

Fibrous dysplasia: a current concepts review

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Abstract

Fibrous dysplasia is a benign tumour-like condition in which normal bone is replaced by structurally poor fibro-osseous lamellar bone. It occurs as a result of an early embryonic postzygotic activating mutation of the GNAS gene which manifests clinically in a wide spectrum of disease. Fibrous dysplasia occurs in a monostotic form with single bone involvement, or polyostotic form with multiple bones of the axial, appendicular and craniofacial skeleton involved. McCune-Albright syndrome occurs when the polyostotic form of the disease is associated with extraskeletal manifestations including endocrinopathies, café-au-lait skin lesions and/or intramuscular myxomas. Presentation is dependent on the extent of tissue involvement and ranges from an asymptomatic incidental radiographic finding to symptomatic disease with pain, deformity, pathological fracture, malignant transformation or sequelae of associated endocrinopathies. Diagnosis is usually made on the basis of typical clinical and radiological findings but further histological and molecular testing may be required in more atypical presentations. Management by a multidisciplinary team is crucial to achieve satisfactory patient outcomes. An individualised approach to patient care is advised. Endocrinopathies need to be managed as they can worsen orthopaedic deformities and bone pain, and increase risk of fracture. Medical management includes analgesia and intravenous bisphosphonates. Denosumab is a new emerging treatment option but needs further research. Surgical management is aimed at relieving bone pain, preventing fracture and correcting deformities that have led to mechanical abnormalities especially around the proximal femur. Intramedullary load-sharing devices with whole bone fixation are a preferred option. Bone grafting can be considered as an adjunct to mechanical stabilisation but is rarely used in isolation. Although rare, worsening pain and lesion expansion should alert the clinician to possible malignant transformation. Prognosis for patients with fibrous dysplasia is dependent on the location and extent of the disease.

Level of evidence: Level 5

Keywords: fibrous dysplasia, McCune-Albright syndrome, polyostotic, ground glass, shepherd's crook deformity

Introduction

Fibrous dysplasia (FD) is an uncommon benign tumour-like condition caused by a $G_{\alpha s}$ protein mutation that leads to the production of fibro-osseous tissue in place of normal lamellar bone. The affected skeleton loses its structural integrity and becomes prone to fractures and deformity, causing pain and functional impairment.¹ The disease occurs clinically in two forms: 1) monostotic FD, which is the most common form and is often asymptomatic; or 2) polyostotic FD, which may or may not be part of a syndrome. The associated syndromes include McCune-Albright syndrome (MAS) which is characterised by café-au-lait skin markings, endocrinopathy and precocious puberty; or Mazabraud syndrome (MS) which is characterised by multiple soft tissue myxomas. Management of FD varies depending on the presentation but is principally holistic in nature, requiring input from various healthcare team members especially in patients with more extensive and syndromic involvement.

The aim of this paper is to provide an updated review of the current literature on FD with particular focus on the latest trends and advancements in the orthopaedic management of the disease. Although FD involves craniofacial structures, this review will focus mainly on the axial and appendicular skeleton.

Epidemiology

FD was first described by Lichtenstein in 1938 and the disease as a clinical entity was originally named Jaffe-Lichtenstein syndrome in 1942.^{2,3} Despite the well-documented history, its epidemiology remains uncertain owing to its variable presentation, ranging from an asymptomatic incidental finding to extensive syndromic association. There is no officially reported incidence or prevalence, but FD is estimated to make up between 5 and 7% of all benign bone tumours.^{4,5} The disease affects males and females equally although association with MAS has a female predominance.⁶ Clinical presentation may occur at any age; however, it is more commonly seen in children and adolescents, with a median age of 8 years at initial presentation.⁶ The majority (more than 75%) will present before the age of 30 years. The most common sites of involvement are the proximal femur, craniofacial bones, pelvis and ribs.⁶

Aetiology and pathogenesis

Genetic

The development of FD occurs as a result of missense mutations in the guanine nucleotide-binding protein/ α -subunit (GNAS) locus

on chromosome 20q13.3.⁷ The mutations associated with FD and MAS typically occur when arginine 201 is converted to either histidine (R201H) or a cysteine (R201C) subunit.⁸ These are the targets of genetic sequencing and analysis of the GNAS gene when performing genetic testing for FD.⁹

The mutations occur sporadically in the early postzygotic stage of embryonic development and is therefore a non-inheritable developmental disorder (except for cherubism).¹⁰ The mosaicism expression and broad spectrum of disease results from the early migration of mutant progeny cells to different parts of the skeleton and extraskeletal tissues. It is further believed that mutations occurring earlier in development result in more widespread disease.^{11,12}

Molecular and cellular pathophysiology

The GNAS gene encodes for G_sα which is a cAMP (cyclic adenosine monophosphate) pathway-associated G-protein subunit.¹³ The coupling of G-protein receptors to adenylyl cyclase and the subsequent production of intracellular cAMP is facilitated by G_sα.⁸

Gain-of-function mutations of the GNAS gene result in constitutive activity of G_sα and therefore abnormally increased intracellular cAMP production.¹⁴

The differentiation of osteogenic progenitor cells into mature osteoblasts and osteocytes is impaired by the uncontrolled G_sα-mediated signalling, resulting in excess formation of abnormal immature bone characteristic of FD.¹³ Osteoclastogenesis is also increased within FD lesions and is believed to be driven by the high levels of interleukin-6 (IL-6) associated with the excess production of cAMP by mutant cells.^{13,15,16}

The effects of G_sα activation are tissue-specific and vary between different organ systems with clinically relevant manifestations occurring according to each tissue's variable sensitivity to cAMP dysregulation.⁸

Clinical features

Skeletal manifestations

The extent of skeletal involvement and the location of lesions of FD determine the clinical manifestations and sequelae of the disease. The clinical presentation of FD, and the spectrum of MAS, varies so widely due to the underlying mosaicism of each of the clinical features.⁸ This variability in turn has a profound effect on an individual's clinical outcomes. FD can occur in two forms: the monostotic form where lesions are found in a single bone, and the polyostotic form where lesions occur in multiple bones. The polyostotic form of FD may or may not be associated with extraskeletal endocrine features but when it is the disease is then termed McCune-Albright syndrome. By convention, solitary lesions affecting multiple contiguous bones, especially in craniofacial FD, are considered monostotic.¹²

