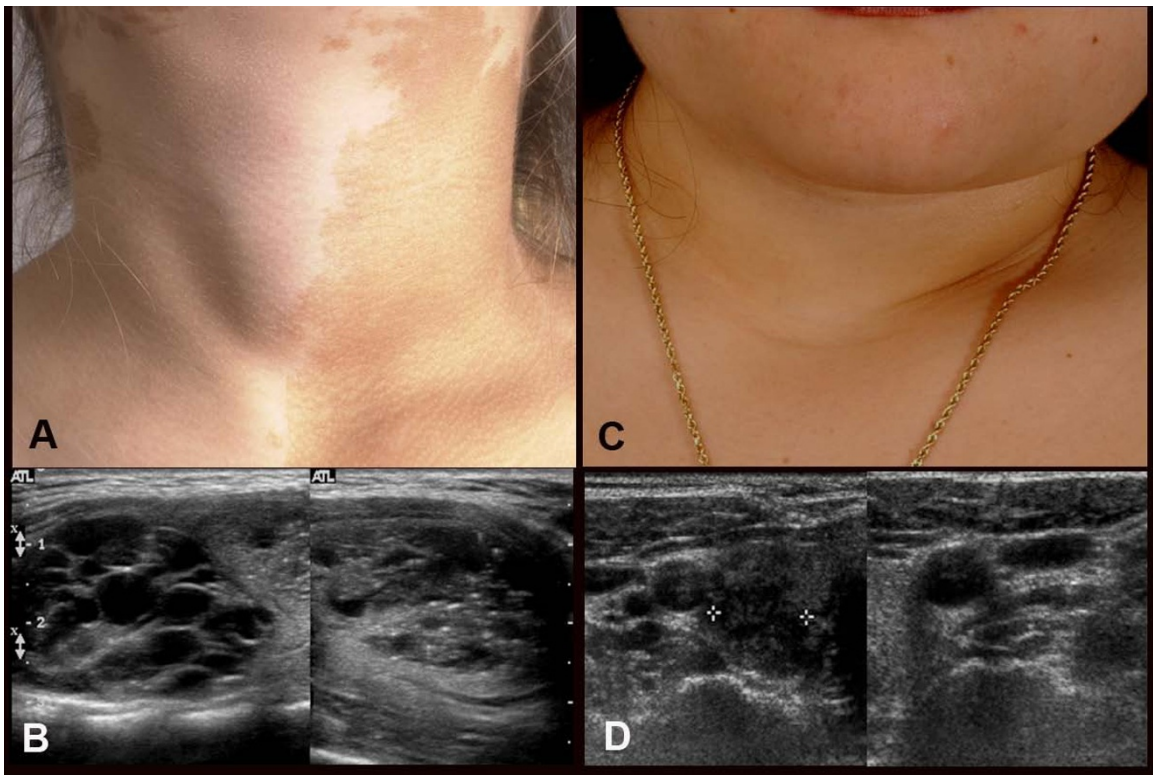

Figure 3 Clinical and ultrasound findings of thyroid involvement in FD/MAS. Panels A & B demonstrate the findings in a 9-year-old girl with MAS and hyperthyroidism. A goiter is clearly seen on inspection (A) and the ultrasound (B) shows the typical cystic (Swiss cheese) appearance that seen in MAS thyroids. Panels C & D demonstrate the findings of a 30-year-old woman with MAS. While no goiter was evident on inspection, nor was one obvious on palpation, the ultrasound clearly demonstrated the typical findings seen in ultrasounds of patients with MAS and thyroid involvement. Adapted from reference [13.]

[16]. Overproduction of FGF23 by FD tissue was found to be the cause [17]. FGF23 is overproduced by FD tissue, such that the greater the disease burden, the higher the FGF23, the greater the degree of renal phosphate wasting, and the lower the serum phosphorus (Fig. 4). Therefore, significant hypophosphatemia is only seen in patients with a very significant skeletal burden of FD. It has also been observed that, unlike many other extraskeletal manifestations aspects, renal phosphate wasting can spontaneously resolve as patients age. This probably reflects intrinsic changes that have been observed at the tissue level and characterized as "normalization" [18].

The clinical sequelae and significance of hypophosphatemia are an earlier age of first fracture, more fractures, and bone pain [19]. There are no controlled studies to support that treating hypophosphatemia decreases fractures or improves pain, but observation of treated patients suggests that treatment may improve outcomes. Treatment of hypophosphatemia is the same as in other FGF23-mediated phosphate wasting disorders, and involves the use of phosphate and active vitamin D (calcitriol or alfacalcidiol). Details for this treatment regimen can be found elsewhere [8,20].

Growth hormone excess

Growth hormone excess in association with FD is the manifestation of *gsp* mutation in the anterior pituitary [21]. It is always accompanied by skull base FD, and the vast majority of patients also have hyperprolactinemia. The usual presenting sign is increased growth velocity. However, if GH excess is accompanied by precocious puberty, the clinical sign of increased growth velocity can be obscured by the increase in growth velocity that is seen as part of precocious puberty. Likewise, if a patient with precocious puberty achieves his/her predicted height, this can be a sign of GH excess, as precocious puberty should have resulted in short stature. For this reason, it is important to do laboratory screening for GH excess in patients with FD, as the clinical evaluation can be confounded by concomitant hormonal excess and make the clinical exam difficult to interpret.

Probably the most important reason to diagnose GH excess in association with FD is that it is associated with an increase in morbidity, specifically in the craniofacial region. GH excess in FD is associated with macrocephaly and vision loss [22,23].

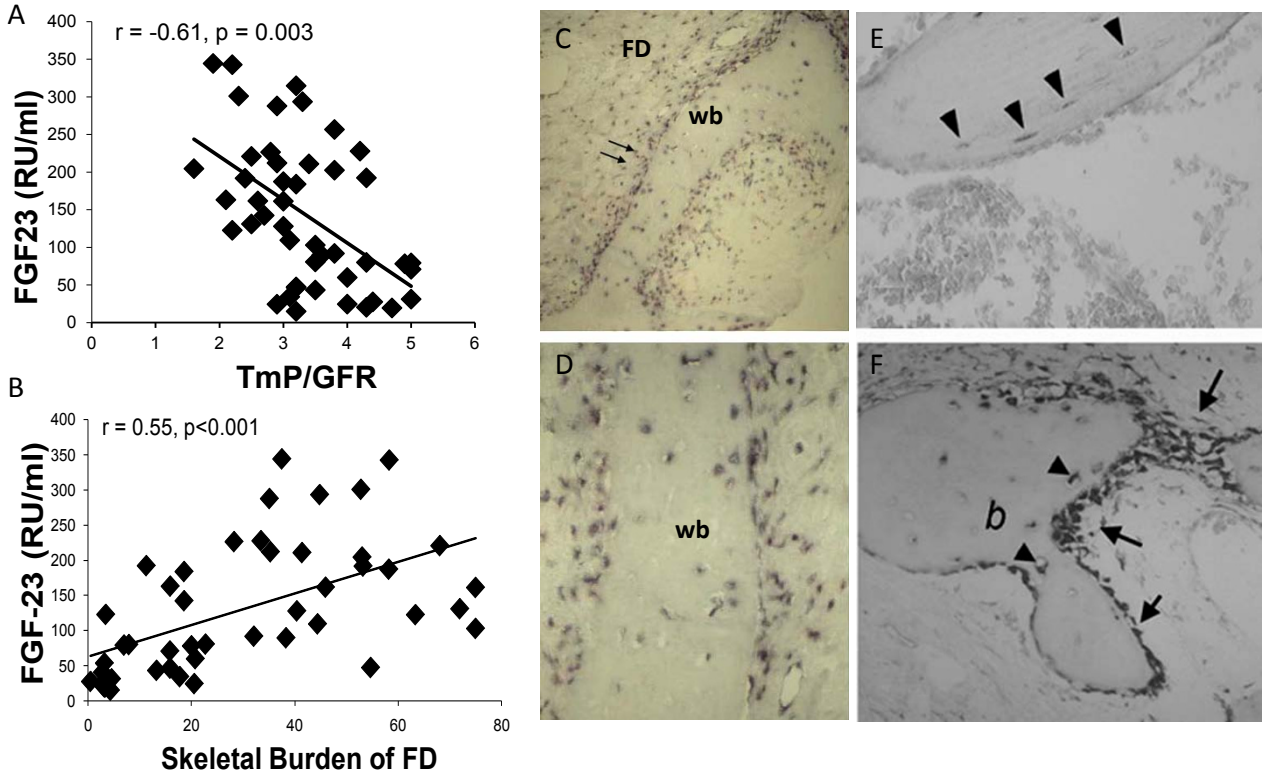

Figure 4 Panel A demonstrates the relationship and significant negative correlation between serum FGF23 and the degree of phosphate wasting, supporting the concept that FGF23 is responsible for the phosphate wasting that can be seen in association with FD. Panel B depicts the relationship and significant positive correlation between the serum FGF23 and the skeletal burden of FD, which supports the hypothesis that the FD tissue is the source of FGF23. Panels C&D are low and high power views, respectively, of in situ hybridization studies using probes for FGF23 that demonstrate that FD tissue demonstrates high levels of FGF23 transcripts. Panels E&F show high levels of FGF23 transcripts in bone from control, normal bone; E osteocytes and F osteoblasts in healing fracture callus. FD = fibrous dysplasia, wb = woven bone, b = bone, double arrows designate FD stromal cells, arrow heads designate osteocytes, single arrows designate osteoblasts. Adapted from reference [17].

The diagnosis of GH excess is usually straightforward. Non-suppressible serum GH on an oral glucose tolerance test (OGTT) is diagnostic of GH excess [21]. However, in subtle disease the results of the OGTT can be equivocal, especially in young children [24]. In these difficult cases, frequent (every 20 min) overnight sampling may be of utility. Children with GH excess will fail to have any intervals when the GH value is below 1 ng/ml. As stated previously, almost all patients with FD/MAS- associated GH excess also have an elevate prolactin. Therefore, the prolactin level can be an additional tool in either confirming or excluding the diagnosis of GH excess.

Our most recent analysis of the NIH cohort of patients with GH excess indicates that early diagnosis and treatment of GH excess may prevent GH excess-associated morbidity, specifically vision loss.

Treatment of GH excess in FD/MAS is almost exclusively confined to medical treatment. Usually, due to the massive expansion of the skull base with FD, which includes obliteration of the sphenoid sinus, the traditional transphenoidal approach to the pituitary is either not possible or extremely difficult. An additional important consideration if surgery is contemplated, is the fact that, in spite of what may appear as a single adenoma on pituitary imaging, the entire anterior pituitary is usually infiltrated with areas of herplastic and/or adenomatous somatotrophs and somatolactotrophs. The implications of this finding are that surgical cure of GH excess in FD/MAS will require a complete hypophysectomy – a treatment that, if it is to be embarked upon, is probably best delayed until young adulthood. Given that treatment doses of radiation directed at FD are associated with an increase in malignant transformation [25,26], radiation is rarely an acceptable approach.

Treatment

The drug with which there is the longest experience in treating FD/MAS-related GH excess is octreotide [21,27-29]. It is usually effective in lowering serum GH and IGF-1 levels. In growing children, the goal of treatment is to decrease the IGF-1 to the middle of the normal range (IGF-1 Z-score = 0). In mature patients, the goal is

to decrease the serum IGF-1 to as low as possible. The GH receptor antagonist, pegvisomant, has also been shown to be effective in treating MAS patients with GH excess [30,31]. Which drug is superior is not known. In some patients a combination of both octreotide and pegvisomant is necessary to achieve control, and in a small minority of patients not even the combination is effective. This is the group that should be considered for surgery and/or radiation. We have attempted to treat the GH excess in MAS with the dopamine agonist, cabergoline as a single agent in several cases, but had no success (unpublished data).

The hyperprolactinemia that usually accompanies GH excess in MAS is not affected by treatment with octreotide or pegvisomant, but is almost always effectively controlled with dopamine agonists, such as cabergoline or bromocriptine.

Cushing's syndrome

Cushing's syndrome is the rarest of endocrine abnormalities found in MAS [32]. It always occurs in the neonatal period, which parallels the involution of the fetal adrenal gland and may suggest a differential effect of the *gsp* mutation on the fetal adrenal, which is supported by the fact that both glands are always involved [33]. Cushing's syndrome is one of the few aspects of MAS that is associated with increased and early mortality. Most of the early mortality associated with Cushing's syndrome in MAS is due to opportunistic infections, and highlights the importance of prophylactic treatment, notably for *Pneumocystis species*. Cushing's syndrome usually only occurs in patients with MAS with significant involvement of multiple other tissues. Patients with Cushing's are also more likely to have many of the manifestations mentioned in Table 2.

