McCune-Albright Syndrome

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Creation date: August 2004

Scientific Editor: Prof Sebastiano Filetti

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Abstract
Classically, McCune-Albright syndrome has been defined by the clinical triad of polyostotic fibrous dysplasia of bone (FD), café-au-lait skin spots, and precocious puberty (PP). It is a rare disease, of which the precise prevalence is not known. In addition to PP, other hyperfunctioning endocrinopathies may be involved including hyperthyroidism, growth hormone excess, Cushing's syndrome, and renal phosphate wasting. Café-au-lait spots usually appear in the neonatal period, but it is usually precocious puberty or FD that brings the child to medical attention. The disease results from somatic mutations of the *GNAS* gene, specifically mutations in the cAMP regulating protein, Gs〈. The stage and location within the developing organism at which the spontaneous mutation occurs may determine the phenotype, *i.e.* the earlier the mutation occurs, the more extensive the disease.
The evaluation of patients with this condition should be guided by knowledge of the spectrum of tissues that may be involved, with specific testing for each. Treatment is dictated by the tissues affected, and the extent to which they are affected. Specifics of the subtleties of diagnosis and treatment are discussed.

Key words
polyostotic fibrous dysplasia, café-au-lait skin spots, precocious puberty, hyperthyroidism, growth hormone excess, Cushing's syndrome, renal phosphate wasting.

Definition / diagnostic criteria

Originally, the McCune-Albright syndrome (MAS) was defined by the triad of polyostotic fibrous dysplasia of bone (FD), café-au-lait skin pigmentation, and precocious puberty (PP)(McCune 1936; Albright, Butler *et al.* 1937). It was recognized that other endocrinopathies, including hyperthyroidism (reviewed in (Mastorakos, Mitsiades *et al*. 1997), GH (growth hormone) excess (Sherman and Ladenson 1992; Akintoye, Chebli *et al*. 2002), renal phosphate wasting (with or without rickets/osteomalacia) (Collins, Chebli *et al*. 2001), and Cushing syndrome (Kirk, Brain *et al*.

1999), could be found in association with the original triad (Danon and Crawford 1987). Rarely, other organ systems may be involved (liver, cardiac,parathyroid, pancreas) (Shenker, Weinstein *et al*. 1993). While MAS is rare, FD is not. FD can involve a single skeletal site (monostotic FD, MFD), or multiple sites (polyostotic FD, PFD) (Lichtenstein L 1942; Bianco, Robey *et al*. 2003). Very rarely one can find PP in association with café-au-lait skin pigmentation in the absence of FD (1%), but in general, FD seems to be the component of the clinical diagnosis most commonly present. Therefore, a more clinically relevant definition of MAS, broader than the original triad of FD + PP + café-au-lait is: **MAS = FD + (at least one of the typical hyperfunctioning endocrinopathies and/or café-au-lait spots), almost any combination is possible**.(Collins and Shenker 1999)

Differential diagnosis

MAS is most commonly confused with neurofibromatosis (NF). This confusion occurs most often in infancy or childhood when a child presents with a large café-au-lait spot. The location and shape of the spots usually can help to distinguish between the two. The spots in MAS have jagged borders (coast of Maine), whereas those in NF are smooth (coast of California). Although the spots can cross the midline, more often, they demonstrate a "respect" of the midline. Frequent locations are the nape of the neck and the crease at the apex of the buttocks (Fig. 1). In MAS, the skeletal disease (PFD) almost always involves one or both proximal femurs and/or the skull base, as well as other locations. Skeletal involvement in NF is uncommon and usually involves the diaphyses of the long bones, especially the tibiae. When precocious puberty is the presenting sign, the primary differential is between idiopathic central precocious puberty, and an ovarian neoplasm. Suppressed gonadotropins exclude central PP. Other components of the MAS (skin pigmentation, skeletal changes on x-ray or bone scan, etc.) can help to assure the clinician that the ovarian cyst is not neoplastic. Isolated skeletal lesions in the absence of skin or endocrine findings represent FD (MFD or PFD). Osteofibrous dysplasia (ossifying fibroma of long bones, so-called Campanacci's lesion) may be confused with FD. These lesions are almost exclusively found in the tibia and fibula, and are histologically distinct from FD (Bianco, Robey *et al*. 2003). Non-ossifying fibromas (NOF) also may also share radiological and histological similarities with FD in the long bones. Lack of multiple skeletal foci and absence of extraskeletal findings may help to distinguish FD from NOF. FD in the jaw may share several histological features with cemento ossifying fibromas, which can be confused with FD. The cemento ossifying fibroma lesions tend to behave more aggressively than do FD lesions. Testing for the *GNAS* mutation, if available and if deemed necessary, may help to distinguish cemento ossifying fibroma lesions from FD.

Etiology

The observation that the G protein/cAMP/adenylate cyclase signalling pathway was central to all of the tissues involved in MAS eventually led to the discovery that mutations in the regulatory $G_{s\alpha}$ protein (encoded by the *GNAS* gene) were the underlying molecular etiology of MAS (Weinstein, Shenker *et al*. 1991; Schwindinger, Francomano *et al*. 1992) (fig. 2). In all published cases of MAS, PFD, and even MFD, activating mutations of $G_{s\alpha}$ at the R201 position have been identified.(Bianco, Riminucci *et al*. 2000) The lack of vertical transmission of the disease, along with the observation that skin and bone lesions tend to lateralize and respect the midline, has led to the unproven, but accepted, concept that the disease is the result of postzygotic mutations, and patients are therefore somatic mosaics. The earlier in development the mutation occurs, the greater the disease tissue burden. Therefore, in cases in which tissues of endodermal, mesodermal, and ectodermal origin are involved, it would appear that the mutation occurred at the embryonic stem cell stage (Fig. 3).

Clinical description

Typically, the signs and symptoms of either PP or FD usually account for the initial presentation. In girls with PP, it is usually vaginal bleeding or spotting, accompanied by development of breast tissue, with little or no pubic hair. In boys, it can be bilateral (or unilateral) testicular enlargement with penile enlargement, scrotal rugae, body odor, pubic and axiallary hair, and precocious sexual behavior. FD in the axial skeleton usually presents with a limp and/or pain (sometimes reported by children as being "tired"), but occasionally a pathologic fracture may be the presenting sign. The radiograph will demonstrate typical expansile lesions arising in the medullary cavity with a "ground glass" appearance (Fig. 4). Alternatively, FD in the craniofacial bones will usually present as a painless "lump" or facial asymmetry. Representative radiographic findings and the histological appearance of FD are shown in Figure 4.