The polyostotic form is usually diagnosed based on typical clinical and radiological features. Isolated monostotic lesions, however, can pose more uncertainty and generally require biopsy and molecular testing for diagnostic confirmation.¹⁷

Appendicular skeleton

The clinical sequelae of FD in the appendicular skeleton arise primarily due to bone fragility and include pain, bowing deformities, pathological fractures, leg-length discrepancies and gait disturbances.¹² Deformities may result from a combination of factors including malalignment from fractures, surgery, muscle weakness and uncontrolled endocrinopathies associated with MAS.⁸ The proximal femur is commonly affected resulting in progressive coxa vara or classically described 'shepherds crook' deformity.¹⁸ Coxa valga and mixed varus/valgus deformities are

also possible.¹⁸ The upper extremities are also prone to deformity, but they usually cause less functional disability.

Axial skeleton

The involvement of the spine and pelvis in polyostotic FD is relatively common with reported prevalence ranging from 21–63%.^{19,20} Scoliosis develops in 33–52% of patients with spine involvement, with severity ranging from mild to severe progressive deformity resulting in mortality due to pulmonary compromise.¹⁹⁻²¹ Patients with leg-length discrepancies, FGF23-mediated hypophosphataemia and uncontrolled endocrinopathies are at higher risk of scoliosis progression.²¹ Rib involvement is common and can be a source of great pain and in rare cases, pleural effusions.

Craniofacial skeleton

The craniofacial skeleton is involved in up to 87% of patients with polyostotic FD and tends to present early with most lesions established before the age of 3 years.²² A slow-growing mass causing facial asymmetry and cosmetic deformity is typical of its presentation.²³ The lesions, however, often progress to cause dental problems, visual and hearing impairment, as well as life-threatening base-of-skull abnormalities in severe cases.²⁴ Sinus and nasal passage occlusion, as well as dental abnormalities, may also occur.²⁴ The orthopaedic surgeon should be cognisant of these sequelae and assist with appropriate specialist referral when present.

Fibroblast growth factor-23-mediated hypophosphataemia

The overproduction of FGF23 is an inherent feature of FD.⁸ Its mechanism is unknown, but it is presumed to be related to the effects of GS alpha protein activation in abnormal osteocytes,²⁵ resulting in a higher degree of FGF23 overproduction in patients with more extensive FD burden.^{26,27} Hypophosphataemia may wax and wane as skeletal bone activity increases during periods of rapid growth and decreases between growth spurts.⁸ Patients with hypophosphataemia are associated with a higher fracture rate,²⁸ earlier time to first fracture, higher propensity for deformity, and the development of bone pain.²¹

Extraskeletal manifestations

The extent of extraskeletal manifestations is highly variable and in keeping with the mosaicism of the underlying disease. MAS was initially described as a triad of precocious puberty, FD and café-au-lait skin markings,²⁹ but with improved understanding of the condition and its pathophysiology, more extraskeletal features have been attributed to the disease and have become critical in its overall management.

Skin

The characteristic café-au-lait skin macules are seen in two-thirds of patients with MAS. The lesions develop early in life and may be present at birth.³⁰ They are typically described as having ragged 'coast of Maine' borders and characteristically have an association with the midline of the body, which reflects embryonic cell migration.^{8,30} Skin lesions have no correlation with the location of bone lesions or other extraskeletal manifestations.³⁰

Endocrinopathies

Approximately 85% of females with MAS will experience gonadotropin-independent precocious puberty.³⁰ About 85% of males with MAS experience testicular abnormalities and can present with macro-orchidism but only about 15% will develop precocious puberty.³⁰

Thyroid abnormalities occur in about two-thirds of patients with 50% experiencing frank hyperthyroidism.³⁰ The presentation is

typical for hyperthyroidism with patients experiencing tachycardia, growth acceleration and sleep disturbances.⁸ Thyroid storm has also been reported in patients with MAS undergoing anaesthesia for orthopaedic procedures, and should be considered in any work-up prior to surgery.³¹

Excess growth hormone (GH) occurs due to GNAS mutations in the anterior pituitary gland and affects 10–20% of patients with MAS.^{30,32} Elevated GH causes expansion of FD lesions especially in the craniofacial region resulting in morbidity in the form of hearing loss,³³ visual impairment,³⁴ macrocephaly and facial deformity.^{32,35}

Adrenal dysfunction is characterised by hypercortisolism and is the least common extraskeletal manifestation of MAS, occurring in about 5% of patients.^{30,36} Presentation is almost always in the first year of life with neonatal hypercortisolism being the most common presentation due to the autonomous hypersecretion from the adrenal gland at birth.^{36,37} Infants typically are of low birthweight, and have failure to thrive, facial plethora and hirsutism.³⁸

Intramuscular myxomas

The association between intramuscular myxomas and FD was initially noted in 1926 but later formally described by Mazabraud and colleagues in 1967, with this association since being labelled Mazabraud syndrome.³⁹ Boyce et al. suggest rather that due to the multisystem involvement of GS alpha protein activation, it may be more pathophysiologically sound to consider the myxomas as a feature of MAS, rather than a distinct syndrome.⁸ The prevalence of myxomas in patients with FD is around 2%.⁴⁰ The myxomas present as firm, painless, partially mobile masses that rarely enlarge but can occasionally cause compressive symptoms, pain and discomfort on adjacent structures.⁸

Radiological features

Radiographs

The appearance of FD on plain radiographs varies widely.⁴¹ Normal bone is replaced by solid fibro-osseous tissue, which is more radiolucent, causing the typical 'ground glass' appearance.^{41,42} The abnormal bone has a similar density to bony callus but is more homogenous and lacks trabeculae. A fluid-filled cavity may occur within the fibro-osseous tissue mass and appears as a cystic component on radiographs.⁴³ The lesions characteristically have a well-defined border with typically a more prominent inner rim compared to its outer rim.⁵ The reactive sclerotic rim of the lesion is termed the 'rind sign' (Figure 1).⁴³ The lesions arise from within the medullary canal but typically expand, replacing both cancellous and cortical bone while maintaining its reactive shell, causing deformity and the bone itself to enlarge.⁴¹ Endosteal scalloping occurs due to slow resorption of the endosteal surface causing variation in cortical thickness.⁴¹ The periosteal surface remains smooth, and periosteal reaction or associated soft tissue mass does not occur unless in the setting of a pathological fracture or secondary malignant transformation.⁴⁴