A review of all the published cases of Cushing's syndrome in MAS [32] listed the following signs and symptoms: small for gestational age (50%), round facies (67%), failure to thrive (60%), hypertension (33%), nephrocalcinosis (30%), hirsutism (27%), hyperglycemia (20%), and linear growth arrest (10%). While it is clearly documented that some cases of Cushing's syndrome can resolve spontaneously [34], it is impossible to predict in which patients this will occur. Therefore making the diagnosis necessitates treatment. This usually involves surgical removal of diseased adrenal glands. However, medical treatment is sometimes able to lower serum cortisol to normal or lower. Since many children with MAS and Cushing's syndrome also have evidence of a cholestatic hepatitis, the often effective drug ketoconazole is avoided due to it is potentially hepatotoxicity. Metyrapone is frequently effective. The initial dose is 300 mg/m2/day. It may be increased to as high as 1200 mg/m2/day, as needed. In particularly sick children, medical treatment with metyrapone may buy time until the child is healthy enough for surgery.

Long term sequelae of Cushing's syndrome in MAS include a significantly increased prevalence of cognitive disorders, including specific learning or speech disorders, or global developmental delay and speech apraxia.

Other extraskeletal manifestations

The additional less common extraskeletal manifestations associated with MAS are outlined in Table 2. Some will be discussed below. Hepatitis, when it occurs, is more pronounced after birth, has laboratory manifestations consistent with cholestasis, progressively wanes with age, usually persists into adulthood, albeit mild, and is virtually never associated with a functional defect in synthesis of important hepatic factors [6].

Gastrointestinal reflux

Gastroesophageal reflux is infrequently seen in MAS, and primarily in patients with multiple extraskeletal manifestations. It usually manifests in childhood and can be a source of significant discomfort to patients. The etiology is unknown, but is presumed to be incompetence of the lower esophageal sphincter from unknown mechanisms. Hyperacidity does not appear to be the primary issue. Treatment is usually medical and involves the use of histamine blockers or proton pump inhibitors. It has not been reported to be associated with metaplasia of the lower esophagus (Barrett's esophagus).

Gastrointestinal polyps

Gastrointestinal polyps, especially in unusual locations (gastric and duodenal) and of significant size have been observed in association with MAS (personal observations, MTC). They can become clinically significant if they reach a size that can cause obstruction. The long term significance and malignant potential is unknown, although reports of a role of activating mutations of $G_s\alpha$ have been seen in association with gastrointestinal malignancies [35]. To date, no gastrointestinal malignancies have been reported in association with FD/MAS.

Pancreatitis

Idiopathic pancreatitis has been observed in patients with FD/MAS. The prevalence observed in the NIH (approximately 3%) is greater than would be expected in an unselected population, however a direct association with MAS has not been demonstrated and there are no known associations between *gsp* mutations and a predisposition to pancreatitis.

Cardiac

There are several cardiac abnormalities that have been reported in association with FD/MAS. These include

sudden death, tachycardia, high output heart failure and aortic root dilatation. While much has been made of sudden death as part of MAS [7,36], and the fact that the *gsp* mutation was found in cardiac tissue of children who had sudden death, evidence that the cause of death was cardiac, and/or that the *gsp* mutation played a role is lacking. While patients with FD/MAS are clearly at cardiac risk due to hyperthyroidism and other endocrine abnormalities, the risk for sudden cardiac death is probably minimal if any.

Tachycardia

Tachycardia can be seen in patients with FD/MAS who are hyperthyroid [13,15]. Tachycardia in the absence of hyperthyroidism (unexplained tachycardia) was seen in approximately 4% of the NIH cohort of patients with FD/MAS. There are at least two possible explanations for this; it could represent the presence of the *gsp* mutation in the heart, or it could represent the physiologic response to increased demand placed on the heart due to extensive FD, which is a very vascular tissue. The two explanations are not mutually exclusive. In fact, more extensive extraskeletal involvement is usually seen when there is extensive skeletal involvement. Therefore, cardiac *gsp*, which has been demonstrated [7] may be more likely to be seen in patients with extensive disease. All of the patients with unexplained tachycardia in the NIH cohort had extensive FD. Therefore, it is not clear if the cause was primary cardiac (*gsp* mutation in the heart), or a secondary, physiologic response to increased demand placed on the heart by extensive bone disease. How to treat these patients is a conundrum. Untreated pathologic tachycardia, as can be seen in hyperthyroidism, can lead to a cardiomyopathy and heart failure. However, inappropriate suppression of physiologically-induced tachycardia that can be seen as part of increased demand could also lead to heart failure. In one patient with total skeletal involvement with FD an effort to suppress demand (vascularity) by aggressive bisphosphonate treatment had no effect – at least in part because it did not appear to have any effect on vascularity. To date, we have opted not to treat these patients with beta blockers. However, they are monitored closely with cardiac echocardiogram and cardiac MRI for any early signs of decompensation suggestive of impending heart failure. Any sign of decompensation will ben and indication for treatment. Thus far, with a follow-up of almost 10 years there has not been any decompensation.

Aortic root dilatation

We have observed dilatation of the aortic root in several patients with GH excess in the NIH cohort. We have made the assumption that this is the direct effect of GH excess on the heart, as this has been reported in association with acromegaly [37]. In one of the patients the aortic root dilatation is clinically significant. In this subject, who had many years of untreated GH excess and extensive morbidity due to untreated GH excess, the disease led to aortic root dilatation, marked aortic valve insufficiency, atrial dilatation and atrial fibrillation [54]. In the other subjects who started treatment at an earlier age, there has not been any progression and there is no associated cardiac morbidity.

Platelet dysfunction

Platelet dysfunction has also been reported in association with FD and it has been suggested this may play a role in the extensive bleeding that can be seen during operations on FD tissue [38]. However, FD tissue is also extremely vascular and it is difficult to determine whether platelet dysfunction may contribute to bleeding beyond what is expected from vascularity. Whether or not all patients should be screened for platelet dysfunction is not clear. However, in subjects with a history of difficult to control bleeding, platelet dysfunction should be considered preoperatively.

Cancer

The cancers that have been reported in association with FD/MAS, and in which the presumably etiologic *gsp* mutation has been identified in the malignant tissue, include malignant transformation of FD, thyroid, and breast. In addition to these, we have received personal communications of cancers of the testes and lung; however these have not been checked for *gsp* mutation. The activating mutations that cause FD/MAS were given the designation as an oncogene (*gsp*) because they were originally found as the cause of benign endocrine adenomas [39]. However these diseases are almost invariably benign and suggest that for malignant transformation to take place additional mutations probably arise in addition to *gsp* mutations. This concept is supported by the finding that *gsp* mutations are not uncommonly seen as part of the genomic landscape of common cancers such as breast and colon, mutations in many other genes known to be associated with cancer development are found [35]. This concept is further supported by the detailed chromosomal and genetic analysis of a cell line that was derived from a patient with FD in whom the FD transformed into a malignant fibrous histiocytoma [40]. In addition to the expected *gsp* mutation there were multiple structural and numerical abnormalities of chromosomes with a large number of unidentifiable chromosomes as well as a p53 mutation in exon 7 accompanied by loss of heterozygosity in the counterpart allele.

Bone cancers

There are a number of very good reviews that catalogue the reports of cases of FD that have transformed to

various types of bone cell-related cancers including, among others osteosarcomas, fibrosarcoma, chondrosarcoma, and even a malignant mesenchymoma that demonstrated multiple cell types all with malignant features [25,26,41-45].

It is difficult to determine what the risk of malignant transformation in FD is from the published literature. Series and centers report the number of cases of cancers, but it is difficult to know what the appropriate denominator is to determine the prevalence, and/or it is difficult to judge what the impact of the referral bias is for that given institution and that series. For example, a review of the Mayo Clinic data identified 28 cases of malignancy out of 1122 total cases, for a prevalence of about 2% [46]. This would be considered by most experts to be a high estimate of the risk of malignant transformation of FD and probably reflects a referral bias of the institution for bone cancers. In the NIH cohort of approximately 140 patients with disease on the more severe end of the spectrum, we have seen only one case in over 20 years of experience, for a prevalence of <1%.

Malignant transformation is suggested by an expanding, previously stable lesion, new focal pain, with the radiographic hallmark being a breach of the bone cortex with the extension of a soft tissue mass beyond the cortex.

In terms of other factors that may impart additional risk (or protection), there is little guidance in the literature. Here the problem is that it is not clear to what extent any individual patient has been studied to identify additional risk factors. It is possible that the presence of GH excess may add additional risk for malignant transformation. The two cases of breast cancer and the single case of malignant transformation of FD observed in the NIH cohort all occurred in women with GH excess. In addition, while not systematically studied, there is a sense from the literature in the patients who appear to have been thoroughly investigated, that GH excess may impart additional risk for the malignant transformation of craniofacial FD [47-50], as well as for bone cancer in general [51,52].

Thyroid

Thyroid cancer has been observed in two patients in the NIH cohort (prevalence approximately 1.3%). Support for the fact that this was a true relationship between the presence of the *gsp* mutation and thyroid cancer was the fact that in both cases the mutation was found in the neoplastic tissue, but not in the adjacent normal tissue [53]. Further support is lent by the fact that in both cases there were unusual features further suggesting an association, specifically young age and tumor type (clear cell carcinoma, which is a rare variant of thyroid cancer that has been reported in association with hypothyroidism-associated goiter, in which case there will be increased TSH/$G_s\alpha$/cAMP signaling).

Diagnosis of cancer within the thyroid of a patient with MAS is difficult, given that the gland is often diffusely abnormal and it is difficult to identify malignant changes on this diffusely abnormal background (Fig. 3). Suggestive clinical findings are an expanding firm nodule, and/or an expanding solid nodule on ultrasound. If these findings are present, a fine needle aspiration should be performed with cytological examination to exclude malignant findings. Given that definitive treatment of hyperthyroidism, which includes thyroidectomy, is often recommended, one should have a low threshold to perform a thyroidectomy on a fine needle aspiration specimen that is inconclusive.

Breast cancer

Two cases of breast cancer have been reported in association with FD/MAS [54,55]. In neither case did the investigators examine the malignant tissue for *gsp* mutations, so it is not possible to determine whether or not the development of cancer in these women was directly related to the underlying gene defect. In both cases, the women had had precocious puberty, and since prolonged estrogen exposure is known to be a risk factor for the development of breast cancer, it is reasonable to assume that precocious puberty as part of MAS can be considered a risk factor for breast cancer. We have seen two cases of breast cancer in the NIH cohort; both women presented before the age of 30 and both women had had precocious puberty and GH excess. (One of these patients was the patient reported by Huston et al.,[55]) While it is enticing to consider GH excess as an additional risk factor for the development of breast cancer in MAS, it is impossible to say at this point. In fact, whether or not there is a relationship between breast cancer and sporadic GH excess is not clear [56].

Testicular cancer

While there are no reported cases of testicular cancer in men with MAS, one of the authors has encountered one case (FRS).

Hyperparathyroidism

While there have been a number of reports of FD/MAS in association with hyperparathyroidism [57-61], in none of these cases was there molecular confirmation, and in the one report where there was a very thorough effort to show molecular confirmation, there was none [62]. This led the authors to conclude that the association of primary hyperparathyroidism with FD/MAS was chance and that hyperparathyroidism did not represent a molecularly-driven association. Furthermore, in reconsidering some of the cases in light of new information, there is a question as to whether the disease described was FD or

hyperparathyroidism jaw syndrome (HPT-JT). In HPT-JT, the osseous lesion is a fibroosseous lesion with significant histopathological similarities to FD, and confusion with FD is not difficult. In addition, our current understanding of the molecular regulation of parathyroid function and parathyroid neoplasms does not predict that an activating mutation in $G_s\alpha$ would lead to hyperparathyroidism or a parathyroid adenoma. For these reasons, most investigators today conclude that hyperparathyroidism should not be considered to be part of the spectrum of FD/MAS.

