**PERSPECTIVES**

**Fibrous Dysplasia of Bone and McCune-Albright Syndrome**

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**Abstract**

Fibrous dysplasia of bone (FD) is a genetic, non-inheritable disease, characterized by bone pain, bone deformities and fracture, involving one or several bones, and due to missense mutations occurring postzygotically in the gene coding for the α subunit of the stimulatory G-protein, Gs, in the GNAS complex locus in chromosome 20q13. This mutation results in osteoblastic differentiation defects. Bone resorption is also often increased, driven by increased osteoblastic IL-6 secretion. The bone lesions may be associated with endocrine dysfunctions and café-au-lait spots; this is McCune-Albright syndrome (MAS). Patients with polyostotic FD often have renal phosphate wasting. Many patients, however, are affected with a mild form of FD, which does not deserve any aggressive therapy. Bisphosphonates have been used to treat bone pain and strengthen bone, based on results from open studies. Targeted therapies might be used in the future.

**Keywords:** Fibrous dysplasia of bone; McCune-Albright syndrome; bisphosphonates; interleukin-6; stem cell

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**Introduction**

Fibrous dysplasia of bone (FD) is a rare bone disease leading to bone pain, fracture or deformity, and sometimes to neurologic compression. The prevalence of this disease has been estimated at approximately 1 in 30,000 individuals (1). A small proportion of FD patients also have endocrine abnormalities (fewer than 5%), most often precocious puberty. Many patients have limited bone involvement with no or few symptoms, but the disease can be responsible for significant disabilities among those who have bone pain, fracture, deformity, neurological compressions, and endocrine dysfunctions. The typical McCune-Albright syndrome (MAS) associates FD, endocrine abnormalities (precocious puberty in general) and café-au-lait cutaneous spots.

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**Fibrous Dysplasia of Bone: A Stem Cell Disease**

**Role of the GNAS mutation**

FD is a genetic, non-inheritable disease due to postzygotic missense mutations in the gene coding for the α subunit of the stimulatory G-protein, Gs, in the GNAS complex locus in chromosome 20q13 (gsp mutation) (2;3). The two dominant acting mutations (replacement of the arginine residue in codon 201 by either cysteine or histidine) are responsible for a somatic mosaic. The resulting proteins display reduced GTPase activity, leading to increased adenylyl cyclase activation (4;5) and thus high levels of cAMP (6;7). Activation of the Gsα/PKA/CREB pathway induces c-fos overexpression in FD lesions (8), and Fos overexpression in transgenic mice results in bone lesions reminiscent of FD (9). It has been suggested that increased cAMP might down-regulate the osteoblastic transcription factor Runx2, thus contributing to abnormal osteoblastic differentiation (10).
In those osteoblastic cells, IL-6 secretion is increased as a result of Gs activation, with consequent activation of surrounding osteoclasts, allowing the FD lesion to expand and create osteolytic lesions (6). In human skeletal progenitors engineered to stably express R201C mutated, constitutively active Gsα using lentiviral vectors, a very potent upregulation of RANKL expression has been observed, correlating with the osteoclastogenesis observed in FD lesions in vivo (11).

In bone tissue, one can observe fusiform fibroblast-like cells, corresponding to highly proliferative, poorly differentiated osteoblasts. The histological hallmark of FD is extensive proliferation of fibrous tissue within the bone marrow, produced by these abnormally differentiated pre-osteoblastic cells. It can be considered that the mutation occurs before gastrulation (i.e., when the three germ layers – ectoderm, endoderm and mesoderm – separate with cell lineage determination) because MAS involves multiple tissues originating from the three embryonic germ layers. In addition, bone cells also derive from two layers: the mesoderm and the ectoderm. As the disease presents with a large clinical spectrum, from benign monostotic FD to severe MAS including polyostotic FD associated with multiple endocrine dysfunctions and skin spots, it has been speculated that the time of mutation determines the severity of the disease (12;13), and the current view is that the earlier the time of the mutation, the more widespread the organ involvement. The severity of the disease is proportional to the number of mutated cells (14). Those individuals with few mutated cells have monostotic disease, while those with a higher number of mutated cells can have polyostotic disease, with or without endocrine involvement.

Elevated cAMP production has been observed in MAS tissues (15). In MAS, endocrine gland growth and hormone secretion are stimulated even in the absence of stimulatory hormones, which is the main biologic characteristic of this syndrome (15). Specifically, precocious puberty, which is the most common endocrine complication in MAS, is a peripheral one, i.e., without evidence of hypersecretion of gonadotrophic hormones but with gonadal autonomous steroid secretion. Similarly, cAMP is increased in melanocytes (16) and dendrites from MAS patients (15). Some endocrine dysfunctions can also have a central origin, due to pituitary tumors related to pituitary-activating Gsα mutations.