Clinical Feature	Presentation
Café-au-lait spots	appearance: "coast-of-Maine", location: nape of neck, base of spine; respect midline; trunk & face more commonly involved than limbs
Fibrous Dysplasia	common locations: skull base, proximal femora, elevated alkaline phosphatase, medullary based on xray, (Dorfman HD 1998; Leet, Chebli *et al*. 2003)
Craniofacial FD	skull/facial asymmetry. vision rarely affected. prophylactic optic nerve decompression is contraindicated, (Lee, FitzGibbon *et al*. 2002)
Axial FD	usually asymptomatic, scoliosis common and possibly progressive (Leet, Magur *et al*. 2004), rib pain develops late
Appendicular FD	fractures common up to 15 y.o., disease quiets later in life, lesions often painful in adults, but pain is quite variable (Leet, Chebli *et al*. 2003)
Gonadal - Female	Vaginal bleeding, breast development with little or no pubic hair, secondary central PP often develops, GnRH test (Feuillan 1997)
Gonadal - Male	asymmetric testicular enlargement, testicular lesions without PP common, detectable by ultrasound only,
Thyroid Abnormalities	cancer rare, but possible T3 thyrotoxicosis (suppressed TSH with nl/low T4, spontaneous resolution rare, ≈2% of patients), follow with ultrasound and biopsy large solid or changing lesions (Mastorakos, Mitsiades *et al*. 1997), cancer can occur (Collins, Sarlis *et al*. 2003)
Phosphaturia	low TmP/GFR common, hypophosphatemia uncommon, can be intermittent, worsens pain, (Collins, Chebli *et al*. 2001) etiology FGF-23 of bone origin (Riminucci, Collins *et al*. 2003)
Growth Hormone Excess	can be subtle, normal height despite h/o PP suggests GH excess, worsens craniofacial FD (Akintoye, Chebli *et al*. 2002)
Cushing Syndrome	only in the first year of life, failure to thrive, infants usually quite ill, spontaneous resolution possible (Kirk, Brain *et al*. 1999)

Table 1. Clinical Presentation

The areas most commonly involved are the proximal femora and skull base. In retrospect, café-au-lait spots are the most common but unappreciated "presenting" sign, usually present at birth or shortly thereafter. Other features of the presentation related to the specific aspect of the disease are outlined in Table 1.

Malignancies in MAS

While malignancies associated with MAS are distinctly rare occurrences, they warrant mentioning due to their importance. Malignant transformation of FD lesions is probably the most common and best described malignancy that occurs in association with MAS (Ruggieri, Sim *et al*. 1994; Dorfman and Czerniak 1998; Bianco, Robey *et al*. 2003). This occurs in probably less than 1% of the cases of FD/MAS. There may be a greater tendency for malignant transformation to occur in patients who have concomitant GH excess (Blanco, Schaeverbeke *et al*. 1999). While some have suggested that sarcomatous transformation of skeletal lesions may occur more commonly in patients with Mazabraud's syndrome (benign intramuscular myxomas in association with long standing FD) (Lopez- Ben, Pitt *et al*. 1999), this may represent selection bias.

In addition, breast cancer risk may be considered to be elevated in patients with MAS (Scanlon, Burkett *et al*. 1980; Tanabeu, Nakahara *et al*. 1998). Besides the published reports, in the series of patients seen at the National Institutes of Health (approximately 80), the prevalence of breast cancer (n=2) is approximately 3 %. In this group, there also seems to be an effect of GH excess, in that both patients who had breast cancer also had GH excess (unpublished data).

Cancers of the thyroid (Collins, Sarlis *et al*. 2003) and testes (unpublished data) are also rare occurrences.

Diagnostic methods

Diagnosis of MAS is established on clinical grounds. Plain radiographs are often sufficient to make the diagnosis of FD (Fig. 4). Isotopic bone scans are the most sensitive tool for detecting the presence of FD lesions, and are often useful, especially at the initial evaluation, for determining the extent of the disease (Fig. 5). FD has a typical appearance on radiographs described as "ground glass." In general, in the long bones, these lesions have a "lytic" appearance. The lesions usually arise in the medullary cavity and expand outward replacing normal bone with the result of thinning of the cortex (Fig. 4). It is usually the metaphysis and/or the diaphysis that are involved, with sparing of the epiphysis. It is possible for any

bone to be involved, but the proximal femur is the site most commonly involved (Dorfman and Czerniak 1998; Ippolito, Bray *et al*. 2003). Due to the fact that these lesions are undermineralized (Bianco, Riminucci *et al*. 2000), the bones are "soft" and prone to deformation, with the classical lesion being the "shepherd's crook" deformity of the proximal femur. FD in the craniofacial bones tends to have a "sclerotic" appearance on plain radiographs (Fig. 4). This is due to the relatively greater degree of mineralization of FD tissue in the craniofacial bones (Riminucci, Liu *et al*. 1999). CT scanning is the best technique for imaging FD in the skull, and with this technique lesions have a "ground glass" appearance. In children and young adults, the lesions appear homogeneous on CT, but in older patients the appearance is mixed, with the development of "cystic" lesions in some areas. The density of these areas is that of soft tissue, so while they may have a cystic appearance they are not true cysts (Lee *et al*, unpublished data). That said, it is possible for true cysts to develop in FD – both in the long bones, and (more often) in the craniofacial bones (Fig. 4). This occurs in about 5% of the patients with FD (unpublished data). The cysts tend to have a more aggressive course. They can expand rapidly and produce symptoms, which vary, depending on the location. These usually require surgical intervention. Biopsy of FD lesions can confirm the diagnosis if doubt remains after review of the radiographs. FD typically is described as "Chinese writing" pattern, and with stains used to detect mineralized and unmineralized tissue, extensive areas of unmineralized osteoid are evident (Fig. 4). For an extensive description of the histopathological changes that can be observed in FD, the reader is referred to Corsi et. al. (Corsi, Collins *et al*. 2003).

As stated earlier, a clinically based definition of MAS, broader than the original triad of FD + PP + café-au-lait is:

MAS = FD + at least one of the typical hyperfunctioning endocrinopathies and/or café-au-lait spots (Collins and Shenker 1999)**.** Almost any combination is possible. Genetic testing is possible, but is not routinely available (see below). Because of the somatic mosaic nature of the disease, a negative result from readily available (but unaffected) tissue, does not exclude the presence of the mutation. Testing on leukocyte DNA is possible (Hannon, Noonan *et al*. 2003), but it is unreliable. In most cases, genetic testing contributes little to diagnosis and not at all to management. In regard to diagnosis, by the time affected tissue as been obtained, the diagnosis can be established by histopathological examination of the affected tissue. And, in regards to management, there is no known genotype/phenotype correlation, so knowledge of the specific mutation does not affect management. For this reason, when the diagnosis of MAS is suspected or established, it is important to be cognizant of the spectrum of tissues that possibly can be involved, and to screen for involvement. Screening, at a minimum, requires a directed medical history, physical examination, and usually involves specific imaging and biochemical testing.