Neuropsychiatric

While there has been passing, ill-defined mention of "mental retardation" in association with FD/MAS [63], the most thorough chronicle of a possible association between FD/MAS and any neuropsychiatric problems was the evaluation of the NIH cohort by Brown et al [32]. In this study a number of findings were seen including learning and speech disorders, such as speech apraxia, and global developmental delay. While these findings were seen in approximately 9% of the cohort as a whole, they were found in 44% of the subjects who had had Cushing's syndrome, indicating that Cushing's syndrome is a significant risk factor for neuropsychiatric findings in patients with FD/MAS. As Cushing's syndrome is invariably found in the neonatal period in MAS, it suggests that in utero exposure to high levels of cortisol may be deleterious to brain development. That said it is also possible that Cushing's syndrome in MAS may be a marker for widespread distribution of the *gsp* mutation and the presence of neuropsychiatric symptoms is a manifestation of central nervous system involvement. In several papers from the Abel laboratory in which the Q227L activating mutation of $G_s\alpha$ (Q227L), a mutation that is also an activating mutation functionally similar to the R201C/H mutations that cause FD/MAS, was targeted to the central nervous system of mice, the animals developed a spectrum of neuropsychiatric findings including learning disorders [64-70]. One of the more striking findings seen in these mice was the counterintuitive finding that treatment with phosphodiesterase inhibitors seemed to reverse the phenotype. Phosphodiesterases breakdown cAMP, and given that the evidence thus far that much of the pathophysiology of FD/MAS is the direct effect of excess cAMP, one would assume that inhibition of cAMP breakdown would exacerbate, not treat, symptoms of *gsp* expression. Clearly there is much more to learn.

Summary

From this review, it is clear that the spectrum of extraskeletal manifestations that can be found in MAS is broad – as broad as the tissue distribution of $G_s\alpha$ expression. While clinicians should consider that almost any finding seen in association with FD/MAS may be the result of tissue-specific *gsp* expression, the majority of the extraskeletal manifestations of MAS are confined to those listed in Table 1. While effective treatments for FD remain elusive, most of the conditions listed in Table 1 are readily amenable to treatment. Given that many of these conditions will worsen the FD if untreated, it is important to suspect, screen for, and treat these extraskeletal manifestations.

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Competing interests

The authors declare that they have no competing interests.

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Pathophysiology and medical treatment of pain in fibrous dysplasia of bone

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Abstract

One of the most common complications of fibrous dysplasia of bone (FD) is bone pain. Usual pain killers are often of inadequate efficacy to control this bone pain. The mechanism of bone pain in FD remains uncertain, but by analogy with bone tumors one may consider that ectopic sprouting and formation of neuroma-like structures by sensory and sympathetic nerve fibers also occur in the dysplastic skeleton. Bone pain has been reported in up to 81% of adults and 49% of children. It affects predominantly the lower limbs and the spine. The degree of pain is highly variable and adults reports more pain than children. Bisphosphonates have been shown to reduce bone pain in uncontrolled studies. Their influence on bone strength remains unknown. In a randomized trial testing alendronate, bone pain was not significantly improved. Another trial assessing the effect of risedronate is ongoing. Possible future therapies include tocilizumab, denosumab and drugs targeting nerve growth factor and its receptor TrkA.

Introduction

Fibrous dysplasia of bone (FD) is a rare disease responsible for bone deformities, fractures, nerve compression and bone pain. There are specificities in the pathophysiology of bone pain compared to other tissues, including the role of increased bone resorption. The treatment of bone pain can involve non specific drugs and bone-specific drugs, such as bisphosphonates.

We will review the pathophysiology of bone pain, the current therapeutic possibilities and the treatment perspectives.

Pathophysiology of bone pain

Pain is a common occurrence in FD and is often the presenting symptom of the disease [1-3]. When the health-related quality of life was assessed in FD subjects, both adults and children had significantly more skeletal pain than the U. S. population [4]. A common misconception is that FD pain dissipates with age; however, recent population studies suggest that FD pain actually increases with age [3]. The analgesics that are most commonly used to control FD pain are non-steroidal anti-inflammatory drugs (NSAIDS), bisphosphonates and opiates [2,3]. However, lack of recognition by the medical community that FD pain can be both severe and increase in adulthood has led many FD patients to be labeled as "drug seeking" and inadequately treated [3]. Adequate pain management of FD pain, like nearly all other types of pain, is clearly required for FD patients to maintain their functional status and quality of life.

Currently, our understanding of the factors that drive FD pain and how to best treat FD pain comes mainly from empirical studies concerning the ability of available therapies to relieve FD pain. Two seminal clinical studies included one where it was demonstrated that FD pain was attenuated following infusion of the bisphosphonate pamidronate [5]. The second showed that there was not a clear correlation between FD pain and disease burden, and that in terms of frequency and severity FD pain increases with age [3]. This later finding may in part be explained by the fact that whereas bone mass, density, and strength all decline with age, sensory nerve fibers

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that innervate bone and which sense noxious stimuli and transmit this information to the spinal cord and brain, do not appear to decline with age [6].

While there are currently no direct studies examining what mechanisms drive FD pain, in the last decade significant strides have begun to be made in understanding the specific populations of sensory nerve fibers that innervate the skeleton [7,8], what mechanisms drive malignant and non-malignant skeletal pain [9], what molecules preferentially excite nerve fibers that innervate the bone [9], and what analgesic therapies may be particularly efficacious in alleviating skeletal pain [10].

A select population of sensory nerve fibers innervates the skeleton and drives skeletal pain

Bone is primarily innervated by thinly myelinated sensory nerve fibers (A-delta) and peptide-rich CGRP$^+$ nerve fibers and thus has less "redundancy" than is found in skin. These nerve fibers may express the high affinity nerve growth factor (NGF) receptor, Trk A, which mediates the multiple effects of NGF, including neuronal differentiation and survival. That pattern of innervation is present in the periosteum, mineralized bone, and marrow [7,8] (Figure 1). These results suggest that this differential population may provide a unique therapeutic opportunity for developing novel analgesics that can attenuate FD skeletal pain as fewer populations of nerve fibers will be needed to be blocked to attenuate bone compared to skin pain.

Sensory nerve fibers that innervate the skeleton can undergo a remarkable sprouting and pathological reorganization which may drive FD pain

One possible explanation as to why there is not a direct correlation between disease burden and FD pain is that it is not bone remodeling alone that drives bone pain, but that sensory nerve fibers themselves also have to undergo a pathological change. Recently, it has been shown that when osteosarcoma cells are confined and grow within the bone, there is a remarkable and ectopic sprouting and formation of neuroma-like structures by sensory and sympathetic nerve fibers in the skeleton (Fig. 2). Interestingly, sustained administration of an anti-NGF sequestering therapy blocked the pathological sprouting of sensory and sympathetic nerve fibers, the formation of neuroma-like structures, and significantly attenuated the generation and maintenance of cancer pain in this model [11].

A major question is whether this ectopic sprouting of sensory nerve fibers only occurs when cancer cells express high levels of NGF. However, studies using canine prostate cancer cells, that do not express detectable levels of NGF [12] – as is observed in FD – simultaneously induce

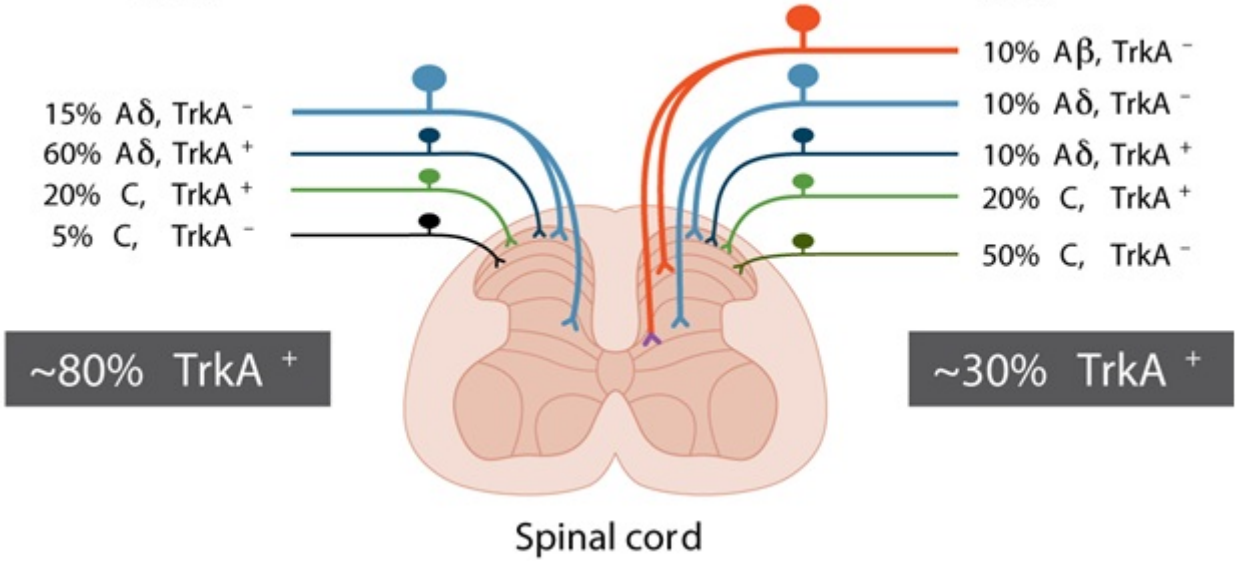

Figure 1 Most sensory nerve fibers that innervate the bone express TrkA whereas fewer than 30% of the nerve fibers that innervate the skin express TrkA. The skin is innervated by thickly myelinated A-beta fibers (TrkA$^-$), thinly myelinated A delta fibers (both TkA$^-$ and TrkA$^+$), unmyelinated peptide-rich C fibers (TrkA$^+$) and unmyelinated peptide-poor C-fibers (TrkA$^-$). In contrast, the bone appears to be predominantly innervated by thinly myelinated A-delta fibers (TrkA$^-$ but mostly TrkA$^+$) and peptide-rich C-fibers (mostly TrkA$^+$ and a small proportion TrkA$^-$). As greater than 80% of all sensory nerve fibers that innervate the bone are TrkA$^+$ whereas only 30% of the sensory nerve fibers that innervate skin are TrkA$^+$, these data might help explain why blocking NGF or its cognate receptor TrkA appears to be more efficacious in attenuating skeletal vs. skin pain.

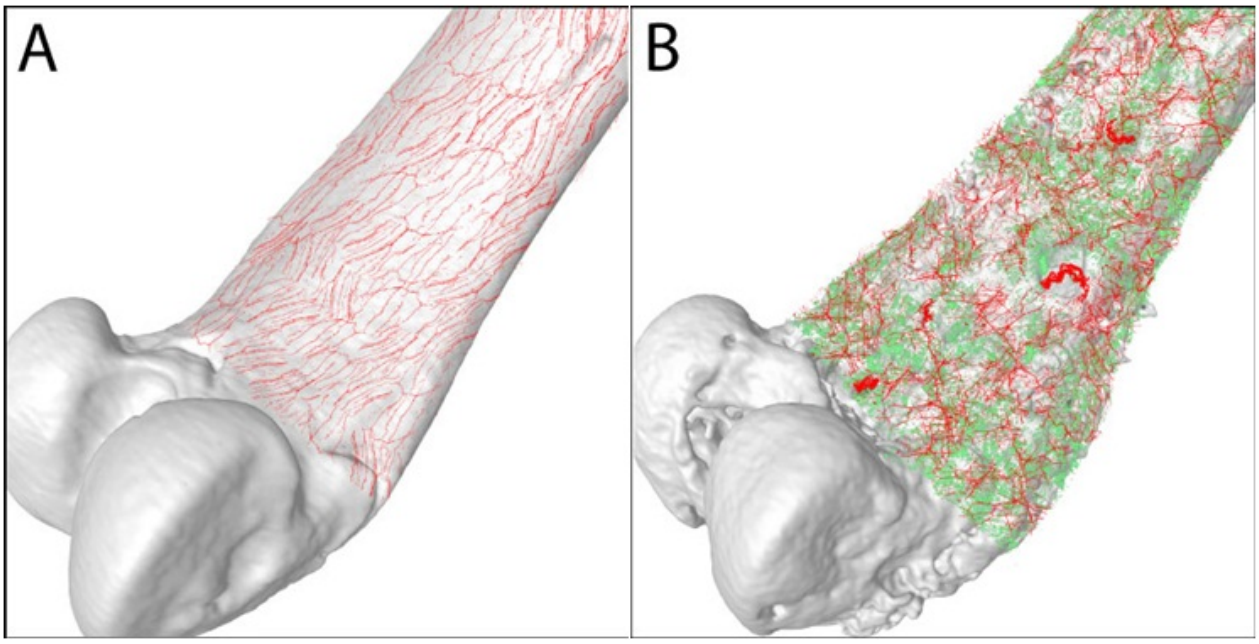

Figure 2 Sprouting and formation of neuroma-like structures in chronic bone pain. Sarcoma tumor cells expressing green fluorescent protein (green) induce a marked sprouting and neuroma formation of $CGRP^+$ sensory nerve fibers (red) that innervate the bone (white). These nerve fibers detect and transmit painful stimuli from periphery to the central nervous system. **A)** In sham bones, $CGRP^+$ nerve fibers that are present in the bone appear as single nerve fibers with a liner and homogenous morphology. **B)** As cancer cells proliferate and grow in bone, these induce significant bone remodeling (pitted appearance) as well as a highly pathological sprouting and formation of neuroma-like structures by sensory and sympathetic nerve fibers which in other conditions drives chronic pain. Confocal images from periosteal whole preparations were acquired and overlapped on a three dimensional image of the mouse femur obtained by microcomputed tomography. Images were rendered courtesy of Marvin Landis (University Information Technology Services, University of Arizona).

excessive bone growth and pathological bone remodeling (Fig. 3). A similar ectopic sprouting of sensory and sympathetic nerve fibers occurs in the bone marrow and mineralized bone [13]. As these prostate cells do not express detectable levels of mRNA coding for NGF, these data suggest that this ectopic sprouting of nerve fibers is not primarily driven by NGF released from tumor cells, but rather by the major source of NGF arising from endogenous stromal, inflammatory and immune cells [14,15]. These newly sprouted nerve fibers are probably also activated and sensitized by released NGF and as such this truly ectopic and pathological reorganization of sensory and sympathetic nerve fibers may provide an anatomical substrate which drives skeletal pain. In support of this hypothesis, preventive treatment with an antibody that sequesters NGF, administered when prostate tumor-induced pain and bone remodeling were first observed, blocked this ectopic sprouting and significantly inhibited the development and severity of cancer pain [13].