Deformities associated with FD include coxa vara, the shepherd's crook deformity (Figure 1), bowing of the tibia and protrusio acetabuli.⁵ A parrot's beak deformity may occur in the setting of an insufficiency fracture of the inferior medial cortex of the proximal femur.⁵

Scintigraphy

Radionuclide bone scans have limited diagnostic value for isolated lesions but can play a useful role in assessing the extent of skeletal involvement in suspected polyostotic disease (Figure 2).⁴⁵ Active lesions in childhood and adolescence show an increased isotope uptake, with the intensity of uptake waning as the lesions mature into adulthood.⁴⁵ Characteristic features of FD lesions on radionuclide

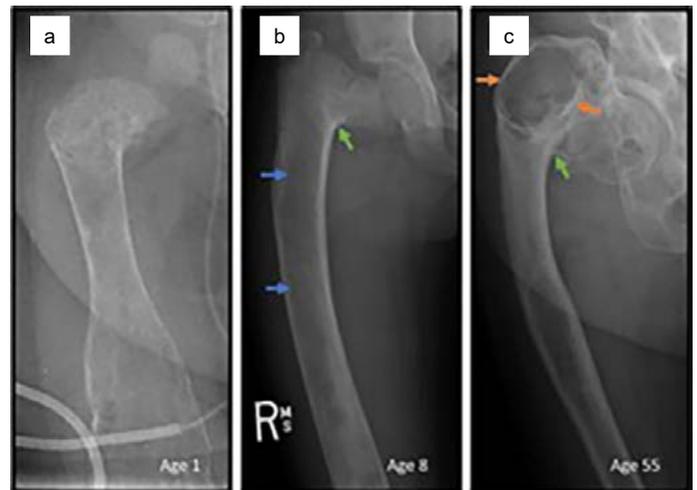


Figure 1. Typical radiographic features and age-related changes of FD are demonstrated in three different patients at different ages with extensive femoral involvement: a) radiograph of a 1-year-old right femur shows a heterogenous appearance seen in infants with FD; b) typical appearance of FD in a child's femur with homogenous 'ground glass' lucency (blue arrows) and shepherd's crook deformity (green arrow); c) in a 55-year-old adult the FD lesion in the femur shows a typical 'rind' sign with a lucent lesion surrounded by a sclerotic rim (orange arrows) and severe shepherd's crook deformity (green arrow) (Reproduced with permission from Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous dysplasia of bone and McCune-Albright syndrome: a bench to bedside review. Calcified Tissue International. Springer New York LLC; 2019;104:517-29)

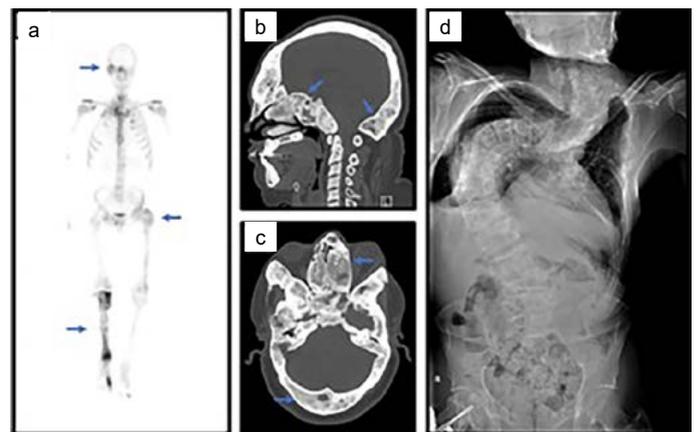


Figure 2. Typical findings of FD on different imaging modalities: a) technetium bone scan showing multiple areas of uptake (blue arrows) in keeping with polyostotic FD in an adult male patient; b and c) sagittal (b) and transverse (c) computed tomography scan views of the skull and facial bones showing extensive involvement (blue arrows) in a young male patient with craniofacial FD. The diffuse expansile lesions of 'ground glass'-appearing bone are best appreciated with CT imaging; d) radiograph of a young male with polyostotic FD showing severe scoliosis (Reproduced with permission from Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous dysplasia of bone and McCune-Albright syndrome: a bench to bedside review. Calcified Tissue International. Springer New York LLC; 2019;104:517-29)

scans include a bar-shaped pattern, whole bone involvement and a close match between the size of uptake on a scan and the size of lesion on a radiograph.⁵ Inaccuracies due to non-specific tracer uptake and potential cold scans can be misleading, and with a significant radiation dosage, their use is not without risk.⁴⁶

The use of FDG PET/CT (18 F-fluorodeoxyglucose positron emission tomography) scans held initial promise, but subsequent studies have showed high false positive rates with multiple case reports of FD mimicking malignancies and metastases on PET/CT scans.⁴⁷

Computed tomography

Computed tomography (CT) scans are the best modality for visualising the bony architecture of FD lesions, providing enhanced detail to plain radiographs (Figure 2). Lesional borders and their extent are more accurately delineated, endosteal scalloping and cortical thinning better defined, and the homogeneity of the fibro-osseous matrix best demonstrated.⁵ Contrast medium enhances FD tissue due to its vascularity. CT is most valuable for preoperative planning of deformities especially due to its 3D reconstruction capabilities and the modelling of patient-specific fixation devices for complex deformity correction.⁴⁶

Magnetic resonance imaging

While CT scans are best used to characterise deformity associated with FD, magnetic resonance imaging (MRI) is the best modality for diagnostic purposes.⁵ The MRI appearance of FD is very typical, and thus its role in differential diagnosis is important in the evaluation of extrasosseous involvement, especially in cases where malignant transformation is suspected.⁴⁸