Genetic testing: The following are listed as potential sources for genetic testing. The only available source for commercial testing is the H.A. Chapman Institute of Medical Genetics. The author has no personal experience with this Institute, and therefore cannot comment on the quality of work. They can be contacted at these web sites:
http://genetics.hillcrest.com/default.htm and http://genetics.hillcrest.com/McCune.htm.
In addition, the research laboratories of Professors Paolo Bianco (Rome, Italy) and Charles Sultan (Montpellier, France) can perform genetic testing on a research basis. (for more information see orphanet database)

Follow up

Specific aspects related to the diagnosis and suggestions for follow-up and care of FD are as follows:

Skeletal

This feature is very common, especially in skull base. Vision and/or hearing loss are uncommon. Sarcomatous degeneration is rare (<1%). While appendicular FD quiets with age, craniofacial may continue to slowly progress into adulthood (Lee, FitzGibbon *et al*. 2002).

Craniofacial FD:

a) CT scan of the skull is the most useful test for diagnosis. Typical ground glass appearance is present (Fig. 4). Periodic (annually, or less frequently if stability has been demonstrated) CT of skull and mandible to assess progression/stability is recommended.

b) An initial and periodic (annually or less frequently if stability has been demonstrated) vision (by a neuro-ophthalmologist) and hearing evaluation is recommended to assess involvement and progression

c) Screen for and treat all endocrinopathies which adversely affect bone (GH excess in particular impacts on CF FD).

d) ^{99}Tc-MDP bone scan at least at baseline and follow-up scans at intervals (no less than one year).

Axial and Appendicular skeleton
They are very common; fractures are frequent, especially before 15 years old (Leet, Chebli *et al*. 2003). Shepherd's crook deformity and pain are common. Sarcomatous degeneration is rare (<1%).
a) Radiographs are usually diagnostic, especially in the context of other signs and symptoms of MAS. FD has a typical ground glass appearance (Fig. 4).
b) Screen for and treat all endocrinopathies which adversely affect bone (Corsi, Collins *et al*. 2003; Leet, Chebli *et al*. 2003).
c) Bone scan, at least at baseline and at some interval (annually, or less frequently if stability has been demonstrated).

Endocrine
Gonads: PP is more common in girls then boys. Small testicular masses of leydig and/or sertoli cell hyperplasia are common in boys.
a) Check for development of secondary central PP in children with PP.
b) Check for leydig (and sertoli) cell masses in men with screening testicular ultrasounds. Masses should undergo excisional biopsy to exclude cancer. Follow residual lesions with ultrasound (annually, or less frequently if stability has been demonstrated).

Thyroid: hyperthyroidism is common (38%) (Mastorakos, Mitsiades *et al*. 1997). Evidence of thyroid involvement (relatively suppressed TSH with elevated T3 + abnormal thyroid ultrasound, with or without frank hyperthyroidism, is even more common (63% in the NIH series).
a) Check TSH, FT4, T3, and T4 (T3 dominant is most common).
b) Periodic ultrasounds (annually, or less frequently if stability has been demonstrated) to follow lesions. Biopsy clearly dominant, large (especially solid) or changing lesions.
Renal Phosphate Wasting
It is considered as part of a proximal tubulopathy with or without hypophosphatemia, and/or rickets/osteomalacia is common (Collins, Chebli *et al*. 2001). The etiology is likely elaboration of the phosphaturic factor FGF-23 by affected tissue (Riminucci, Collins *et al*. 2003).
a) Check serum phosphate and renal phosphate handling and/or TmP/GFR.

Pituitary
GH and PRL (Prolactin) excess are common (21%), and the signs and symptoms can be very subtle. GH excess can worsen craniofacial bone disease (Akintoye, Chebli *et al*. 2002; Lee, FitzGibbon *et al*. 2002).
a) All patients should have an OGTT (oral glucose tolerance test) testing to look for non-suppressible GH at least once (GH > 1.0 ng/ml at 60 min on standard OGTT is diagnostic).
b) Most GH secreting tumors are co-secretors of GH and prolactin, so prolactin needs to be checked, since it independently may have an adverse affect on gonadal function.

Parathyroid: primary hyperparathyroidism is rare, secondary (due to vitamin D deficiency) is common. Hyperparathyroidism worsens FD (Corsi, Collins *et al*. 2003)
a) Check ionized Ca^{2+} and PTH (parathyroid hormone) periodically (annually, or less frequently if stability has been demonstrated).

Adrenal: Cushing's in the neonatal period occurs, but has not been reported past the first year. Some cases of neonatal Cushing's resolve spontaneously (Kirk, Brain *et al*. 1999).
a) Cushings must be considered and screened for in the very young. The physical examination is usually suggestive.
b) Check 24-hour urine for urinary free cortisol.
c) Check midnight, or salivary cortisol.
d) Perform dexamethasone suppression test.
e) Check adrenal reserve in resolved patients with a history of neonatal Cushing's.

Epidemiology
MAS is a rare disease and reliable estimates of prevalence are not available. In contrast, the skeletal aspect of the disease, FD (especially monostotic) is not rare (Dorfman and Czerniak 1998).

Genetic counseling
The most important aspect of counseling families is to assure them that there is no vertical transmission of the disease, nor are there any known environmental associations or predilection for ethnic groups. Therefore, parents need not feel "responsible," and patients can be assured they will not transmit the disease to their offspring.

Antenatal diagnosis
Not relevant.

Management/treatment
Skeletal
Management of the skeletal disease is outlined below:
Craniofacial FD: craniofacial disease may continue to slowly progress into adulthood (Lee, FitzGibbon *et al*. 2002).
a) Find a craniofacial and neurosurgical team experienced in treating craniofacial FD!

b) Check vision and hearing periodically (annually, or less frequently if stability has been demonstrated). Vision should be checked by a neuroophthalmologist.
c) Severe pain or severe disfigurement may be an indication for surgery.
d) Avoid surgery in the absence of visual or hearing impairment (nerves may be surrounded by and unaffected by FD bone for years/decades).
e) Perform periodic (annually, or less frequently if stability has been demonstrated) CT of skull and mandible.
f) Screen for and treat all endocrinopathies which adversely affect bone.
g.)There is little evidence that bisphosphonates are effective in craniofacial FD, even for pain, but in the case of difficult to manage pain bisphosphonate treatment should be considered (Appendix 1).
h) ^{99}Tc-MDP bone scan at least at baseline and follow-up scans at intervals (annually, or less frequently if stability has been demonstrated).

Axial and Appendicular skeleton
a) Find an orthopedic surgeon experienced with FD. In general, less may be better in the surgical treatment of FD. Intramedullary devices may be preferable (in general) (Ippolito, Bray *et al*. 2003).
b) Bracing may be helpful.
c) Screen for and treat all endocrinopathies which adversely affect bone (Corsi, Collins *et al*. 2003).
d) Bone scan at least at baseline and at some interval (annually, or less frequently if stability has been demonstrated).
e) Bisphosphonates are usually effective at decreasing pain (and markers of bone turnover). Their effect on the course of the disease and fracture rate is unknown (Liens, Delmas *et al*. 1994; Chapurlat, Delmas *et al*. 1997; Plotkin, Rauch *et al*. 2003).
g) Maintaining strength is important. Swimming is an excellent exercise. Cycling is good. Scoliosis is common, and may be progressive, monitor the degree of curve and operate when indicated (Leet, Magur *et al*. 2004).