While it is not known whether sprouting of sensory nerve fibers occurs in FD, this phenomenon has been observed in non-malignant skeletal pain states in human and animals. Previous studies have reported that human chronic discogenic pain may in part be due to a growth of $TrkA^+$ nerve fibers into normally aneural and avascular areas of the human intervertebral disc [16]. Other studies have demonstrated significant sprouting of $CGRP^+$ nerve fibers following bone fracture in rat and in the arthritic joints of humans and animals [17-19]. These reports suggest that following injury or disease of the skeleton, significant sprouting of $TrkA^+$ nerve fibers can occur, and it appears that endogenous stromal cells as well as inflammatory and immune cells are the source of NGF [14,15].

The burden of bone pain in fibrous dysplasia

Methods and patients (adapted from Ref. 4)

We have studied a relatively large population of patients with FD in an effort to understand their experience with pain [4]. All subjects enrolled in a National Institutes of Health (NIH) Institutional Review Board approved study of FD and MAS were invited to complete the self report Brief Pain Inventory (BPI) and a demographic data questionnaire during their initial evaluation at NIH between July 2000 and July 2005. Ninety-one subjects were enrolled during that period, and 78 (86%) completed the pain form and had a ^{99}Tc-MDP bone scan, including 56 subjects 14 or older (72%) and 22 under the age of 14 (28%). The

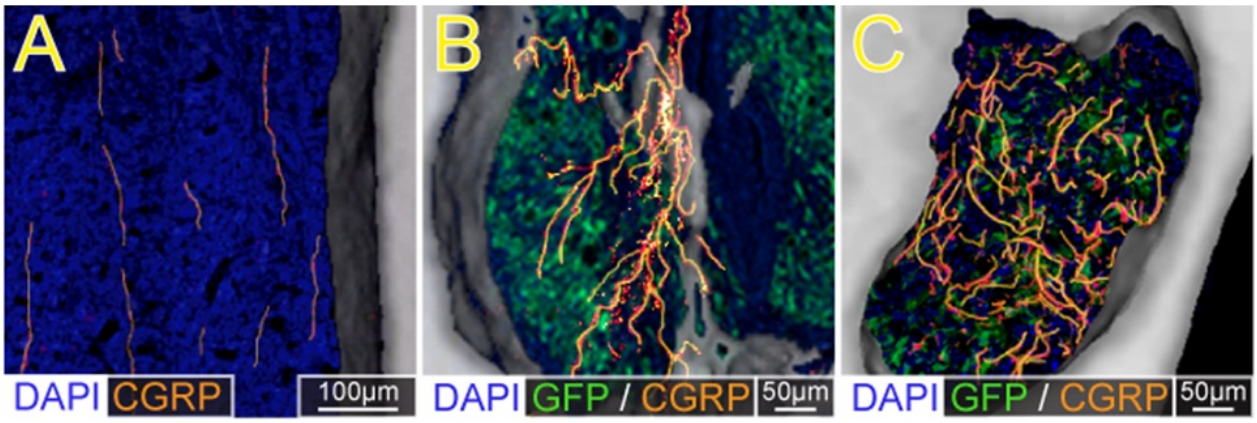

Figure 3 Prostate cancer cells induce sprouting of sensory nerve fibers in the bone marrow of tumor bearing femurs. High power μCT slices of bone (100 μm-thick) overlaid with confocal images (20 μm-thick) obtained from a sham femur (**A**) and tumor-bearing femur from mice sacrificed at early (**B**) and more advanced stages of the disease (**C**). In these images the DAPI stained nucleus of cells appear blue, the green fluorescent protein expressing (GFP) prostate cancer cells appear green, and the calcitonin gene related peptide (CGRP) sensory nerve fibers appear yellow/red. Note that in the sham mice, $CGRP^+$ nerve fibers that are present in the marrow space of normal mice appear as single, nerve fibers with a highly linear morphology. As GFP^+ prostate tumor cells proliferate and form tumor colonies (**B,C**), the $CGRP^+$ sensory nerve fibers undergo marked sprouting which produces highly branched, disorganized and dense meshwork of sensory nerve fibers (**B,C**) that is never observed in the normal marrow (**A**).

diagnosis of FD was established in all patients based on clinical history, histopathological findings, radiographic findings, and when necessary, an analysis of the *GNAS* gene for R201 mutations. Bone scans were assessed for sites of FD involvement, which were identified as areas of non-physiologic tracer uptake, and disease severity was determined using a validated scoring tool [20]. The fact that tracer uptake sites represented FD was confirmed by radiograph and/or CT. Pain was assessed using a human figure drawing and the numeric rating scale (NRS) of the Brief Pain Inventory (BPI). The BPI is a short, self-administered questionnaire developed to assess the severity and impact of pain primarily in cancer patients [21]. It has been shown to be valid and reliable in adults when used to assess cancer pain [21], chronic and acute nonmalignant pain and pain in osteoarthritis patients. The goal was to assess pain "intrinsic" to the FD and not pain that occurred in relation to a fracture. Therefore, acute or healing fractures were excluded from the analysis (i.e., > 6 months since radiographic evidence of complete healing at a site at which there had been a recent fracture). Analgesic use and perceived relief information was obtained as part of the questionnaire, and confirmed during patient interviews.

Results

The study population was made up of a group of subjects with a broad spectrum of disease, from isolated monostotic FD, to total skeletal involvement. The lower extremities were the sites most likely to be affected by FD (86% of adults, 97% of children, p=NS for differences between adults and children). The head was also commonly affected (86% of adults, 94% of children, p=NS). FD lesions were found less frequently in the upper extremities (72% of adults, 89% of children, p=NS), the ribs (72% of adults, 57% of children, p=NS) and the spine (72% of adults, 46% of children, $p<0.05$). The spine was the only site at which there was a significant increase in FD involvement over time.

Pain was prevalent in the FD population; 67% reported pain at FD sites. Pain was more common in adults than children, and was reported by 81% of adults and 49% of children ($p<0.005$) (Fig. 4). Adults reported significantly more pain than children in both the lower extremities (adults 81%, children 53%, $p<0.05$) and the spine (adults 52%, children 13%, $p<0.05$) (Figure 2). The degree of pain reported was considerable, but quite variable. The mean pain score (on the 0 to 10 pain scale) for adults was 4.1 (range 1 to 8, ± 1.8), and 2.8 for children (range 1 to 7, ± 1.8) (Table 1). Adults had significantly more pain than children ($p<0.01$). In an effort to assess how pain prevalence changed with aging, we examined the prevalence of pain in age group increments of 10 years. No pain was reported by children less than 10 years old, while 50-60% of those age 11 through 30 reported pain and 85-100% of the patients over 31 years of age experienced pain (Table 1).

There was no correlation between pain prevalence and gender, phosphate wasting, vitamin D status (serum vitamin D level < 32 ng/ml was used as a cutoff for the diagnosis of vitamin D deficiency), or any endocrinopathy in children. Growth hormone excess correlated with pain prevalence at FD sites in adults (p=0.031).

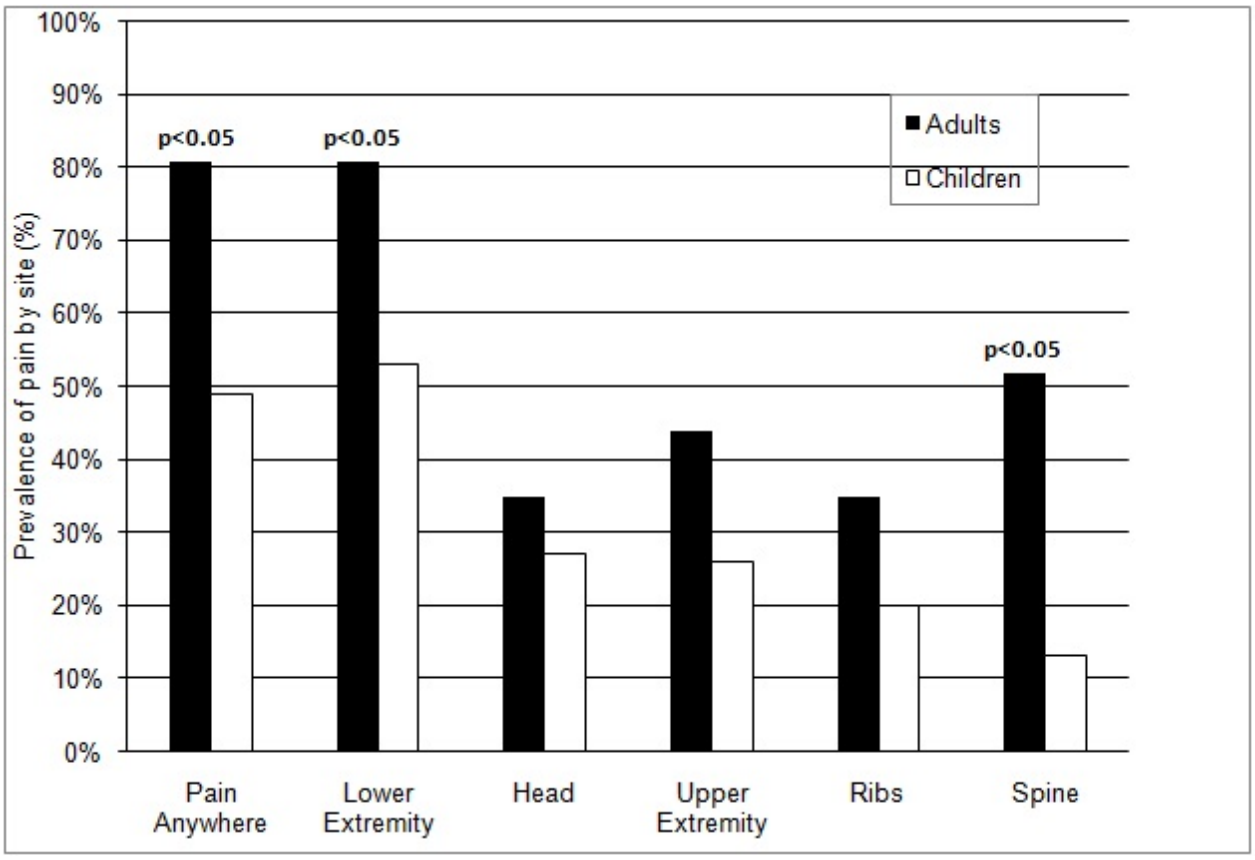

Figure 4 Prevalence of pain at skeletal sites involved with fibrous dysplasia in adults and children. Sites at which patients reported pain was recorded. 99Tc-MDP bone scans were reviewed to confirm the presence of FD at the reported site of pain. Only those sites at which there was a concordance of pain and FD involvement were recorded. Adults had significantly more pain than children in general ($p<0.05$), and at both the lower extremity and the spine ($p<0.05$ for both).

Patients reported using a variety of treatments to control pain (Table 2). NSAIDs were most commonly used (57% of adults and 56% of children who had pain). Some subjects reported using more than one treatment. There was a trend for children who reported pain to be less likely to be treated for pain than adults ($p=0.21$).