Signal intensity on T1 and T2-weighted images depends on the degree of fibrous tissue, bony trabeculae, collagen and cystic changes within the lesions. There is a hypointense or intermediate signal on T1-weighted images because the lesion is composed mainly of fibrous tissue and osteoid with a low water content. There is a higher intensity signal on T2-weighted images, although not as high as fluid, fat or malignant tissue. There may also be a heterogenous intensity with contrast enhancement owing to areas of degenerative cysts, haemorrhage or cartilaginous differentiation.⁴⁸

Pathology

Gross pathology

The fibro-osseous tissue of the FD lesion has a yellowish-white appearance with a distinctive gritty texture caused by small bony trabeculae throughout the tissue.⁵ The abnormal tissue is usually easily separated from its surrounding cortical shell of reactive bone. The lesion almost never penetrates the bony shell into the surrounding soft tissue, and in cases where it does, a secondary pathology should be suspected. FD lesions have a high concentration of small blood vessels and often bleed when incised. Bleeding is, however, easily controlled by complete curettage down to normal bone.⁵

Histopathology

FD has some unique histological features that assist in making a diagnosis when faced with an ambiguous clinical and radiological

presentation. The characteristic features include fine trabeculae of immature bone absent of osteoblastic rimming, surrounded by a fibrous stroma of dysplastic spindle-shaped cells that are devoid of any cellular features of malignancy.⁵ Osteogenic cells on the surface of the bony trabeculae have an abnormal stellate appearance with a retracted cell body instead of the normal cuboidal shape (Figure 3).¹³ This is a result of exposure of the osteoblasts to excess cAMP, which is cardinal in the cellular pathophysiology of FD.¹³ The overall impression is typically termed an 'alphabet soup,' as it describes the irregularly shaped, non-stress-oriented, disconnected dysplastic trabeculae in a bed of immature mesenchymal cells devoid of collagen.⁵ Lesions of the cranial bones often display a slightly different histology to that typical of the axial and appendicular skeleton.¹⁵ The sclerotic or pagetoid type of FD consists of thick, interconnected non-lamellar trabeculae with less abundant surrounding fibrous tissue and a trabecular bone matrix containing rich cement lines that resemble the Schmorl's mosaic pattern seen in Paget's disease.¹²

Natural history

The natural history of FD correlates closely with age and the form in which the disease presents. Monostotic disease is more common but presents later as lesions enlarge with advancing skeletal growth.⁴⁹ Polyostotic disease occurs less frequently, and lesions may continue to enlarge beyond skeletal maturity, often causing more severe deformities and more extensive skeletal involvement.

Age-related changes

Skeletal development in utero is relatively normal despite the mutation of GNAS that occurs early in embryogenesis, and as a result there are rarely any obvious clinical signs of FD at birth. Lesions then become apparent in the early years of life and expand during childhood and adolescence. In a study by Hart et al., serial scintigraphy scans showed that FD burden was established in a region-specific pattern. By age 3.4 years, 90% of craniofacial FD was present, by 13.7 years 90% of extremity FD was present and by 15.5 years 90% of axial FD was present. Furthermore, 90% of clinically significant FD was present by the age of 5 years.²² The expansion of established lesions or appearance of new lesions after skeletal maturity is atypical and should raise suspicions of secondary processes.⁸

Clinical and radiographic changes with age

The clinical manifestations and sequelae of FD also follow an age-related pattern.⁸ In patients who develop significantly impaired ambulation, it is often established early. Hart et al. reported that the median age of initiating assistive devices was 6 years, with

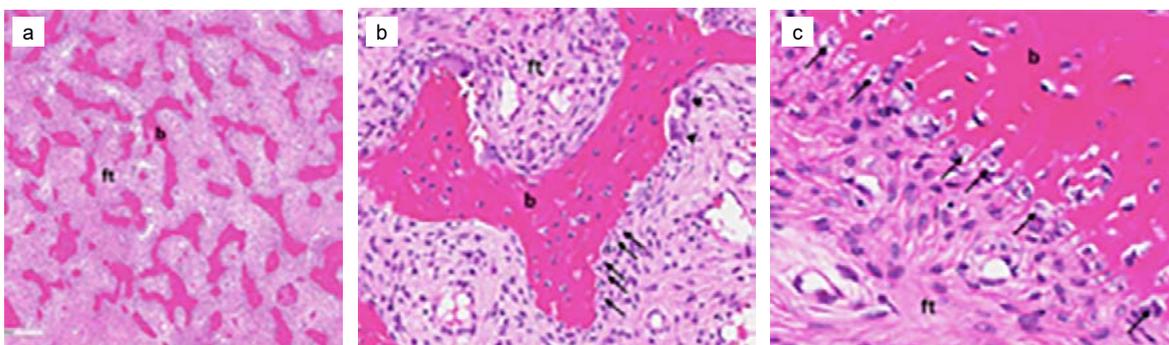


Figure 3. Histological features of FD: a) low power slide showing typical pattern of FD bone with thin discontinuous trabeculae (b) surrounded by abundant fibrous tissue (ft); b) Sharpey's fibres (arrows) and abundant osteoclasts (arrowheads) at the surface of FD bone trabeculae; c) osteogenic cells on the surface of the bone trabeculae have a retracted stellate appearance (arrows) (Reproduced with permission from Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous dysplasia of bone and McCune-Albright syndrome: a bench to bedside review. *Calcified Tissue International*. Springer New York LLC; 2019;104:517-29)

92% of assistive devices initiated by the age of 17 years. The peak age for fractures is between 6 and 10 years, with a steady decline in adulthood.²² This is particularly true for femoral fractures that rapidly decline in incidence after adolescence once skeletal maturity is established.²²

The radiological appearance of FD also changes with age. In infancy the lesions are typically heterogeneous with streak-like features on radiographs, and by age 6 to 7 years, the appearance changes to the more classic homogenous 'ground glass' appearance (Figure 1).⁴³ Later into adulthood, the lesions evolve and again become more heterogeneous with areas of sclerosis, particularly along the borders (Figure 1).⁴³