Endocrine
Management of the endocrine dysfunction is outlined below:
1. Gonads: PP (86% of patients) (more common in girls then boys; small testicular masses of leydig and/or sertoli cell hyperplasia are common in boys)
a) Check for development of secondary central PP in children with PP.
b) In men, check for leydig (and sertoli) cell masses with testicular ultrasounds. Masses should undergo excisional biopsy to exclude cancer; follow residual lesions annually with ultrasound.

2. *Thyroid*: Hyperthyroidism (64% of patients) (Mastorakos, Mitsiades *et al*.1997)
a) Antithyroidals (methimazole, etc.) are usually effective in controlling hyperthyroidism.
b) Occasionally cannot be controlled medically and surgery or radioiodine is required. Surgery is preferred due to the already increased risk of thyroid cancer in MAS (Collins, Sarlis *et al*. 2003).
c) Definitive treatment is often eventually required, as spontaneous resolution occurs rarely. Again, surgery or radioiodine are options.
d. Periodic ultrasounds (annually, or less frequently if stability has been demonstrated) to follow lesions. Biopsy clearly dominant, large (especially solid) or changing lesions.

3. Renal: Phosphate wasting (50% of patients)
a) Treat patients with frankly low or low-normal serum phosphate.
b) Treatment is the same as that for patients with X-linked hypophosphatemia and tumor induced osteomalacia: high dose oral phosphate with high dose calcitriol (see appendix 2).

4. Pituitary: GH excess (20% of patients)
a) Non-suppressible GH with elevated IGF-1 should be treated (Akintoye, Chebli *et al*. 2002).
b) How to treat non-suppressible GH and normal IGF-1 is not clear (these patients will have an abnormal overnight GH secretion pattern).
c) Surgical cure should be the primary goal. However, this is often not possible due to inability to visualize the tumor, and/or the fact that the skull base is too thick for transphenoidal surgery, and the frontal bone is too thick for transfrontal surgery.
d) Long acting somatostatin analogues (Sandostatin LAR, etc.) are often effective at normalizing serum IGF-1 (insulin-like growth factor-1). It is important in growing children to not over-suppress, yet, at the same time, on some assays, the normal range for IGF-1 can be quite large. Using a normal serum IGFBP-3 (insulin-like growth factor-binding protein-3 **)** as a clinical endpoint of effective control can be useful.
e) Tumors usually co-secrete GH and prolactin. Dopamine agonists (cabergoline, etc.) are usually effective at normalizing the serum prolactin.

5. Parathyroid: Hyperparathyroidism (rare)
a. Typical treatment as indicated for hyperparathyroidism with parathyroidectomy (primary) or vitamin D replacement (secondary).

6. Adrenal: Cushing's syndrome (rare)
a) Adrenalectomy is probably the treatment of choice. If the child is too ill, adrenal blockade may provide stabilization and time to recover. Liver function abnormalities usually accompany neonatal Cushing's, so ketoconazole is usually not an option. Metryrapone, 300 mg/m^2/day, initially, is recommended. The dose may be escalated to as high as 1200mg/m^2/day.
b. Check adrenal reserve in resolved patients with a history of neonatal Cushing's.

Unresolved questions
While the efficacy of bisphosphonates in relieving FD-related pain is clear, whether or not the treatment of FD with bisphosphonates changes the natural history of the disease remains an open question. The most recent, and strongest data to date, suggests that they do not (Plotkin, Rauch *et al*. 2003). Ongoing placebo controlled trials should help to resolve this open question. More effective treatment for FD is needed. The development of cell based and/or $G_s\alpha$ directed therapies may hold promise.
The best treatment for PP is also not clear. The single study suggesting that tamoxifen, the estrogen agonist/antagonist, may be effective looks promising (Eugster, Rubin *et al*. 2003). However, this and all trials for the treatment of PP have been uncontrolled, and this fact, combined with the extreme variability in the clinical course of the disease makes conclusions about relative efficacy very difficult. Newer generation aromatase inhibitors are being tested and pure antiestrogens may be tested in the future. Ideally, controlled and/or head-to-head comparison trials eventually will establish the best treatment for PP in MAS.

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Acknowledgements
The author is indebted to Drs. Pamela Robey, Paolo Bianco, and Shlomo Wientroub for mentoring, guidance, and collaboration. In addition, many other collaborators including Mara Riminucci, Andrew Shenker, Penelope Feuillan, Caroline Chebli, Sunday Akintoye, Nicholas Sarlis, Janice Lee, Arabella Leet, Harvey Kushner, Alesandro Corsi, Navid Ziran, Clara Chen, Marilyn Kelly, Beth Brillante, Serge Kuznetsov, and Natasha Cherman have been essential to this work. Most importantly, I think the patients and their parents, whose bravery, sacrifice, and willingness to confront their illness and share the findings have made this work possible.

Appendix 1 : Bisphosphonate Treatment

Pamidronate

The greatest experience in treating FD is with pamidronate, so for that reason it may be preferred.

Basic infusion

after (Liens, Delmas *et al*. 1994; Chapurlat, Delmas *et al*. 1997; Plotkin, Rauch *et al*. 2003) 1 mg/kg/day for 3 days, every 3 months mixed in 1 liter normal saline, infused over 2-4 hours infiltration can cause a significant phlebitis; make sure the intraveinous line is adequate

It can cause a flu-like response, but usually only on the first one or 2 infusions. So pretreatment with acetaminophen before the first infusion and around the clock during the days of infusions is recommended.

It can rarely cause hypocalcemia, so educate the patients and their families on the signs and symptoms (s/s) of hypocalcemia and recommend calcium fortified orange juice, or milk, and/or calcium supplements if s/s occur

Dose Modification

The dose should be modified so that the lowest dose needed to control pain is being used. The regime can be modified by decreasing the dose, (ex: 1mg/kg/day X 2 days or 1 day, and/or the frequency can be increased to every month or increased to every 3 – 6 – 12 months). If the indication is pain, let pain relief/recurrence be the motivation. Bone metabolism (turnover) markers will decrease with treatment, but this should not be the goal of treatment. Pain relief is the goal of treatment.

Zoledronate

There is less experience with zoledronic acid, but it appears to be more potent, so there maybe some advantages to its use. In addition, there are advantages to the dosing in terms of infused volume and time required to infuse

Basic infusion

6mg per day for 2 or 3 days, every 3 months. If needed, it can be given as frequently as monthly ; but this very frequent dosing should rarely be needed, and the number of infusions at this frequency is limited. More often, a schedule of 3 every 3 – 6 months is enough. Less frequently is possible, and a single 6 mg dose may be enough.