Treatment of fibrous dysplasia bone pain with bisphosphonates

The use of an antiresorptive agent in the treatment of an osteoblastic lineage disease, such as FD, is counterintuitive. The rationale for doing so is based on the presence of abundant osteoclastic bone resorption within and around the fibrous tissue. Therefore, in an early study that took as an example the treatment of Paget's disease, 9 patients

Table 1 Prevalence of pain by age groups

Age group (years)	n	% of subjects with pain
<10	7	0
11-20	27	59
21-30	10	50
31-40	13	85
41-50	14	100
>50	7	86

Table 2 Pain severity, treatment and response to treatment[1]

	Adults		Children	
Average pain	4.1*		2.8	
Treatment	% treated	% with releif	% treated	% with releif
No treatment	26%		44%	
NSAIDs	57%	56%	56%	50%
Narcotics	26%	47%	17%	90%
Bisphosphonates	26%	73%	17%	75%
Alternative Treatments	17%	52%	11%	No report

[1]Only subjects who had FD-associated pain are recoded in this analysis.

*=$p<0.05$, NSAIDs = non steroidal anti-inflammatory drugs

were treated with intravenous pamidronate (180 mg every 6 months), with striking radiographic improvements and decreases in bone pain and biochemical markers of bone remodeling [5]. Patients were also receiving calcium (500-1500 mg/day) and vitamin D (800-1200 IU/day) supplements.

Long-term effects of this regimen have been assessed with additional patients and longer follow-up, still in an open design, with similar results [2,22]. A dose of 3 mg/kg/treatment cycle was used in children and adolescents, who represented 30% of this cohort. Fifty-eight patients have been treated with intravenous pamidronate and followed-up for an average 50 months (ranging from 1 to 11 years). Pain intensity was reduced after the first course of treatment, with an additive effect observed after several treatment cycles. Bone pain disappeared in 60% of these patients, diminished in 24% and did not improve in 16% of them. In parallel, biochemical markers of bone turnover – such as total alkaline phosphatase, serum osteocalcin, and urinary CTX – were also significantly reduced compared to baseline. Half of those treated patients had discernable radiological improvement, characterized by filling of osteolytic lesions and/or cortical thickening. In addition, total hip bone mineral density (BMD) measured in patients who had hip involvement was substantially increased [23]. Results were similar in adults and children or adolescents. These biochemical and radiological changes, however, were not associated with bone pain reduction.

Favorable outcomes have also been observed in other open studies using intravenous pamidronate, administered at 6-month intervals. Thus, bone pain was significantly relieved in a study involving 7 patients with various forms of FD treated with intravenous pamidronate [24]. A greater increase in BMD was also observed in affected areas than in unaffected areas, using whole body DXA to compare the affected to the unaffected side, after 1 year of treatment. Simultaneously, the level of bone turnover as assessed by biochemical markers was reduced but most patients still had increased bone turnover.

A few patients have also been treated successfully with alendronate. For example, an increase of 158% in total hip BMD over 2 years has been observed in a 22-year old woman who had received four 90 mg infusions of pamidronate every 4 weeks, followed by oral alendronate 10 mg/day [25], with a parallel relief in bone pain and decrease in urinary NTX. In another case report [26], a 45-year old woman who received alendronate 5 mg/day was relieved of her bone pain after several months of treatment. Bone turnover was diminished and the radiological appearance improved slightly. In a series of 6 adult patients who had been treated with pamidronate followed by alendronate or who had used alendronate alone, bone pain decreased substantially in response to therapy, bone resorption was reduced with intravenous pamidronate but not with oral alendronate, and four out of six patients exhibited radiological improvement [27].

Although most patients respond favorably to pamidronate therapy, a subset (15% in our group's experience, RDC) did not exhibit any improvement in bone pain. Other patients, with an initial positive response to treatment with pamidronate, have suffered from a relapse of bone pain or failed to maintain reduced levels of biochemical markers of bone turnover. When those patients who relapsed or failed treatment with pamidronate were switched to zoledronic acid, we were not able to obtain significant reductions in bone pain or improvement in the radiographic appearance [28]. Zoledronic acid was well-tolerated, with only two patients with an acute phase reaction associated with the first infusion. Those patients switched to zoledronic acid tended to have more serious disease than the other patients on pamidronate only.

In another study [29], however, no convincing evidence of radiographic benefit could be observed in 18 children and adolescents with polyostotic FD, despite significant reduction in levels of bone turnover markers. The explanation for the discrepancy between this study conducted in young patients and those in adults or other pediatric series [30-32] remains unclear, but some of the difference might relate to the absence of use of phosphate supplements in those patients with renal phosphate wasting. The difference may also stem from the difficulty in defining appropriate radiographic outcomes in studies of FD, as lesions are heterogeneous and radiographs are not always reproducible over time.

All these results were obtained in uncontrolled open studies. The role of the placebo effect and regression to the mean is likely to explain some of the effect on bone pain. The radiologic effect might be confounded by the age-related sclerosis of lesions [33], but this phenomenon arises over long periods of time, whereas the improvement associated with bisphosphonate use could be observed over shorter periods of time, e.g., 2-3 years. These shortcomings led to the design of two randomized placebo-controlled clinical trials, one conducted in the USA to test alendronate [34], and the other in Europe, the PROFIDYS trial, testing risedronate [35]. The results of the first trial are not yet published, and the latter is still recruiting patients.

Perspectives

Some patients fail to respond to bisphosphonates or relapse after an initial improvement in bone pain. These individuals do not seem to respond better to more potent bisphosphonates, such as zoledronic acid [28]. Those patients often have severe polyostotic disease, with a history of several fractures, substantial bone pain, and sometimes optic nerve compression. There is no current satisfactory therapeutic option in these severely

disabled patients whose disease is resistant to bisphosphonates.

We know that *GNAS* mutations result in abnormal proliferation and differentiation of bone marrow stromal cells. In those osteoblastic cells, IL-6 secretion is increased as a result of Gs activation, with consequent activation of surrounding osteoclasts, allowing the FD lesion to expand and create osteolytic lesions [36]. A direct link has been established between the *GNAS* mutation in stromal cells and IL-6 production, so that FD, which is an osteoblastic lineage disorder, is also often associated with a hyperosteoclastic component [37].

This is the rationale to selectively inhibit the IL-6 driven increased bone resorption that is observed in FD by targeting the IL-6 receptor with tocilizumab, in those patients who fail to respond to bisphosphonates primarily or secondarily. Tocilizumab - a human monoclonal antibody to IL-6 receptor - is a drug currently used in rheumatoid arthritis (RA) treatment. It can reduce symptoms, and block localized periarticular bone loss induced by the disease. A recent study has also shown that the level of systemic bone resorption, as assessed by markers such as serum ICTP and CTX could be significantly decreased in RA in response to tocilizumab [38].

Therefore, a randomized placebo-controlled cross-over trial testing the value of tocilizumab to decrease bone resorption among patients with FD who do not respond to bisphosphonate therapy will be launched in Europe in 2011. A total of 12 patients will receive either tocilizumab during 6 months followed by 6 months of placebo (6 patients), or 6 months of placebo followed by 6 months of tocilizumab (6 patients). The study is powered to show a 30% difference in bone resorption between the two treatments. Decrease in bone resorption (primary endpoint) will be assessed with serum CTX. Secondary endpoints will be: decrease in bone pain, assessed by visual analogic scale in the most painful skeletal site, decrease in other markers of bone remodeling (serum osteocalcin, bone alkaline phosphatase, P1NP), and improvement in the short-form 36 (SF-36) quality of life scale.

Another way to develop new therapies to treat pain associated with fibrous dysplasia is to understand the unique populations of nerve fibers that innervate bone and the mechanisms by which these nerve fibers signal skeletal pain. Unlike skin, the majority of sensory nerve fibers in bone express TrkA, TRPV1 antagonists, inhibitors of CSFR1 and pregabalin (Table 3). In addition to assessing the efficacy of these therapies to reduce FD pain, endpoints which need to be included in these

Table 3 Therapies that may be useful in treating FD pain

CURRENT AND POTENTIAL THERAPIES FOR TREATMENT OF FIBROUS DYSPLASIA PAIN			
DRUG CLASS	**TARGET**	**ACTION**	**POTENTIAL COMPLICATIONS**
Current therapies			
Biphosphonates	Osteoclasts	Osteoclast apoptosis Osteoclast activity suppression	Inhibition of bone remodeling/ growth Osteonecrosis
Opioids	CNS neurons	Stimulates opioid receptors	Sedation Dependence Constipation
NSAIDS	Prostaglandin synthesis	Blockade of peripheral and central sensitization	GI toxicity Cardiotoxicity Nephrotoxicity
Recently approved therapies/ ongoing clinical trials for treating other skeletal pain states			
Denosumab (OPG) (Amgen)	Blocks RANKL	Blocks osteoclast activation	Inhibition of bone remodeling/ growth Osteonecrosis
Tanezumab (anti-NGF) (Pfizer)	NGF/TrkA pathway	Blockade of peripheral sensitization Blockade of nerve sprouting	Developing sensory and sympathetic nerve fibers
Potential therapies			
NGF/TrkA inhibitors (Array, JNJ, Abbott)	NGF/TrkA pathway	Blockade of peripheral sensitization Blockade of pH sensitive neurons	Developing sensory and sympathetic nerve fibers
TRPV1 antagonists (Pfizer, JNJ, Abbott, Merck, GSK, etc.)	TRPV1 channel	Blockade of pH sensitive neurons	Hyperthermia (transient?)
CSFR1 inhibitors response (Plexxikon, Roche, JNJ)	Inhibition of CSFR1	Reduction in osteoclasts, macrophages, etc.	Decreased immune response to infection
Pregabalin (Pfizer)	Calcium channel, $\alpha 2$, $\delta 1$ subunit	Aberrant neuronal discharge	Lethargy Drowsiness

clinical trials are effect on disease progression, side effect profile and risk/benefit to the patient. Additionally, developing an animal model of FD and understanding how the density, morphology, phenotype, and response characteristics of skeletal sensory nerve fibers changes in a preclinical model of FD may help in the development of more targeted therapies to treat FD pain.

Denosumab is currently approved to treat osteoporosis as it targets RANKL and is remarkably effective at reducing osteoclast-induced bone remodeling. As such it may represent a potential treatment for FD bone pain. Pregabalin has been shown to attenuate a wide variety of neuropathic pain (i.e. pain originating from damaged or ectopic reorganization of nerve fibers) and as ectopic reorganization of nerve fibers may play an important role in driving FD induced skeletal pain, pregabalin might be useful in reducing FD pain, however no clinical study data currently exists that specifically investigates the efficacy of pregabalin in FD.

Conclusion

Bone pain is commonly observed in FD. Bisphosphonates can provide some relief of bone pain, but the development of mechanism-based therapies to treat neuropathic bone pain or the bone disease itself is needed to improve the management of FD patients.

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Competing interests

The authors declare that they have no competing interests.

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A Randomized, Double Blind, Placebo-Controlled Trial of Alendronate Treatment for Fibrous Dysplasia of Bone

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Abstract

Go to:

Context:

Go to:

Fibrous dysplasia (FD) is a rare skeletal disorder, resulting in deformity, fracture, functional impairment, and pain. Bisphosphonates have been advocated as a potential treatment.

Objective:

Go to:

To determine the efficacy of alendronate for treatment of FD.

Design:

Go to:

Two-year randomized, double-blind, placebo-controlled trial.

Setting:

Go to:

Clinical research center.

Patients:

Go to:

Forty subjects with polyostotic FD (24 adults, 16 children). Subjects were randomized and stratified by age.

Interventions:

Go to:

Study drug was administered over a 24 month period in 6 month cycles (6 months on, 6 months off). Alendronate dosing was stratified: 40 mg daily for subjects >50 kg, 20 mg for 30–50 kg, 10 mg for 20–30 kg.

Main Outcome Measures:

Go to:

Primary endpoints were bone turnover markers, including serum osteocalcin, and urinary NTX-telopeptides. Secondary endpoints included areal bone mineral density (aBMD), pain, skeletal disease burden score, and functional parameters including the 9-min walk test and manual muscle testing.

Results:

Go to:

Clinical data was collected on 35 subjects who completed the study. There was a decline in NTX-telopeptides in the alendronate group ($P = .006$), but no significant difference in osteocalcin between groups. The alendronate group had an increase in areal BMD in normal bone at the lumbar spine ($P = .006$), and in predetermined regions of FD ($P < .001$). There were no significant differences in pain scores, skeletal disease burden scores, or functional parameters between the groups.

Conclusions:

Go to:

Alendronate treatment led to a reduction in the bone resorption marker NTX-telopeptides, and improvement in aBMD, but no significant effect on serum osteocalcin, pain, or functional parameters.