Biochemical and histological changes with age

Biochemical markers of bone turnover (alkaline phosphatase, osteocalcin and N-terminal telopeptide) are highest at younger ages and then decline steadily through adolescence and following skeletal maturity.⁵⁰ This pattern correlates with the clinical and radiographic changes seen with age progression. Boyce et al. suggested a model whereby FD lesions increase in childhood because of greater proliferation of mutation-bearing stromal cells relative to unaffected cells.⁸ Then once the final disease burden is established, the metabolic activity of FD lesions diminishes over time, probably as a result of a decreased life span of the abnormal cells via apoptosis and senescence.⁸ Clinical improvements, reduction in biochemical bone turnover, and changes in radiographic appearance and bone histology are likely to be a result of the reduction in mutated cell proliferation. This decline in abnormal cells allows the proportion of non-mutated stromal cells in the lesions to increase with time.⁸ In vitro studies have demonstrated the recurrence of histological features of normal bone, restoration of haematopoiesis and a decreased prevalence of mutated cells, further supporting the model of age-related changes.⁵¹

Malignant transformation

The prevalence of malignancies originating from FD is difficult to accurately ascertain due to its rarity and variability in clinical presentation. Ruggieri et al., with the largest study cohort of this nature, reported a 2.5% prevalence of sarcomas in 1 122 cases of FD that were referred to a specialised tumour centre, which may represent an overestimation due to referral bias.⁵² In this same study, the rate of malignant transformation of monostotic lesions was 1.9%, whereas the rate for polyostotic disease was 6.7% and the majority were diagnosed in patients over the age of 30 years.⁵² Radiation therapy is a significant risk factor for malignant

transformation of benign bone lesions and is no longer used in the treatment of FD for this reason.^{46,52} The histological subtypes of skeletal malignancies reported to arise from FD include osteosarcoma, chondrosarcoma, fibrosarcoma and malignant fibrous histiocytoma.^{52,53}

Malignant transformation should be suspected in cases where a change in the clinical and radiographic nature of the lesion occurs. This typically presents with a rapid increase in the size of a previously quiescent lesion associated with new pain or paraesthesia.¹² Radiographically, rapid growth of a lesion, a new soft tissue component, osteolysis and cortical destruction are all suggestive of malignancy.¹² Treatment is dependent on the histological subtype of the sarcoma. Prognosis is worse for patients with malignant transformation of FD lesions than for those with primary sarcoma not associated with FD.⁵³

Aneurysmal bone cysts (ABC), which cause rapidly expanding fluid-filled cystic lesions, can be associated with FD.⁵⁴ ABCs are best distinguished from malignant lesions by their typical magnetic resonance imaging (MRI) findings of fluid-filled cysts and are typically treated surgically.⁴³ There is no indication that the prognosis in a patient with FD is altered by the association with an ABC.⁵⁵

Differential diagnosis

FD may present with clinical, radiological and/or histological features that are similar to other fibro-osseous skeletal lesions, requiring more advanced workup and diagnostic studies for differentiation. The non-FD lesions are typically solitary, not associated with extraskeletal features, and do not harbour pathogenic variations in GNAS. Fibro-osseous lesions on radiographs include a differential of simple bone cysts, nonossifying fibromas, osteofibrous dysplasia, adamantinoma, low grade intramedullary osteosarcoma and Paget's disease of bone.⁵ A full comparative description of each of these lesions is beyond the scope of this paper but a diagnostic approach, adapted from Bousson et al., to a suspected FD lesion is outlined in Table 1.⁴⁴

Tissue biopsy is reserved for cases of radiological uncertainty and where concern for secondary malignancy requires histological assessment. Differential diagnosis for the histological appearance of FD includes osteofibrous dysplasia, low-grade central osteosarcoma and Paget's disease.⁵⁶ In cases where histology remains uncertain, molecular diagnosis can be made by testing for the GNAS gene mutation in the abnormal fibrous tissue. The GNAS mutation is specific of FD in patients with fibro-osseous lesions.⁵⁶

Table 1: Diagnostic strategy for the workup of a suspected radiological lesion of FD

Definite diagnosis of FD	<ul style="list-style-type: none"> • Lesion has a constellation of typical radiological features of FD • Typical radiological lesion with associated skin lesions, precocious puberty or myxoma • Plan: No need for further diagnostic investigations
Probable diagnosis of FD	<ul style="list-style-type: none"> • Radiological lesion exhibiting several radiological features of FD but no associated skin lesions, precocious puberty, endocrinopathy or myxomas • Plan: Further imaging with CT ± MRI ± bone scan to identify additional foci
Doubtful diagnosis of FD	<ul style="list-style-type: none"> • Lesion exhibiting only a few radiological features of FD • History of cancer • Lesion discovered incidentally by MRI or bone scintigraphy • Plan: Perform further imaging (CT, MRI, scintigraphy) <ul style="list-style-type: none"> ▫ If persistent doubt for an active or aggressive lesion, or with history of cancer, perform bone biopsy

(Adapted from Bousson V, et al. Fibrous dysplasia and McCune-Albright syndrome: Imaging for positive and differential diagnoses, prognosis, and follow-up guidelines. Eur J Radiol. 2014 Oct 1;83(10):1828-42)

Management

General

Patients with FD should be managed by a multidisciplinary team at tertiary academic centres. Multidisciplinary care pathways have been shown to reduce pain and improve quality of life.⁵⁷ The orthopaedic surgeon needs to work closely with the endocrinologist, radiologist, physiotherapist and other subspecialists such as ophthalmologists, neurosurgeons and otolaryngologists.¹² With input from all members of the care team, an individualised approach to patient care is recommended.