The drug can be mixed in as little as 50mL of normal saline, and infused over as little as 15 min. Larger volumes and slower infusions may decrease the acute phase reaction, which frequently occurs with the first dose or set of doses.

Infiltration can cause a significant phlebitis, so make sure the intraveinous line is adequate.

It can cause a flu-like, acute phase response, but usually only on the first one or 2 infusions; so pretreatment with Tylenol before the first infusion and around the clock during the days of infusions is recommended

It can rarely cause hypocalcemia, so an extra of 1 mg of calcium per day for 7 days after the infusion is often given

Again, pain is the primary indication for treatment and should be the clinical end point. Markers of bone metabolism will decrease, but this should not be the treatment end point.

Oral Bisphosphonates

Oral bisphosphonates (alendronate, residronate, etc.) can also be used for less severe pain. For the treatment of FD, these are used at higher doses (as in Pagets disease) than those used to treat osteoporosis. Again, pain is the clinical endpoint, and the dose should be adjusted to the minimum dose needed to relieve pain. As in Pagets disease, the regimen is usually cycled, with several months on drug, followed by several months off drug, until pain recurs.

Appendix 2: Recommendations for Treatment of Hypophosphatemia in MAS

Goal
Serum phosphorus in the age-appropriate normal range

Treatment
Phosphorus: 15-60 mg/kg/day (1-3 g/day adults), ***divided, 4-5 times q d*** Phosphorus treatment usually causes secondary hyperparathyroidism, so 1,25 vitamin D is added. Treatment with 1,25 vitamin D not only prevents secondary hyperparathyroidism but also increases gastrointestinal phosphorus absorption, improves bone healing (especially at high doses, and might also improve renal tubular maximum for phosphate reabsorption (i.e. increase the renal tubular reabsorption of phosphate TmP/GFR).
1,25 vitamin D: approximately 30 ng/kg/day (1.5 □g/day, (six 0.25□g pills/day) for a 70 kg man), range15-60 ng/kg/d (three-twelve 0.25□g pills/day)

Possible Complications

Hypercalciuria
With resultant nephrocalcinosis, nephrolithiasis and decreased creatinine clearance.

Hypercalcemia
Less common than hypercalciuria.

Gastrointestinal upset
Due to the phosphate. Dividing the doses over 4-5 times per day and with food helps.

Follow-up
1. Baseline ultrasound to rule out nephrolithiasis (which some patients are at risk for at the outset).
2. q3 month urine (second A M void) for calcium and creatinine, if Ca/Cr ≥0.20, dip urine for heme, if + decrease 1,25 D, 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 1,25 D again. If Ca/Cr ≤0.20 and serum phos and PTH ok, maintain regimen
q3 month serum calcium, phosphorus, and PTH

Appendix 3: Treatment of Precocious Puberty

Girls
While vaginal bleeding in a young child can be quite distressing for the parents and the child, the primary goal in treating PP in girls is to prevent severe short stature.

Aromatase inhibitors
These are the drugs we have the longest experience with, and therefore the greatest reassurance of their safety.

Testolactone
This is one of the first generation and less potent aromatase inhibitors. While this therapy was reported to be quite effective early on (Feuillan, Foster *et al*. 1986), subsequent studies have been less positive (Feuillan, Jones *et al*. 1993).
The dose is: 40 mg/kg/day in doses divided tid.

Newer aromatase inhibitors
Trials with letrazole and anastrazole are ongoing. These newer, longer acting drugs may be more effective.
The dose of **letrazole** is: 1.5 mg/m^2 per day divided bid.
The dose of **anastrozole** is: 1 mg per day.

Tamoxifen
A single uncontrolled study indicates that tamoxifen may be beneficial in the treatment of precocious puberty in MAS (Eugster, Rubin *et al*. 2003). Longterm safety data is lacking, but tamoxifen does appear to be effective in stopping bone age advancement.

Boys
The goals are to prevent short stature, and control the behavioral issues related to androgen excess. The medications and doses used to prevent short stature in boys (with the exception of tamoxifen) are the same as used in girls (see above). The medications used to treat the symptoms of androgen excess are:

Spironolactone
This is the medication with the longest record of safety and efficacy in children, and should be used first. It is usually effective.
The dose is: 5-7 mg/kg/day divided bid.

Flutemide
The record of safety and efficacy in children is not as long as those of spironolactone, but some clinicians feel quite comfortable using it. It has been associated with abnormal liver function tests in men with prostate cancer using higher doses. For this reason, it is prudent to check liver function tests at baseline and periodically.
The dose is: 10 mg/kg/day divided bid.

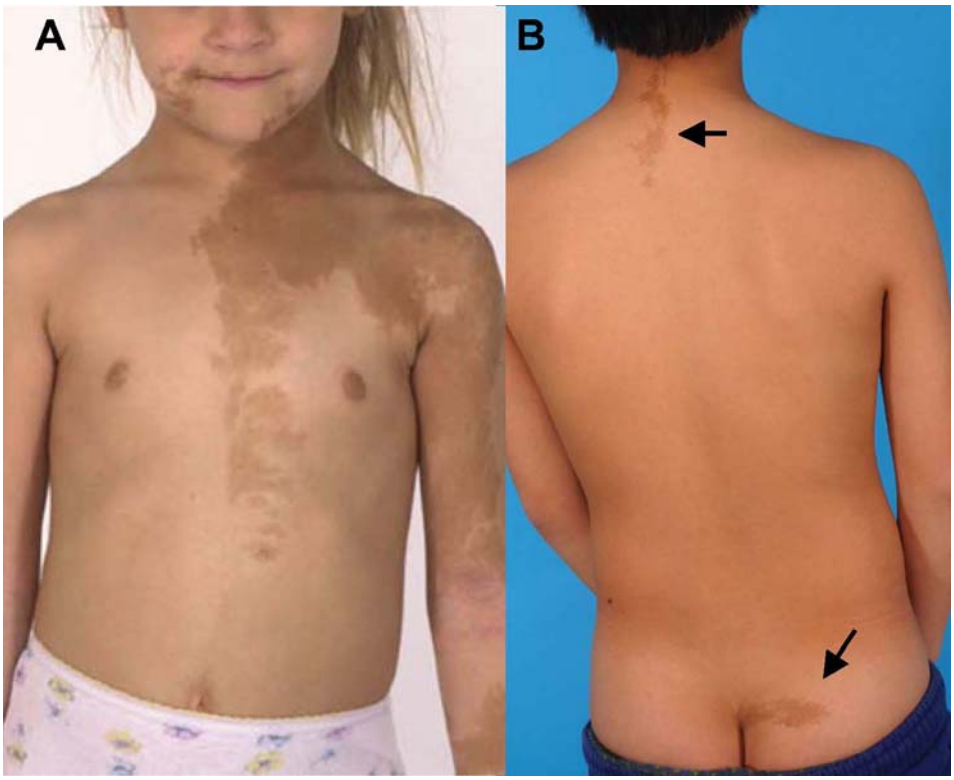

Figure 1. Café-au-lait Skin Pigmentation.