Fibrous dysplasia (FD) is an uncommon skeletal disorder in which normal bone and bone marrow are replaced by fibro-osseous tissue (1,–3). Clinical sequelae result from bone weakness and fragility, including fracture, functional impairment, deformity, and pain. FD arises from activating mutations in *GNAS*, which encodes the α-subunit of the G_s stimulatory protein ($G_s\alpha$) (4, 5). Mutations occur postzygotically, leading to mosaic disease with wide clinical variability between individuals (6). FD may occur in one bone (monostotic) or multiple bones (polyostotic), and may be associated with café-au-lait macules and hyperfunctioning endocrinopathies, termed McCune-Albright syndrome (MAS) (7, 8). The downstream cellular effects of constitutively activated $G_s\alpha$ result in increased adenylyl cyclase activity and inappropriate intracellular cyclic adenosine monophosphate (cAMP) production (4). In bone, this is associated with proliferation of undifferentiated bone marrow stromal cells resulting in marrow fibrosis, abnormal matrix production, and increased osteoclastogenesis (3, 9,–11).

Currently there are no effective medical treatments for FD. Antiresorptive therapy with bisphosphonates has been advocated due to high levels of bone resorption frequently seen in FD tissue (10). Early studies showed encouraging results, including a report by Liens et al of 9 patients treated with pamidronate who demonstrated improvement in pain, a decrease in bone turnover markers, and improvement in the radiographic appearance of FD lesions (12). Longer-term studies of this regimen reported similar results (13, 14). Additional studies showed consistent benefit in pain and turnover markers, but were unable to replicate the previously reported radiographic improvement (15,–17). Until now, determining the role of bisphosphonates in management of FD has been limited by a lack of controlled studies. Here we report the results of the first controlled trial of bisphosphonate treatment for FD in a 2-year randomized, double-blinded, placebo-controlled study of alendronate.

Subjects and Methods

Go to:

Subjects

Subjects were recruited from an existing FD/MAS natural history study at the National Institutes of Health (NIH). Inclusion criteria included polyostotic FD with at least 2 skeletal lesions, and age > 12 years. When safety had been demonstrated in 5 children under age 18, the age requirement was lowered to 6 years. Exclusion criteria included antiresorptive (specifically bisphosphonate) treatment within one year of enrollment, severe esophageal motility problems, pregnancy, and history of skeletal sarcomas. The

protocol was approved by the Institutional Review Board of the National Institute for Dental and Craniofacial Research, and all subjects and/or their guardians gave informed assent/consent.

Study design

Randomization to the alendronate and placebo groups was stratified by age, and subjects and investigators were blinded to intervention group. Alendronate and placebo were provided by Merck & Co under an Investigational New Drug Application. Alendronate or placebo was administered over a 24-month period in 6-month cycles (6 months on, 6 months off), with no crossover. A cyclical design was chosen due to the unavailability of robust safety data for long term, high dose, and continuous treatment with alendronate at the time of study initiation. Alendronate was chosen over an intravenous (IV) bisphosphonate due to its greater ease of administration. Alendronate dosing was chosen based upon available data in Paget's disease (18), and was approximately 4 times the typical dose used for osteoporosis (19). Dosing was stratified by weight, with 40 mg daily for adults > 50 kg, 20 mg for 30–50 kg, and 10 mg for subjects 20–30 kg. Subjects were instructed to take each dose in the morning prior to eating, with a full glass of water, and to remain upright for at least 30 minutes. Calcium and vitamin D intake was monitored with diet questionnaires and maintained in accordance with the recommended daily allowances. Subjects were evaluated at baseline at the NIH Clinical Center, with follow-up assessments at 6, 12, 18, and 24 months. Compliance was assessed at each visit through subject report and pill counts. Between visits, telephone interviews and outpatient laboratory tests were obtained for safety monitoring.

Outcome measures

The primary endpoint was effect of alendronate on biochemical markers of bone turnover, including urine NTX-telopeptides (reflecting bone resorption), and serum osteocalcin (reflecting bone formation). Secondary endpoints included effects on FD-related bone pain, areal BMD (aBMD) of FD lesions, and functional parameters including walking speed and muscle strength.

Biochemistry

Standard laboratory panels were assessed on all subjects at baseline and at each follow-up visit, including complete blood count (CBC), chemistry panel, and mineral panel (calcium, phosphorus, PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, urinary calcium, phosphorus, and creatinine). Bone turnover markers were assessed at baseline and at each follow-up visit. All subjects were evaluated at baseline and treated for endocrine complications of MAS. Specifically, all subjects with FGF23-mediated hypophosphatemia were treated with phosphorus and calcitriol supplementation to maintain normal serum phosphorus levels for the duration of the study.

Radiographic imaging

^{99}Technetium (Tc-99) bone scintigraphy was used at baseline and 24 months to identify areas of the skeleton affected by FD, and to quantify skeletal FD burden using previously described methodology (20). Areas of the skeleton affected by FD were visualized by plain radiographs at baseline, 12 and 24 months. To quantify the effects of treatment on FD lesions radiographically, aBMD of FD lesions was measured by dual x-ray absorptiometry (DXA) (Hologic 4500A device, Hologic, Inc) at baseline, 12, and 24 months. As an internal control of the effect of drug on unaffected bone, bone density of the lumbar spine was assessed in all subjects who did not have FD in this location. To assess the effect of drug on FD, sentinel sites of FD were identified and aBMD measured by DXA. Using the whole body DXA image, the region of interest (ROI) software was used to create a ROI around an FD lesion that that had been identified on plain radiograph. A ROI was created around an FD lesion and the borders modified to include only the area of the bone that included FD. The ROI and the location of the sentinel lesion, as determined by adjacent anatomical landmarks, were noted and saved electronically. The same areas were analyzed on

repeat scans at 12 and 24 months. On repeat scanning the difference in area of the ROI had to be ≤ 5% of the baseline scans. Areas that included metallic devices were excluded from analysis, and if metallic devices were introduced into a site during the study, the site was excluded from repeat analysis. Analyses were performed after completion of the study by a single co-investigator (MHK), experienced at reading DXA scans and blinded to the treatment.

Pain

Bone pain was evaluated at baseline and at each follow-up visit using the Wisconsin Brief Pain Questionnaire, a validated pain assessment tool (21).

Functional testing

Subjects underwent functional assessment at baseline and each follow-up visit. Ambulation endurance and efficiency were evaluated using the 9-minute walk test (9 MW), a standardized, validated measure (22). Subjects were instructed to walk and/or run at the fastest comfortable pace that they would be capable of sustaining for 9 minutes. Endpoints for the analysis included walking velocity and distance covered.

Muscle strength was evaluated using manual muscle testing (MMT) of the lower limbs. This was performed using a standard technique scored on the Medical Research Council (MRC) ordinal scale of 0–5 (23). The median score for each muscle (gluteus maximus, gluteus medius, iliopsoas, quadriceps, hamstrings, and ankle plantar and dorsiflexors) was determined. Endpoints for analysis included overall strength of the right and left hips, and combined total median strength of all lower extremity muscle groups.

Statistical analysis

All analyses were based on an a priori approved analysis plan and performed using SAS (version 9.2). The primary statistical comparison was based on all treated subjects (ITT population of adults and pediatric cases combined) at 18 months. The primary endpoint was the percentage change from baseline in each of the two separate measures of bone turnover between treated and placebo. The *P*-value to establish statistical significance for the primary efficacy analysis was set at $\alpha = 0.025$ divided by 2, 1-sided. Bonferroni adjustments for all nonprimary analyses were not performed. All numerically continuous data are summarized using mean ± SD with differences between means compared using a repeated measures mixed model analysis of variance (ANOVA). Categorical data are presented using proportions with categorical comparisons between treatment groups tested using Fisher's exact test.

Results

Go to:

Subjects

Fifty-two subjects were screened and 40 were enrolled, including 24 adults and 16 children (Figure 1). Screening and enrollment data are included in Table 1. There were no significant differences between the alendronate and placebo groups with respect to age, sex, or MAS-associated endocrinopathies. There was a trend toward higher skeletal disease burden in the alendronate group ($P = .07$) (Table 1).

Two alendronate-treated subjects withdrew shortly after study initiation due to gastrointestinal (GI) side effects. Two subjects in the placebo group voluntarily withdrew due to personal preference. At 18 months a subject in the placebo group was taken off study drug after developing diarrhea and weight loss. Data from these subjects were not included in the analyses.

Bone turnover markers

There was a significant decline in the bone resorption marker NTX-telopeptides in the alendronate group as compared to the placebo group at 18 months ($P = .006$) (Figure 2A). These differences were statistically significant when children were analyzed separately (observed $P = .03$, Bonferroni adjusted $P = .06$), with a trend toward significance for adults (observed $P = .07$, Bonferroni adjusted P value = .14). For osteocalcin, there were no significant effects of alendronate on any analysis (Figure 2B). Alkaline phosphatase levels were analyzed as a secondary endpoint with no Bonferroni adjustments, with no significant effect on any group (data not shown).

Radiographic imaging

To confirm the established effect of bisphosphonates on normal bone and indirectly assess compliance, aBMD was measured in the lumbar spine in subjects without spinal FD, as determined by examination of bone scintigraphy. Eleven subjects in the alendronate group (6 adults, 5 children) and 14 in the placebo group (8 adults, 6 children) did not have FD in the spine. At 24 months there was a significant difference in the change in aBMD from baseline in the subjects treated with alendronate ($P = .006$), that was not apparent at 12 months ($P = .26$). When adults and children were analyzed separately, there was a significant difference in aBMD at 24 months in treated children ($P = .01$), however the changes in adults did not reach statistical significance ($P = .13$) (Figure 3A). Analyses were also performed using a comparison to normative data (Z-scores for both children and adults), which showed similar findings (data not shown). To assess the effect of alendronate on FD, sentinel lesions (as defined in Methods) were selected in 6 adults and 5 children treated with alendronate and 8 adults and 6 children treated with placebo. There were 9 lesions in femora, 13 in humeri, and 8 in tibiae. When there was more than one lesion in an individual subject, the changes in aBMD in the lesions were averaged. At 24 months there was a significant change in the aBMD at the FD sites in subjects treated with alendronate ($P < .001$), that was not apparent at 12 months ($P = .81$) (Figure 3B). When children were analyzed separately the change in aBMD at 24 months was significant ($P = .001$), however there was no significant change detected in a subanalysis including only adults ($P = .25$).

Skeletal disease burden scores determined from Tc-99 bone scintigraphy were compared at baseline and 24 months to determine the effect of alendronate on the development of new, or expansion of existing FD lesions using previously described methodology (20). Previous investigation of our cohort has shown that most FD disease burden is determined by age 15 years (24), therefore a subanalysis was performed on subjects age 15 and younger. Four out of 6 children in the alendronate group and 3 out of 4 in the placebo group had progression in bone scan score over the course of the treatment period. There were no significant differences in mean bone scan score at baseline or 24 months in either group of those subjects $\leq$ 15 or > 15 years (data not shown).

Skeletal radiographs were performed at baseline and 24 months to verify the presence of FD lesions seen on bone scintigraphy. Because of the inherent subjectivity in interpretation of radiographs (due in part to inconsistencies in exposure and positioning), changes in FD radiographic appearance were not quantified. A member of the study team reviewed the radiographs over the course of the study (M.T.C.). As expected there was variation in the progression of FD lesions between individuals, however there was no subjective improvement in FD appearance in alendronate-treated subjects, and no subjective differences between groups over the treatment period (Figure 4).

Pain

There was no difference in mean pain score between the two groups at baseline, and no significant differences in pain between groups at any point during the treatment period (Figure 5). Separate analyses of adults and children likewise failed to detect an effect of alendronate on bone pain.

Functional testing

There was no significant difference in 9 MW distance or walking speed between the alendronate and placebo groups at baseline, or at any point during the treatment period. Likewise there was no difference between the groups for MMT of the hips and lower extremities at any point.

Safety

Six fractures occurred over the treatment period; three in the alendronate group and three in the placebo group. Of note, the study was not powered to detect an effect of alendronate on fracture incidence. No subjects developed disturbances in biochemical safety measures, including markers of mineral metabolism, renal function, blood count, or liver function. Two adverse events were determined to be likely related to alendronate use. An esophageal stricture developed in an adult subject shortly after starting alendronate; the subject was subsequently found to have an undisclosed history of gastroesophageal reflux. A pediatric subject developed nausea and vomiting shortly after starting alendronate, which resolved after the drug was discontinued.