Low-impact exercise is essential in maintaining muscle strength. Along with range of motion exercises, these can drastically improve function and preserve ambulation ability.⁵⁸ Limb length discrepancies may occur due to fractures, deformities or overgrowth. Conservative management with shoe inserts or other orthotic devices is effective in managing mild leg length discrepancies.⁸ Any new focal or acute pain and lesion expansion should be assessed for a possible underlying fracture or malignant transformation.¹²

Coexisting endocrinopathies, especially hypophosphataemia and hypothyroidism, should be investigated and managed as their presence can contribute to bone pain and risk of fracture and deformity.^{12,59} Patients should be advised to achieve adequate dietary calcium and vitamin D levels. Supplements should be prescribed if levels are low. Recommended dosages are calcium 500–1 500 mg daily and vitamin D 800–1200 IU daily. Smoking cessation, alcohol moderation and maintaining a healthy weight are encouraged.⁶⁰

Psychosocial stress is common in patients with FD. This can be attributed to physical disability, physical deformity, chronic pain, and impaired quality of life. Clinicians should be aware of the potential psychological impact of the disease and refer appropriately.⁶¹

The incidental asymptomatic lesion which is mechanically insignificant should be treated with observation alone.⁶² Follow-up and monitoring need to be individualised to the patient depending on their risk of detrimental outcomes. Deciding factors that may influence follow-up protocol include: anatomical location of the lesion (upper or lower extremity), monostotic or polyostotic lesions, age of the patient, extent of the lesions, presence of deformities and symptoms. A generalised protocol is a biannual follow-up including a physical examination and radiological surveillance in skeletally immature patients. For skeletally mature patients, regular follow-up may not be necessary unless there is a change in symptomatology.⁴⁶

Medical management

Analgesia

Pain is a predominant feature of FD with up to 80% of adults and 50% of children with FD experiencing pain.⁶³ It is often multifactorial and requires careful evaluation and a patient-individualised approach. The response to treatment is variable and the disease

burden as determined by extent of radiographic lesions and bone turnover markers does not correlate to pain severity.⁵⁹

NSAIDs and paracetamol are first-line treatment options with the addition of opioid analgesia if required.⁴⁶

While managing the pain component of FD, clinicians must be cognisant of a possible neuropathic element to pain, which can occur in up to one-third of patients.⁶⁴ Neuropathic pain is especially present in patients with a higher pain score and has been correlated with anxiety, depression, poor quality of life and poor sleep.⁶⁴ These patients may benefit from the addition of agents targeting neuropathic pain, such as tricyclic antidepressants, pregabalin and gabapentin, in their treatment plan.⁶⁵

Bisphosphonates

Treatment with bisphosphonates has previously been controversial in the literature but there is a growing body of evidence through systematic reviews to show that intravenous (IV) formulas, including pamidronate and zoledronate, do improve persistent bone pain.⁶⁶ Intravenous therapy has also been shown to increase bone mineral density and had discernible radiographic improvement.^{66,67} Whether this translates to decreased fracture risk and deformity progression remains to be established. However oral bisphosphonates are not advised as they have not been shown to demonstrate a therapeutic effect. Oral alendronate has been tested in randomised control trials and showed no decline in bone pain or improvement in patient function.⁶⁸ The fibrous dysplasia/McCune-Albright syndrome consortium recommends the use of intravenous bisphosphonates to treat persistent moderate to severe bone pain.⁶⁰ Refer to the dosing guidelines in *Table II*.

Denosumab

Denosumab is a human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANK-L). Therefore RANK-L inhibition resulting in decreased osteoclastogenesis hyperactivity is a potential therapy in FD. Denosumab has been shown to halt the progression of the disease and promote bone mineralisation in a mice model.⁶⁹ However, being a newer treatment option, there is scanty literature to evaluate the outcomes in humans. In a series of eight patients, denosumab markedly reduced bone turnover and radiological lesion activity as well as decreased pain scores in all subjects.⁷⁰ Improved mineralisation of bone could theoretically result in decreased fracture risk and the development of deformities.^{71,72} Complications of denosumab treatment included severe hypercalcaemia and marked bone turnover rebound on discontinuation of therapy. Unfortunately, the positive effects of treatment are transient and reversible after treatment discontinuation. Further research is required with larger, more diverse cohorts to define optimal dosing regimens, patient-individualised treatment, and long-term safety.

Surgical management

Surgical intervention is currently the mainstay approach to treating symptomatic FD. The surgical problem list is complex and vast. The challenges that the surgeon must face are managing bone pain,

Table II: Intravenous bisphosphonate regimens proposed by the FD/MAS international consortium for the management of bone pain

	Paediatric regimen	Adult regimen
Pamidronate	1 mg/kg ×2 on consecutive days up to a total of 90 mg If no response, repeat at week 8 Stop if no response after two cycles	90 mg ×2 on consecutive days every six months Stop if no response after two cycles
Zoledronate	0.025 mg/kg If no response, 0.025 mg/kg at week 8 If still no response, 0.05 mg/kg at week 24 Stop if no response after three doses	Up to 5 mg monthly Switch to maintenance dose when response achieved Stop if no response after three doses

(Adapted from Javadi MK et al. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. *Orphanet J Rare Dis*. 2019)

fractures, impending fractures, progressive long bone deformities, scoliosis and concern for malignancy. Techniques need to be individualised to patients, taking into account skeletal maturity, and tailored to the specific anatomical area involved. The patient, parents and family must be adequately counselled before any surgical intervention as surgery does not provide a cure but rather a relief from symptomatology, correction of the deformity and better gait mechanics. Staged procedures or periodic surgeries may be required, especially in the growing child.⁷³

Bone grafting

Bone grafting with allograft or autograft is of limited value in FD. The majority of grafts fail to incorporate, are eventually resorbed and become replaced with dysplastic bone.⁷⁴ Retrospective analysis shows only a 50% graft survival over 15 years.⁷⁴ Poorer outcomes were noted in the polyostotic form and skeletally immature patients. Surgery based on curettage and bone grafting alone is considered inadequate in symptomatic lesions. Treatment in this form has a high risk of failure with a risk of fracture and progression of deformity.⁷⁵ Correction of bone mechanics and support by metal implant should be a priority of all surgical procedures as the surgeon cannot rely on graft incorporation to add mechanical strength. Fixation with the addition of supplementary bone graft, if deemed necessary, is a more reliable option.⁴⁶

Some literature would suggest that cortical strut allografting may be of benefit in the proximal femur in cases without a previous pathological fracture.⁷⁶ It has been reported that their resorption rate is longer. Synthetic bone grafts such as alpha-tricalcium phosphate (calcium phosphate cement) have been of particular interest lately as this intervention provides immediate stability and takes longer to resorb.⁷⁷ Good outcomes scores and pain relief have been reported in the literature. Further studies are necessary to investigate graft dissolution and the potential for new bone formation.⁷⁸ Refer to *Table III* for the characteristics of bone graft.