A) A typical lesion on the face, chest, and arm of a 5-year-old girl with McCune-Albright syndrome which demonstrates jagged “coast of Maine” borders, and the tendency for the lesions to both respect the midline and follow the developmental lines of Blashko.

B) Typical lesions that are often found on the nape of the neck and crease of the buttocks are shown (arrows).

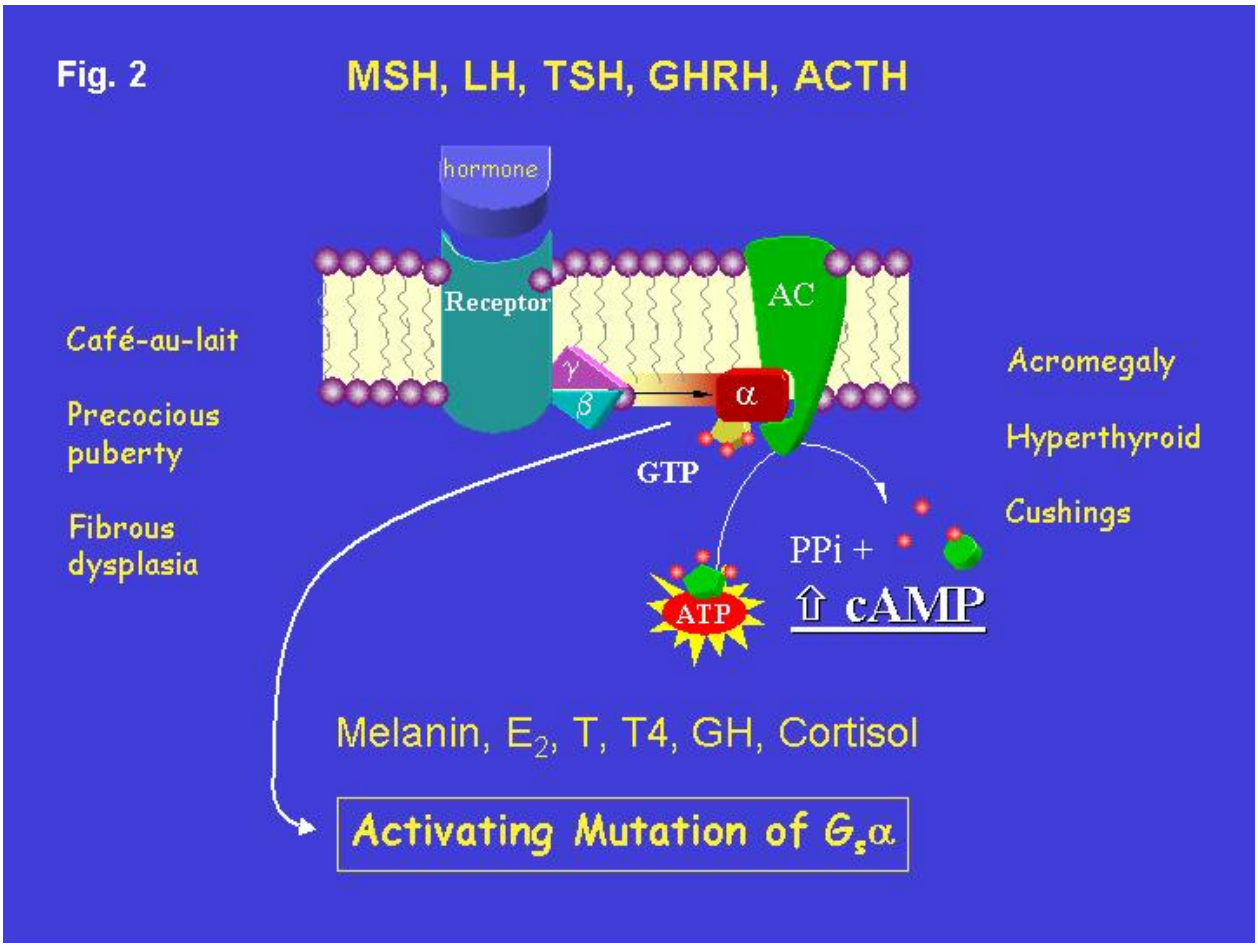

Figure 2. Molecular Defect and Phenotype in McCune-Albright Syndrome (MAS).

The hormones MSH (melanocyte stimulating hormone), LH (leutinizing hormone), TSH (thyroid stimulating hormone), GHRH (growth hormone stimulating hormone), and ACTH (adrenocrotical stimulating hormone) all signal through the G protein (alpha, beta, gamma subunits) pathway. In MAS, the alpha subunit is mutated in such a way as to induce constitutive activation of adenylate cyclase, and thus produce high levels of intracellular cAMP. This results in increased production of melanin, estradiol (E2), testosterone (T), thyroxine (T4), growth hormone (GH), and cortisol. Dysregulated production of these hormones results in café-au-lait spots, precocious puberty, fibrous dysplasia, acromegaly, hyperthyroidism, and Cushings disease, depending on the tissue harboring the somatic mutation.