Discussion

Go to:

In this randomized, double-blind, placebo-controlled trial, alendronate treatment of subjects with FD at 4 times the typical osteoporosis dose resulted in a significant decrease in NTX-telopeptides, a biochemical marker of bone resorption, and a significant increase in aBMD of FD lesions at 24 months. There were no effects on the bone formation marker osteocalcin, or clinical parameters including bone pain, 9-minute walk time, or lower extremity muscle strength.

The decrease in the marker of bone resorption N-telopeptides is concordant with other studies in FD showing that bisphosphonates decrease markers of bone metabolism (13, 25,–28). Because FD is a mosaic disorder, it is unknown to what degree the decrease in bone turnover markers is the result of a decline in metabolic activity of FD lesions vs that of the unaffected skeleton. It is possible that with prolonged antiresorptive treatment there is excessive suppression of the normal areas of the skeleton. Future studies including bone histomorphometry would allow more direct investigation of the effects of bisphosphonates on FD lesions vs unaffected bone. The lack of effect on osteocalcin is of interest. Osteocalcin is the product of mature cells of the osteoblastic lineage, and is considered a marker of bone formation. While the degree of osteocalcin elevation in FD is correlated with disease burden, it is the most weakly correlated bone metabolism marker (20, 29). Generally, treatment with bone resorption inhibitors such as bisphosphonates leads to a concurrent decline in both markers of bone formation and resorption (30, 31). This is believed to reflect a not well-described cross talk between osteoclasts and osteoblasts (32). A potential explanation for the lack of decrease in osteocalcin may be an absence of this cross talk in FD, and/or the fact that FD cells are less differentiated than the bone cells that typically secrete osteocalcin.

The lack of alendronate effect on bone pain contradicts previous uncontrolled studies in which bisphosphonates were consistently reported to have a beneficial effect on FD-related bone pain (13,–17). There are several potential explanations for this disparity: (1) previous studies of bisphosphonates in FD were uncontrolled, and improvements in pain may have resulted from placebo effects; (2) previous studies did not consistently evaluate pain quantitatively, which may have led to an overestimation of pain relief effects; and (3) previous studies involved use of IV bisphosphonates, which may have more potent effects on bone pain than the oral formulations. The lack of an effect on pain of an oral bisphosphonate in a controlled vs uncontrolled study is similar to what was found in studies of bisphosphonates in osteogenesis imperfecta. While the IV bisphosphonates pamidronate and zoledronic acid were reported to improve bone pain in open label studies in osteogenesis imperfecta (33,–35), the oral formulations alendronate and risedronate had no effect on bone pain in placebo-controlled trials (36, 37). Our findings and those in subsequent studies of osteogenesis imperfecta suggest that additional placebo-controlled trials with IV formulations are needed to determine the effect of bisphosphonates on bone pain.

As expected, aBMD increased at the spine by 24 months, confirming that treatment was sufficient to have an impact on non-FD bone (Figure 4A). The effect of alendronate on aBMD of FD lesions is less clear. DXA is a suboptimal tool for evaluating mosaic diseases such as FD due to its inability to distinguish between normal and affected bone. Although efforts were made to select ROIs that appeared to consist primarily of FD tissue, in all cases some amount of normal bone was included, confounding the aBMD measurements. DXA evaluation is also complicated by the heterogeneity of FD tissue, which may include areas of sclerosis adjacent to poorly mineralized bone. It is unknown whether DXA evaluation of FD offers any advantage over plain films, which allow assessment of clinically relevant features such as skeletal deformity and cortical thickness. While the radiographic appearance of FD varied between individuals over the course of the study, we were unable to determine a consistent effect of alendronate on the radiographs (Figure 3).

The clinical significance of these findings is uncertain. Despite the increase in areal BMD, the lack of change in the radiographic appearance of FD lesions calls into question whether alendronate had a significant impact on FD at the tissue level. FD lesions continued to expand in pediatric subjects treated with alendronate, suggesting it is not effective as a preventative therapy. Based on these data, the authors do not recommend alendronate treatment in patients with FD. Additional controlled studies are needed to determine if IV bisphosphonates are effective for treatment of FD. Another potential antiresorptive treatment is denosumab, a monoclonal antibody inhibitor of the osteoclast promoting receptor activator of nuclear-B kappa ligand, which has shown encouraging results in several case reports of patients with FD (38, 39).

Strengths of this study include a randomized, controlled, double-blinded design. It is the first controlled study reported in this disease. A primary limitation was the small number of subjects. Given the rarity of FD/MAS, recruiting enough subjects to demonstrate statistically significant changes in clinical endpoints is challenging. The failure to demonstrate a significant effect of alendronate on NTX and aBMD when adults were analyzed separately likely reflects an insufficient sample size to perform separate subanalyses of this group. Bisphosphonates are thought to have a relatively larger impact on aBMD in children (40), which may explain why the significance in this subgroup was preserved. A potential flaw in the design was studying subjects with a relatively low baseline pain levels (scores of 3.1 and 3.6 out of a possible 10 for the alendronate and placebo groups, respectively). This fact limited the potential for the intervention to affect large changes in pain.

In conclusion, alendronate does not appear to be effective for treatment of FD-related bone pain. Additional controlled studies are needed to determine if there is a role for IV bisphosphonates or denosumab in management of FD-related bone pain. Alendronate may improve bone density of FD lesions, but did not have any effect on FD radiographic appearance or bone scan score. Given the findings from this study and previous open label studies, bisphosphonates are not likely to be effective in altering the FD disease course, and alendronate is not indicated for treatment of FD.

Acknowledgments

Go to:

ClinicalTrials.gov Identifier: NCT00001728

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Disclosure Summary: The authors have nothing to disclose.

Footnotes

Go to:

Abbreviations:

aBMD areal bone mineral density
ANOVA analysis of variance
CBC complete blood count
DXA dual x-ray absorptiometry
FD fibrous dysplasia
GI gastrointestinal
MAS McCune-Albright syndrome
MMT manual muscle testing
ROI region of interest.

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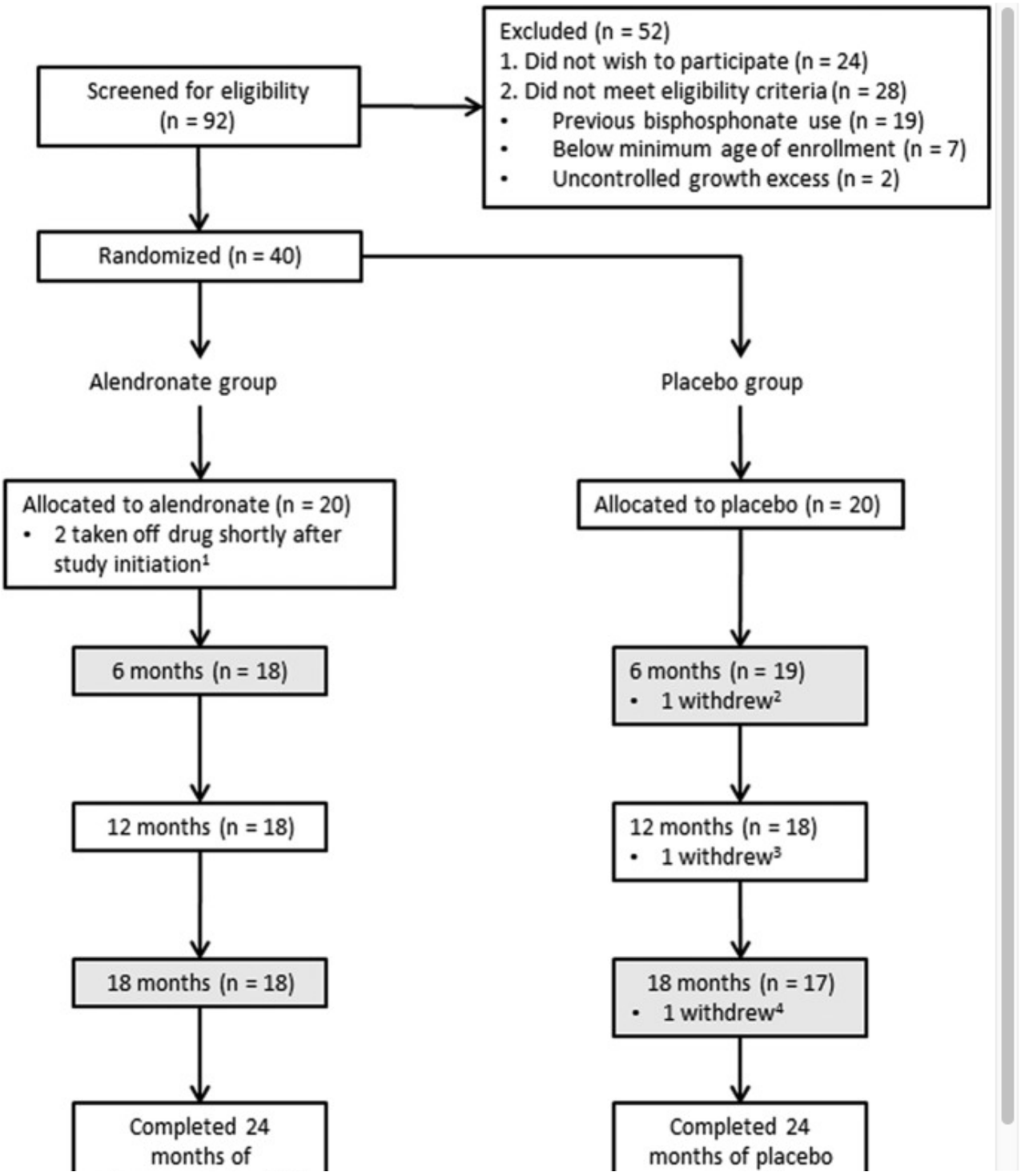
Figures and Tables

Go to:

Figure 1.



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Study flow diagram. 1, Shortly after starting alendronate, an adult subject with an undisclosed history of reflux developed an esophageal stricture, and a pediatric subject developed nausea and vomiting. Both were taken off study drug. 2, An adult subject voluntarily withdrew. 3, An adult subject voluntarily withdrew and was placed on open-label bisphosphonates. 4, A pediatric subject was taken off study drug after developing diarrhea and a 10 pound weight loss.

Table 1.

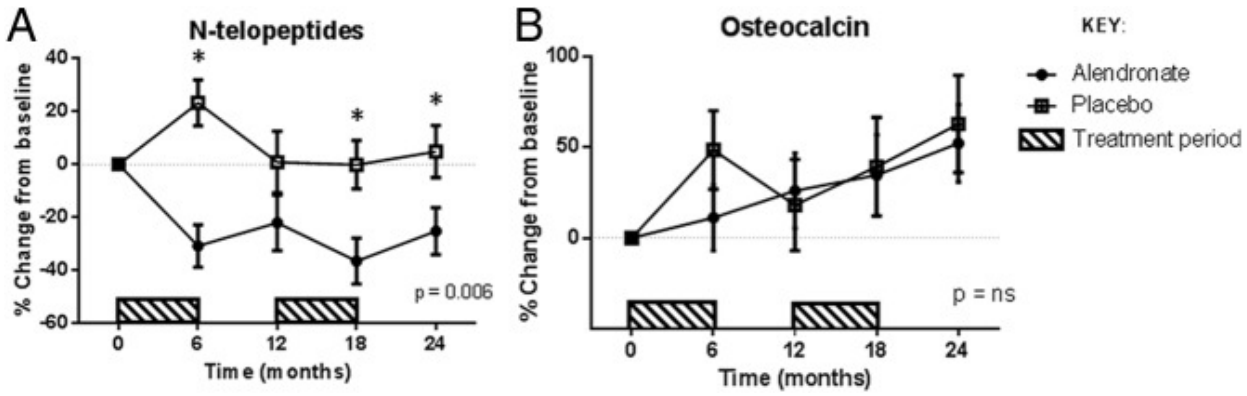
Subject Demographics

	Drug	Placebo	*P*
Number of subjects	20	20	
Age (y):			
Mean/Median	24.5/19	30.3/33	.26
Range	8–52	6–54	
Male	11 (55%)	7 (35%)	.34
Female	9 (45%)	13 (65%)	
Skeletal Disease Burden (%)[a]			
Mean/Median	48/46	32/21	.07
Range	(3–100)	(1–91)	
Endocrinopathies			
None (FD only)	9 (45%)	5 (25%)	.99
Precocious Puberty	6 (30%)	11 (55%)	.20
Hyperthyroid	3 (15%)	5 (25%)	.69
Growth Hormone Excess	1 (5%)	0	.99
Phosphate Wasting	6 (30%)	7 (35%)	.99

Abbreviation: NS, non-significant.