In a bone biopsy study involving 18 patients of different ages assessing the frequency of mutated colony forming unit-fibroblasts (CFU-Fs) from FD lesions, and in some cases, from unaffected sites, there was a tight inverse correlation between the proportion of mutant CFU-Fs and age, suggesting the demise of mutant stem cells, caused by apoptosis (17). In older patients, either partially or completely normal bone/marrow histology could be observed compared to the youngest patients (7-35 years, compared with 35-52 years). Upon in vivo transplantation, FD ossicles were generated only by cell strains in which mutant CFU-Fs were identified; mutation-positive strains lacking mutant CFU-Fs failed to regenerate FD ossicles. These data indicate that GNAS mutations are pathogenic only when expressed in clonogenic skeletal stem cells. As lesions age, mutant stem cells fail to self-renew, and their progeny disappear by apoptosis, whereas residual normal stem cells survive, self-renew, and enable formation of a normal bone structure. This concept has been named “normalization” of FD (17) and could explain why FD lesions are often less symptomatic with aging.

**Improving detection of mutated bone cells**

Pathological diagnosis is often difficult, especially for pathologists who are not accustomed to examining FD bone samples. So, a polymerase chain reaction (PCR)-based technique has been developed, allowing for the selective amplification of products from the mutant allele (18). This technique has been applied to the analysis of patients with FD, to amplify the mutant
gene from bone specimens and from circulating monocytes. It is also possible to detect the proportion of mutant cells in a number of tissue and cell culture samples derived from FD/MAS lesions with a method for quantification of the mutant/normal ratio of cells using a peptide nucleic acid (PNA) hybridization probe-based FRET technique (19). Inclusion of a specific PNA primer in the PCR for GNAS exon 8 allowed the selective amplification of low numbers of mutant alleles, and permitted detection of activating mutations in genomic DNA from peripheral blood cells in patients with MAS and FD with increased sensitivity compared with the simple PCR-based technique (20).

Periostin is a secreted extracellular matrix protein particularly expressed in the periosteum and the periodental ligament (21). Immunohistochemistry and in situ hybridization studies have revealed that periostin is expressed in the fibrous component of fibrous dysplasia (22). Cells adjacent to periostin-positive regions expressed CD51/61. Periostin was also abundantly localized to Sharpey fibers. In transgenic mice overexpressing c-fos, animals that develop sclerotic lesions closely resembling those found in fibrous dysplasia, (23), undifferentiated osteoblasts expressed high levels of periostin, whereas normal osteoblasts did not. The G_{s}α-cAMP-cFos pathway might represent one mechanism of periostin up-regulation in fibrous dysplasia, resulting in altered collagen fibrillogenesis. Consequently, periostin may be a diagnostic tool in FD. It may improve the pathologic diagnosis, with immunohistochemistry and in situ hybridization studies. Serum measurement of periostin – if it were shown to be associated with disease severity – might be a relevant treatment follow-up marker.

Therapies

Pain killers

Paracetamol and non-steroidal anti-inflammatory drugs may be used for mild bone pain, while narcotics may be of interest for severe bone pain. Those medications, however, do not suffice to control pain in many cases, and cannot control the course of the disease.

Bisphophonates

Using an antiresorptive agent in the treatment of an osteoblastic lineage disease, such as FD, might seem counterintuitive. The rationale for doing so is based on the presence of abundant osteoclastic bone resorption within and around the fibrous tissue. Therefore, in an early study that took as an example treatment of Paget’s disease, 9 patients have been treated with intravenous pamidronate (180 mg every 6 months), with striking radiographic improvements and decreases in bone pain and biochemical markers of bone remodeling (23). Patients were also receiving calcium (500-1500 mg/day) and vitamin D (800-1200 IU/day) supplements.

Long-term effects of this regimen have been assessed with additional patients and longer follow-up, still in an open design, with similar results (24;25). A dose of 3 mg/kg/treatment cycle was used in children and adolescents, who represented 30% of this cohort. Fifty-eight patients have been treated with intravenous pamidronate and followed-up for an average of 50 months (ranging from 1 to 11 years). Pain intensity was reduced after the first course of treatment, with an additive effect observed after several treatment cycles. Biochemical markers of bone turnover – such as total alkaline phosphatase, serum osteocalcin, and urinary CTX – were also significantly reduced compared to baseline. Half of those treated patients had discernable radiological improvement, characterized by filling of osteolytic lesions and/or cortical thickening. In addition, total hip bone mineral density (BMD) measured in patients who had hip involvement was substantially increased (26). Results were similar in adults and children or adolescents.