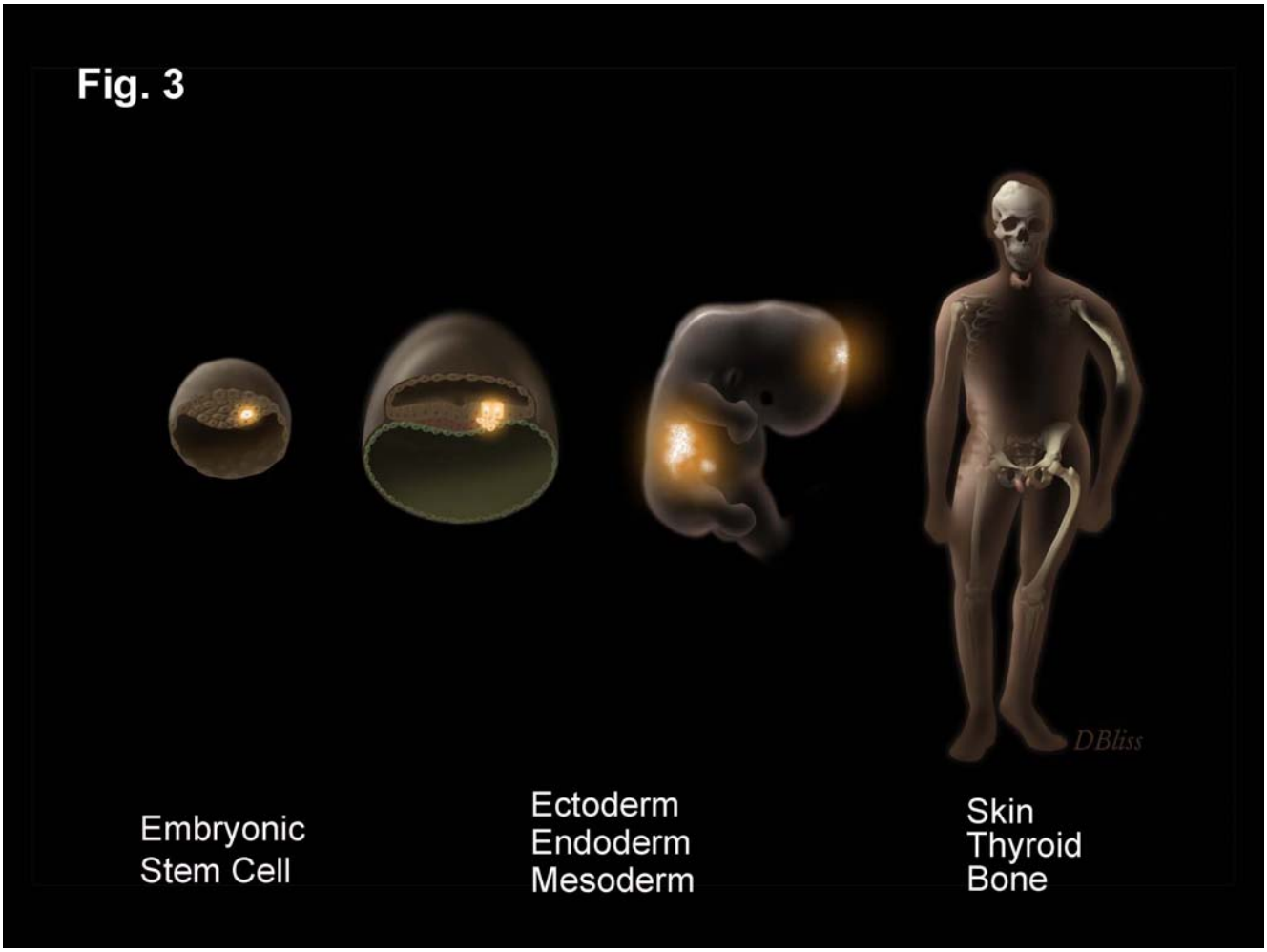

Figure 3. Developmental Defect in McCune-Albright Syndrome (MAS)

A sporadic mutation occurs in a single cell (bright spot) at some point early in development. If this occurs at the embryonic stem cell stage, all 3 germ cell layers will be affected. As the cells derived from this mutated clone are dispersed throughout the organism, the final phenotype emerges, MAS.

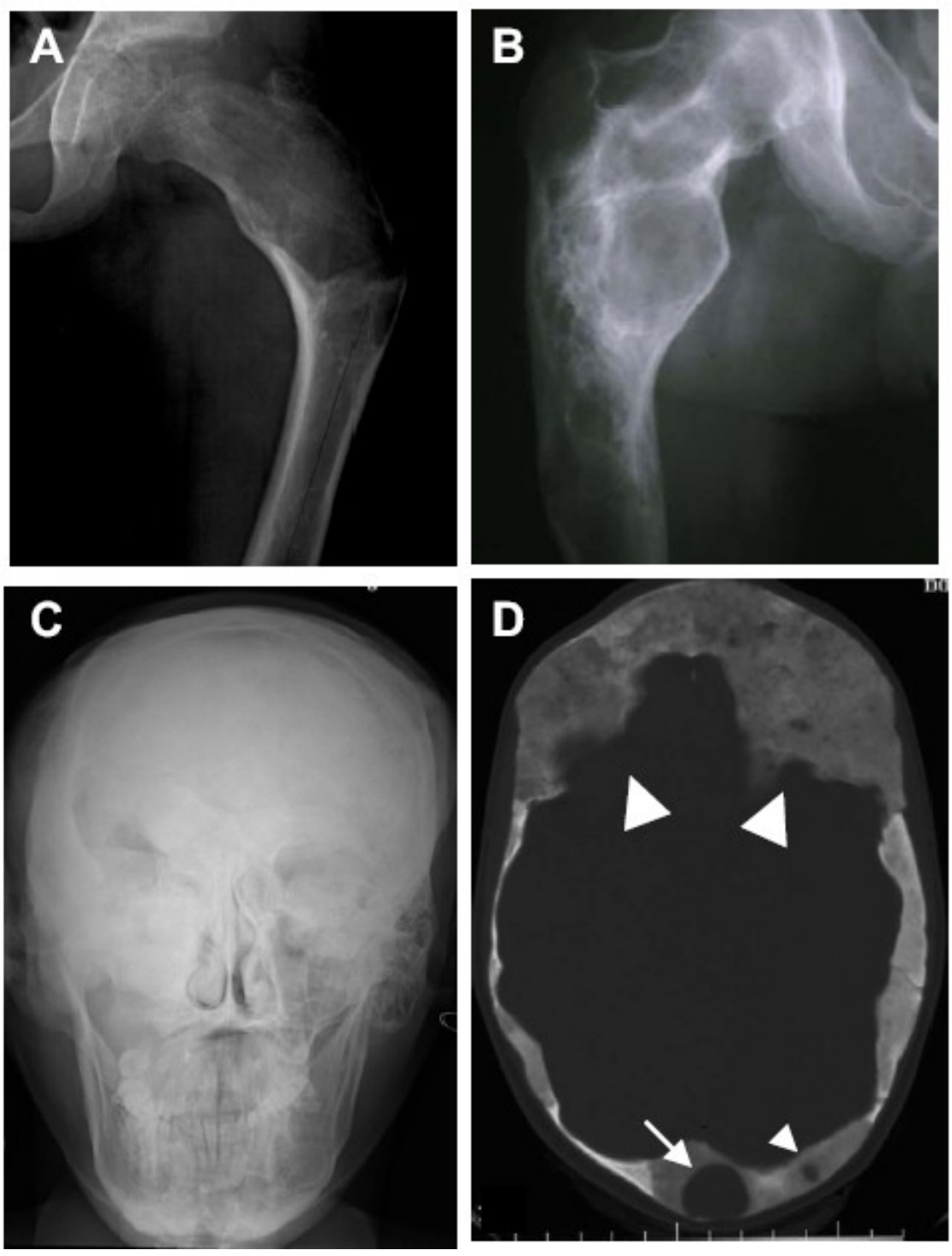

Figure 4. Radiographic and Histological Appearance of Fibrous Dysplasia.

A) A proximal femur with typical ground glass appearance and shepherd's crook deformity in a 10-year-old child is shown.
B) The appearance of FD in the femur of an untreated 40-year-old man demonstrates the tendency for FD to appear more sclerotic with time.
C) The typical sclerotic appearance of FD in the craniofacial region is shown.
D) A CT image demonstrates thickened frontal bone with a mixed solid and cystic appearance (large arrowheads), and lesions in the occipital bone, one with "cystic" changes (small arrowhead) that represents an area of fibrous tissue, as well as a fluid-filled cyst (arrow).