Bone pain and fractures

Long bone fractures are a common complication of FD that are potentially disabling, painful and difficult to treat. They occur more commonly in children and tend to decrease in incidence after the age of 10 years.⁵⁹ The overall prevalence is 59%.²⁸

Early prediction of the risk of fractures is essential to allow prompt prophylactic intervention and reduce fracture incidence. Medical management should be optimised before surgical intervention for bone pain and impending fractures. Chronic weight-bearing pain not relieved by medical management is an indication to operate.⁷³ Upper limbs are generally treated conservatively whereas lower limb lesions, especially peritrochanteric lesions, have a higher risk of pathological fracture that may require surgical intervention.⁸ A review of humeral lesions by Majoor et al. revealed that 54% of humeral lesions sustained fractures. Two-thirds were treated

successfully with conservative measures. They identified cystic degeneration as a risk factor for fracture. These findings may be considered indications of prophylactic treatment; however, the recommended method of prophylactic treatment was not defined in this study.⁷⁹

The remodelling potential in FD is limited. Therefore, if treated conservatively, fractures should not be allowed to heal with residual angulation. The use of internal fixation should be considered in adults and older children.⁶²

Statistically significant individual risk factors for fractures of the proximal femur have been identified by Liu et al.⁸⁰ These include: extensive lesions involving the entire proximal femur, femoral neck-shaft angle not within normal range (normal ranges are: 120–140° in adults and 135–145° in paediatric patients) and raised osteocalcin levels. Early age of the first fracture and high skeletal burden as measured on bone scintigraphy and associated endocrinopathies have also been found to be good predictors of overall fracture risk.⁵⁹ Pain limited to a certain focal area or elicited with weight bearing may indicate a current or impending fracture.⁸ Risk factors need to be identified and a patient-individualised decision made on whether the long bone should be prophylactically fixed.

Intramedullary fixation of fractures or prophylactic intramedullary nailing is a preferred option to plate-and-screw constructs. The longest nail possible with cephalomedullary fixation into the femoral head and neck is preferred. If plate and screw constructs are used, they should extend to healthy normal bone. This is not always possible in cases where FD extends to the femoral shaft.⁶²

Long periods of non-weight-bearing treatment should be avoided in lower extremity fractures. This may worsen already compromised bone with the addition of disuse osteopenia on top of a weakened fibrous dysplasia.

Long bone deformities

Long bone deformities are more common in polyostotic FD and are progressive in nature, even past skeletal maturity.⁸¹ The proximal femur is the most common anatomical location of bone deformities associated with FD. Deformities can occur in the upper extremities but generally these result in fewer functional deficits.

The goals of management include re-establishing the normal mechanical axis, restoring normal biomechanical forces around the hip, preventing progression, maintaining the correction, and improving pain and gait.⁴⁶ The poor biomechanical properties of the diseased bone and the high recurrence rate of deformities make achieving the goals problematic.

Bowing of the lateral proximal femur and decrease in the neck shaft angle below 120° are considered high risk of progression with mechanical disturbances and require deformity correction and whole bone fixation.^{18,46} Stanton also recommended a varus neck-shaft angle of less than 120°, or a decline in neck-shaft angle on sequential radiographs is an indication for surgery, even in the

Table III: Characteristics of bone graft

Type of graft	Mechanical stability	Rate of resorption/ potential to be replaced by dysplastic bone	Possible use
Cancellous autograft	-	+++	Rarely used
Cortical autograft	++	++	Rarely used
Cortical vascularised autograft	++	+	Reconstruction of large cortical defects in cases of tumour resection
Cortical allograft	++	++	Strut in proximal femur Combine with stabilisation procedure
Synthetic calcium phosphate cement	+	+	Scarce literature but promising results Provides immediate stability

(Adapted from both DiCaprio MR, Enneking WF. Fibrous dysplasia: pathophysiology, evaluation, and treatment. *JBJS*. 2005 Aug 1;87(8):1848-64; and Baghdadi S, Arkader A. Fibrous dysplasia: recent developments and modern management alternatives: current concept review. *JPOSNA*. 2020;2[2])

absence of bone pain.⁷³ There is a correlation between normal neck-shaft angle in children and improved functional outcomes; this is, therefore, an important deformity to correct.²²

Load-sharing intramedullary fixation is superior to other modalities including plates and screws and external fixators.⁷⁵ Elastic titanium nails can be considered in the upper extremity or in skeletally immature patients. Non-locking plates have a high risk of screw pull-out and fixation failure due to deficient fibro-osseous tissue. Locking plates are therefore preferred, with extension into normal bone if possible.⁴⁶ Increasing screw density in the locking plate construct will aid in increasing the pull-out strength of the locking plate construct. Titanium is preferred as its modulus of elasticity is closer to bone than other available metal implants.⁸² *Figure 4* shows an example of screw pull-out.

A summary of goals as proposed by Baghdadi et al. gives the surgeon a good stepwise approach to achieving good results in correcting proximal femoral deformities. We should aim to:

1. Correct neck-shaft angle to > 120°
2. Correct lateral bowing of the femur
3. Correct sagittal plane deformity
4. Correct rotational malalignment and version
5. Total bone fixation with an intramedullary load-sharing device and cephalomedullary fixation
6. If cystic degeneration is present, consider the addition of a bone graft or synthetic substitute⁴⁶
7. Overcorrect the proximal femur to more valgus to decrease the risk of recurring deformity and revision surgery⁶²

Careful preoperative deformity correction planning is paramount in restoring mechanical alignment. Obtain full-length standing views of the lower extremity and consider 3D CT imaging of the proximal femur. 3D-printed models, if available, are a useful tool (*Figure 5*).