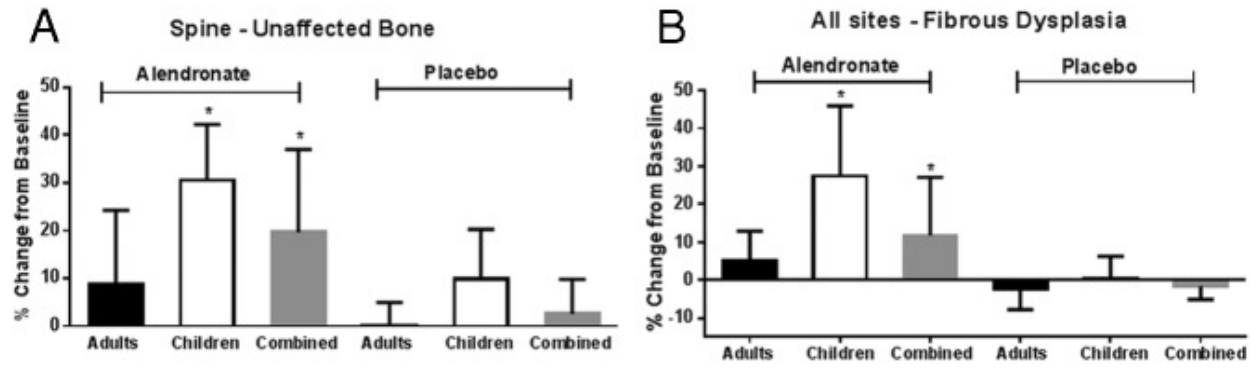
[a]Percent of skeleton involved with FD.

Figure 2.



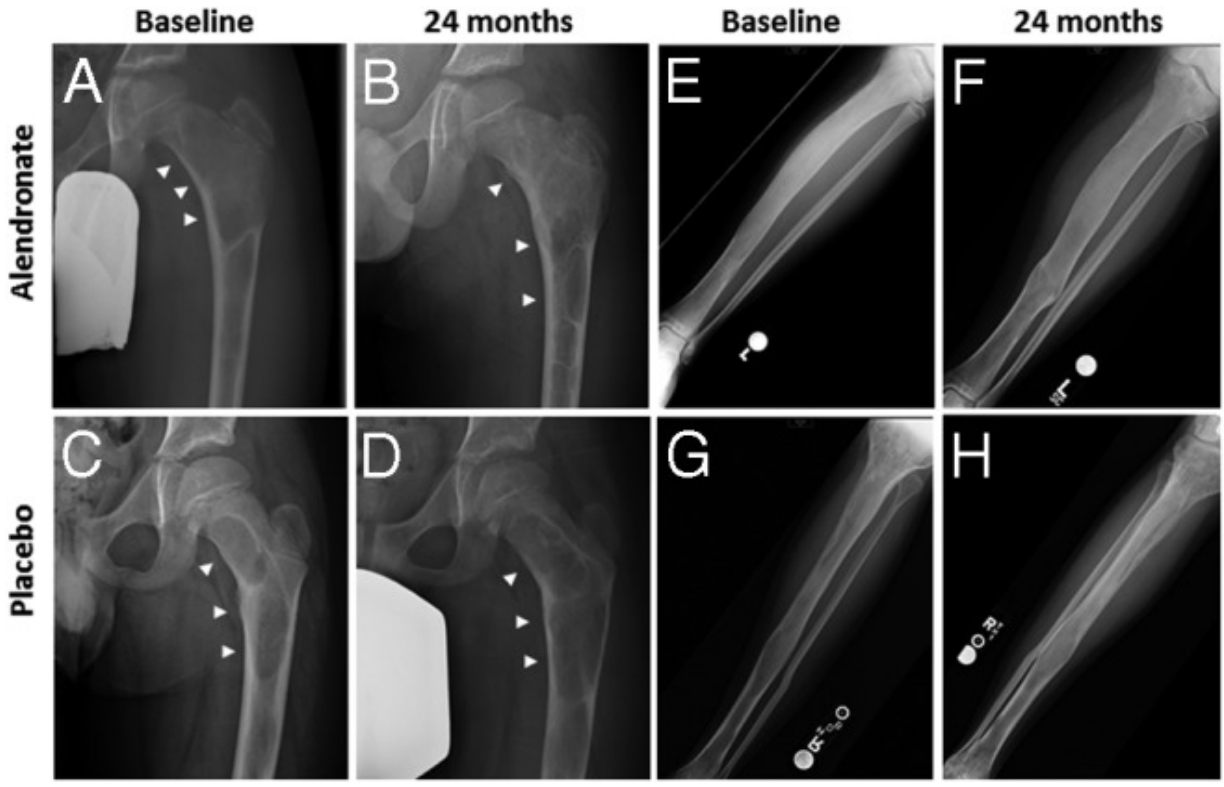
Effects of alendronate on bone turnover markers. A, Subjects in the alendronate group had a sustained decrease in the bone resorption marker urine NTX-telopeptides over the study period, which was significantly different from the placebo group. Time points that were statistically different are marked with an asterisk (*). B, There was no significant change in serum osteocalcin, a bone formation marker, in either group. Error bars represent 1 standard error and the hatched rectangles indicate the periods during which study drug or placebo were administered.

Figure 3.



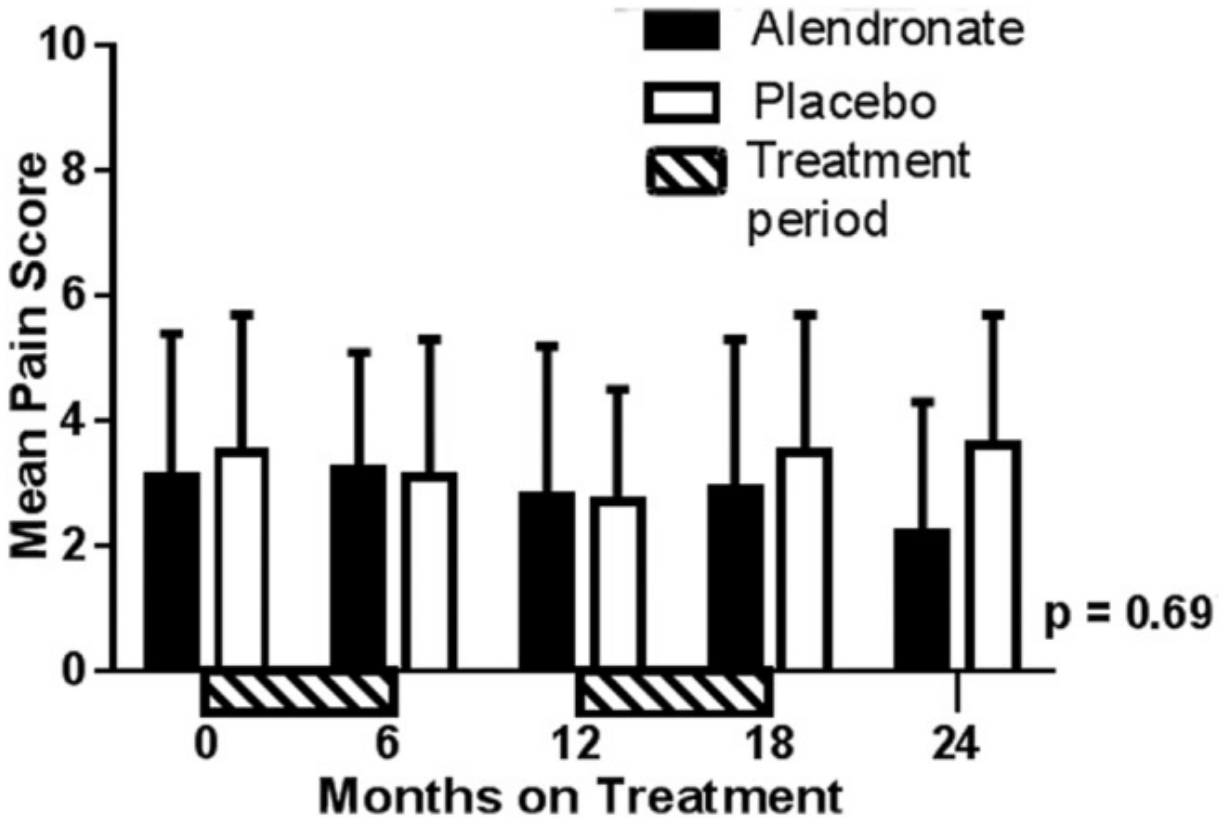
Effect of alendronate on areal BMD of normal and FD bone. A, aBMD was measured by dual-energy x-ray absorptiometry in the lumbar/sacral (L/S) spine of all subjects who did not have FD at the standard L/S sites as determined by bone scan. Differences between groups were measured as percent change from baseline for each individual. Adults are represented by black-filled bars (alendronate n = 6, placebo n = 12), children by open bars (alendronate n = 5, placebo n = 2), and combined adults and children by gray bars (alendronate = 11, placebo n = 14). There was a statistically significant effect of alendronate on bone density at 24 months on the combined group of adults and children ($P = .006$). When adults and children were analyzed separately, there was a significant difference in treated children ($P = .01$), however the changes in adults did not reach statistical significance ($P = .13$). B, Effect of alendronate on aBMD of FD lesions. Areal BMD was measured at sentinel sites of FD as defined in the Methods. Differences between groups were measured as percent change from baseline for each individual. Adults are represented by black-filled bars (alendronate n = 12, placebo n = 5), children by open bars (alendronate n = 9, placebo n = 3), and combined adults and children by gray bars (alendronate n = 19, placebo n = 8). There was a statistically significant effect of alendronate on the combined group of adults and children ($P = .0009$). When children were analyzed separately the change in aBMD was significant ($P = .001$), however there was no significant change detected in a subanalysis including only adults ($P = .25$).

Figure 4.



Representative radiographs. The left upper panels show images of the proximal femur from a 10-year-old boy in the alendronate group at baseline (A) and 24 months (B). Note lucent lesions consistent with fibrous dysplasia (FD) (arrowheads), which do not improve over the course of treatment. The radiographs in the left lower panels are from a 6-year-old boy in the placebo group at baseline (C) and after 24 months of treatment (D), which show mild progression of cortical thinning. The right upper panels show images from a 12-year-old girl in the alendronate treated group with diffuse tibial involvement at baseline (E) and 24 months (F). The images exhibit typical features of FD including radiolucency, cortical thinning, and deformity, with no evidence of improvement over the treatment course. The right lower panels (G and H) show similar views of the right tibia and fibula from a 17-year-old boy in the placebo group, which likewise did not change significantly over 24 months.

Figure 5.



Effect of alendronate on bone pain. There was no significant change in mean bone pain score in either the alendronate or the placebo groups over the study period, as assessed by the Wisconsin Brief Pain Questionnaire (21). Error bars represent 1 standard deviation and the hatched rectangles indicate the periods during which study drug or placebo were administered.

FD/MAS Toolkit: Notes and Follow Up

FIBROUS DYSPLASIA FOUNDATION

Before the Visit

Visit with:_____ Date:_____ Purpose:_____

Questions to consider:

- Are there unanswered questions from your last visit?
- Have your symptoms changed? How and when?
- What other events or changes do you want to remember to tell your doctor?
- What is the most important concern you'd like addressed?
- What priorities does your doctor need to know about?
- What concerns do you have about your treatment options and how they will affect your daily life?

FD/MAS Toolkit: Notes and Follow Up

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Notes During Visit

Use this space to write down the answers your doctor provides to your questions. This can also be a space to document medical terms that you're not familiar with or resources your provider suggests you seek out.

After Visit Notes and Follow Up

Any changes to your treatment plan:_____ Next Follow Up:_____

Use the space below to detail any changes in your care plan or special instructions. If you have new questions based on this visit, document those as well.

Physician Nomination Form

Please fill in the following information about yourself, the nominator.

Your Name _____

Your Address _____

Your Email _____ **Your Phone Number** _____

Your relationship to the nominee _____

Please fill in the following information about the medical professional you're nominating.

First Name_____ **Last Name**_____

Specialty_____ **Phone**_____

Practice_____

City_____ **State**_____ **Zip / Post Code**_____

Country

Submit Your Nomination: You can submit this nomination and any additional nominations to FDF by:

- Emailing this information to info@fibrousdysplasia.org with the subject line: Physician Nomination

- Mailing this form to
  Fibrous Dysplasia Foundation
  2885 Sanford Ave SW #40754
  Grandville MI, 49418

  Your submission will be reviewed by FDF's Medical Advisory Council. Thank you for sharing your positive experience with your clinician.