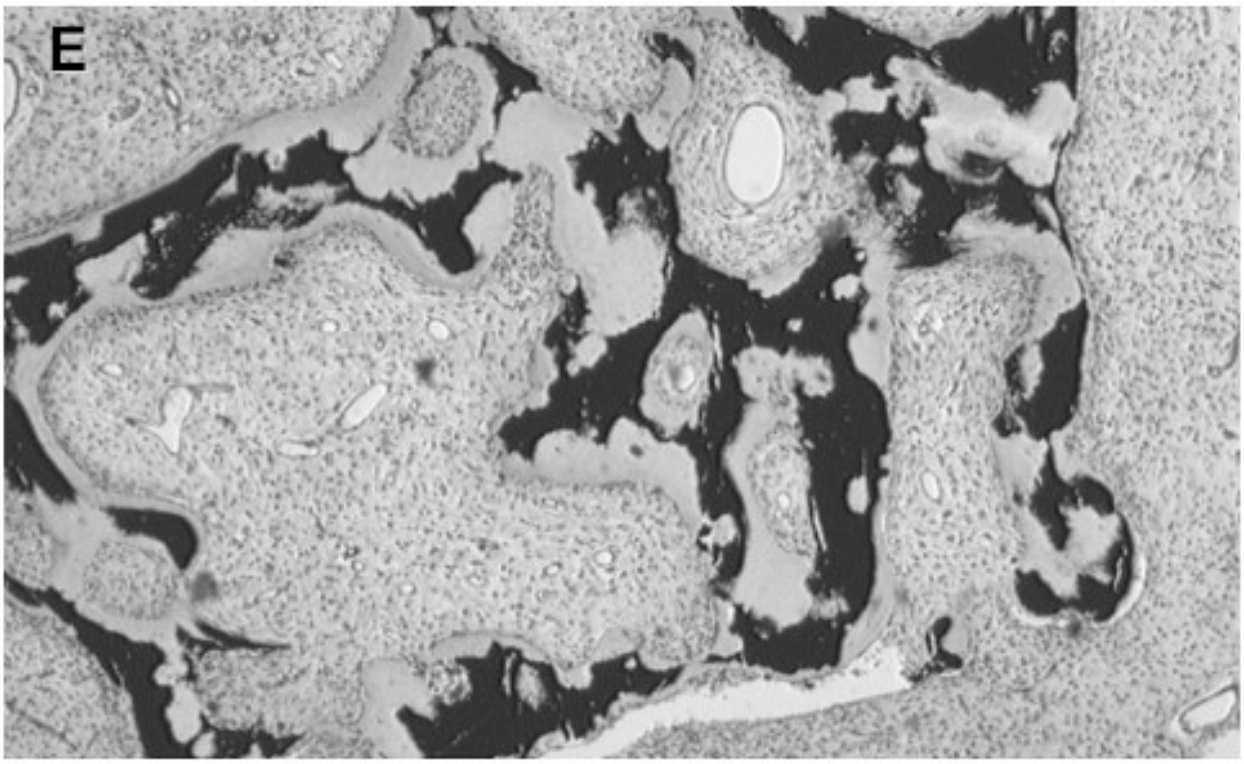

Figure 4. Radiographic and Histological Appearance of Fibrous Dysplasia.

E) Representative histological image of FD. The tissue was processed for undecalcified embedding, which enables to demonstrate excess osteoid in the undermineralized fibrous dysplastic bone. The marrow spaces are filled with “fibrous” tissue, consisting of excess, abnormal marrow stromal cells.

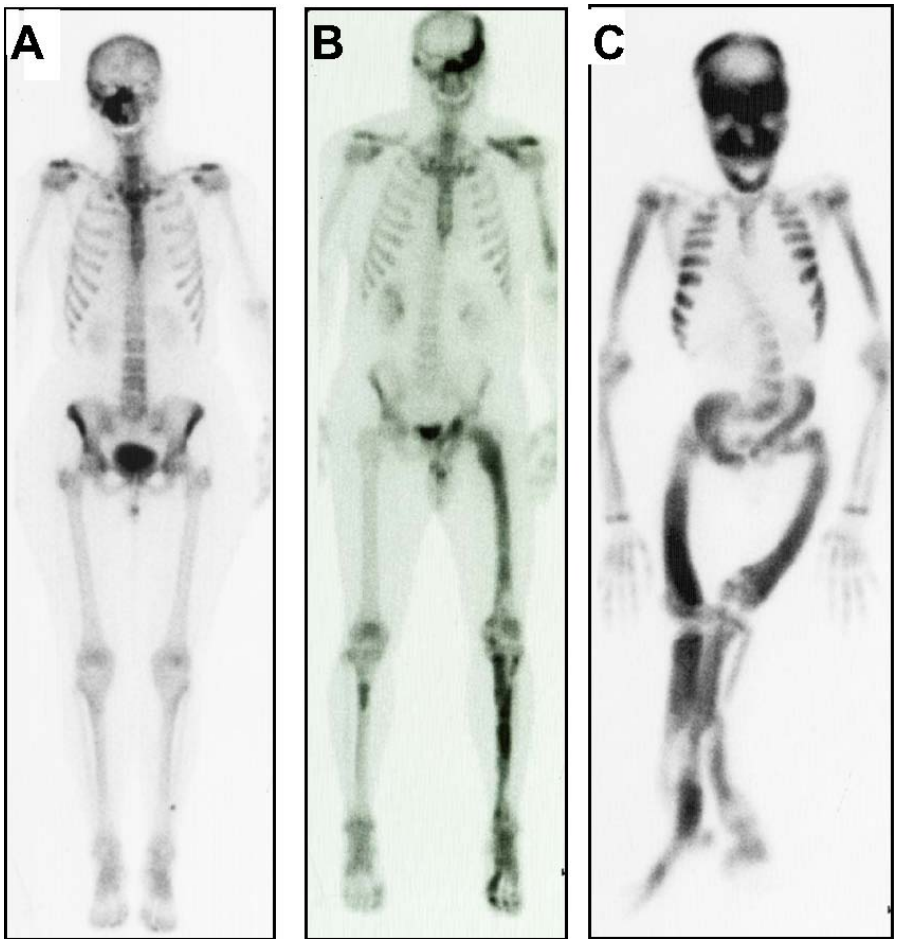

Figure 5. Bone Scintigraphy in FD. Representative 99Tc-MDP bone scans which show tracer uptake at affected skeletal sites are shown.

A) A 50-year old woman with monostotic FD confined to a single focus involving contiguous bones in the craniofacial region.
B) A 42-year-old man with polyostotic FD shows the tendency for FD to be predominantly (but not exclusively) unilateral, and to involve the skull base and proximal femur.
C) A 16-year-old boy with McCune-Albright syndrome and involvement of virtually all skeletal sites(panostotic) is shown.