Expected intraoperative challenges include significant blood loss, poor bone stock and abnormal anatomy with possible loss of the medullary cavity. Possible high radiation exposure to surgeons and patient is a concern. An intraoperative iatrogenic fracture may occur during deformity correction.⁴⁶

Baghdadi et al. described some surgical tips in managing proximal femoral deformities with a valgus-producing osteotomy. These include:

- Obtain a proximal femoral entry point first.
- Then perform single proximal wedge resection osteotomy.
- A second osteotomy may be required if there is a distal femur deformity.
- Once the osteotomy is performed and the deformity corrected, it can be temporarily fixed with a semi-tubular plate and unicortical screws.
- Aim for correction to 130° neck-shaft angle.
- Minimise the use of bone clamps directly onto bone to avoid pathological fracture; rather clamp indirectly onto the plate while preparing the femoral canal.
- The decision whether to cross the proximal femoral physis depends on disease extension and growth remaining (*Figure 6*).

Lengthening bone with FD results in the formation of more fibrodysplastic bone. Wires in circular frames are also unlikely to hold FD bone. This makes lengthening leg discrepancies a challenge. Lengthening should only be considered in segments of good quality, non-diseased bone. Epiphysiodesis is found to be unpredictable and as patients are generally of short stature, they are therefore often unwilling to accept procedures that will further lead to decreased height. Orthotics and shoe raises are good alternatives to treat discrepancies.⁶²

Telescoping intramedullary rods have been investigated for use in paediatric patients with deformities. The results based on



Figure 4. Screw and plate device in upper femur. The weak bone cortex results in poor fixation and eventual failure. The plate has pulled away from the bone due to loss of screw fixation. (Used with permission from Stanton RP, Ippolito E, Springfield D et al. The surgical management of fibrous dysplasia of bone. *Orphanet J Rare Dis.* 2012;7(Suppl 1):S1. <https://doi.org/10.1186/1750-1172-7-S1-S1>)



Figure 5. Coronal (a), axial (b), and 3D reconstruction CT scans of a proximal femoral deformity. 3D-printed bone models are useful in determining the osteotomy sites and the amount of correction (d–f). (Used with permission of Baghdadi S, Arkader A. *Fibrous dysplasia: recent developments and modern management alternatives: current concept review.* *JPOSNA.* 2020;2(2))

five patients showed good outcomes when used in combination with bisphosphonate therapy. Decreased pain scores, decreased fracture rate and improved walking ability were reported.⁸³

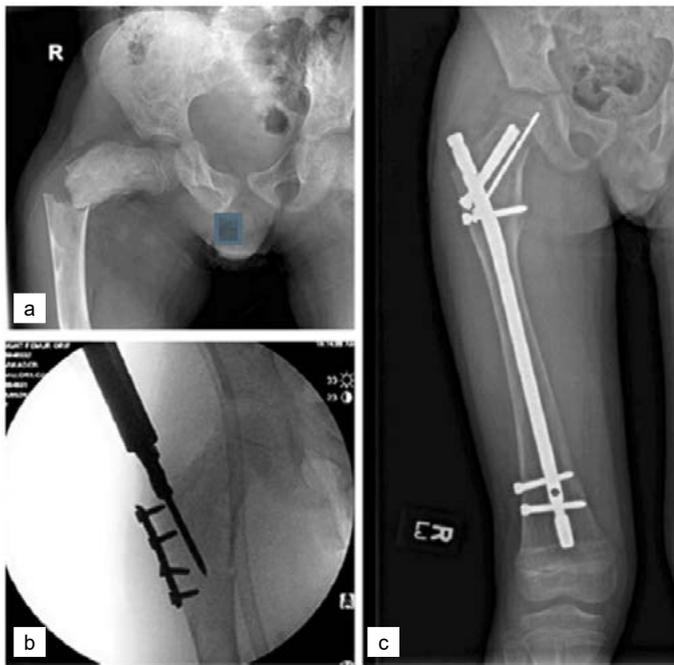


Figure 6. 7-year-old with pathological proximal femur fracture due to FD. A locking plate with unicortical screws provisionally held the reduction before insertion of a cephalomedullary nail. (Used with permission of Baghdadi S, Arkader A. Fibrous dysplasia: recent developments and modern management alternatives: current concept review. JPOSNA. 2020;2(2))

Scoliosis

Scoliosis is a common complication of FD which can be progressive even into adulthood and is potentially fatal.²¹ Patients with scoliosis should be monitored regularly with serial X-rays and clinical examination to assess for possible worsening of the deformity.⁸⁴ There is currently no literature to advocate for the use of bracing in the management of scoliosis secondary to fibrous dysplasia.⁶² Concomitant rib and pelvic involvement may make bracing problematic and ineffective. Bisphosphonate therapy has not been shown to have any effect on halting the progression of the curve.²¹ The total disease burden has been shown to be a major risk factor for progression. Severe deformities and progressive curves require surgical intervention;²¹ however, definitive indications for surgical intervention have not been confirmed in the literature.²¹ Some literature would suggest a Cobb angle of greater than 30° is an indication for surgery but the treating surgeon should also take into account the location of the curve, disease burden and risk factors for progression.^{19,84} A preoperative CT scan is useful in determining the extent of the disease process through the vertebral bodies. Surgical solutions are standard posterior instrumentation and fusion with extension of the construct into non-involved vertebrae for added stability.¹² This has been shown to have durable efficacy.⁶²

Conclusion

FD is a disorder that presents with a wide clinical spectrum and degree of complexity in its approach and management. The genetic and cellular pathophysiology is well established and is the basis on which new treatment therapies are being considered to better control the underlying disease. It is essential to manage FD with a multidisciplinary team. Rehabilitation, psychological support and management of associated endocrinopathies are necessary for good functional outcomes. Medical management includes pain control, keeping in mind the possible contribution of neuropathic pain. Intravenous bisphosphonates have been shown to be effective in pain management. Denosumab is a

new emerging treatment with good results but there are still concerns regarding side effects and relapse on discontinuation. Although rare, clinicians should be alert to possible malignant transformation with sudden changes in symptomatology. Surgical intervention is required for fractures, impending fractures and severe deformities altering mechanics. Intramedullary load-sharing devices with total bone fixation are the preferred implant options. Although cancellous bone graft is unreliable due to reabsorption, supplementary treatment with cortical strut allograft and newer bone graft substitutes may be considered. Despite advancements in the orthopaedic management, there remains a need to develop a treatment capable of altering the underlying course of disease.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

This article does not contain any studies with human or animal subjects.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

CA: literature review, first draft preparation of non-management sections, manuscript revision and preparation

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