Favorable outcomes have also been observed in other open studies using intravenous pamidronate, administered at 6-month intervals. Thus, a substantial increase in BMD has been obtained in a study involving 7 adult patients with various forms
of FD treated with intravenous pamidronate (27). In those patients, a greater increase in BMD was observed in affected areas than in unaffected areas, using whole body DXA to compare the affected to the unaffected side, after 1 year of treatment. During this period, no obvious change was observed on plain radiographs, suggesting that BMD measurements were more sensitive to detect bisphosphonate effects on the dysplastic bone. Simultaneously, bone pain was significantly relieved in those 7 patients, and the level of bone turnover as assessed by biochemical markers was reduced.

A few patients have also been treated successfully with alendronate. For example, an increase of 158% in total hip BMD over 2 years has been observed in a 22-year old woman who had received four 90 mg infusions of pamidronate every 4 weeks, followed by oral alendronate 10 mg/day (28), with a parallel relief in bone pain and decrease in urinary NTX. In another case report (29), a 45-year old woman who received alendronate 5 mg/day was relieved of her bone pain after several months of treatment. Bone turnover was diminished and the radiological aspect slightly improved. In a series of 6 adult patients who had been treated with pamidronate followed by alendronate or who had used alendronate alone, bone pain decreased substantially in response to therapy, bone resorption was reduced with intravenous pamidronate but not with oral alendronate, and four out of six patients exhibited radiological improvement (30).

Although most patients respond favorably to pamidronate therapy, a subset (15% in our group’s experience) does not exhibit any improvement in bone pain. Other patients, with an initial positive response to treatment with pamidronate, suffer from a relapse of bone pain or fail to maintain reduced levels of biochemical markers of bone turnover. When those patients with relapsed or failed treatment with pamidronate were switched to zoledronic acid, we have not been able to obtain significant reductions in bone pain or improvement of the radiological aspect (31). Zoledronic acid was well-tolerated, with only two patients with an acute phase reaction associated with the first infusion. Those patients switched to zoledronic acid tended to have more serious disease than the other patients on pamidronate only.

In another study (32), however, no convincing evidence of radiographic benefit could be observed in 18 children and adolescents with polyostotic FD, despite significant reduction in levels of bone turnover markers. The explanation for this discrepancy between this study conducted in young patients and those in adults or other pediatric series (33-35) remains unclear, but some of the difference might relate to the absence of use of phosphate supplements in those patients with renal phosphate wasting. The difference may also stem from the difficulty in defining appropriate radiographic outcomes in studies of FD, because lesions are heterogeneous and radiographs are not always reproducible over time.

All these results were obtained in uncontrolled open studies. The role of the placebo effect and regression to the mean is likely in explaining some of the effect on bone pain. The radiologic effect might be confounded by the age-related sclerosis of lesions (17), but this phenomenon arises over long periods of time, whereas the improvement associated with bisphosphonate use could be observed over shorter periods of time, e.g., 2-3 years. These shortcomings have led to the design of two randomized placebo-controlled clinical trials, one conducted in the US to test alendronate (36), and the other one in Europe, the PROFIDYS trial, to test risedronate (37). The results of the first trial are not yet published, and the latter trial is still recruiting patients.

**Calcium, vitamin D and phosphorus**

Significant mineralization defects are common within dysplastic bone (38;39), vitamin D deficiency is frequently observed (25;38) and hyperparathyroidism-related changes correlated to serum PTH may be observed on histological examination (38). Such findings support the use of calcium and vitamin D supplements in the subset of
FD patients with deficiency. It has never been shown, however, that such supplementation improves the histological appearance of hyperparathyroidism-related changes.

Around 50% of patients with polyostotic FD have some degree of renal phosphate wasting and most of them have a renal tubulopathy (40). Renal phosphate wasting is due to a phosphatonin that has been identified as being FGF-23. FGF-23 is produced by normal and FD osteoprogenitors as well as bone-forming cells. Mutated cells, osteogenic cells, and cells associated with microvascular walls are specific cellular sources of FGF-23 in FD. Serum levels of FGF-23 are increased in FD/MAS patients compared with normal age-matched controls and significantly higher in those patients with renal phosphate wasting compared to those without (41). The levels of FGF-23 correlate with disease activity. The mineralization abnormalities are correlated to the degree of renal phosphate wasting observed in many patients with polyostotic FD (38). As fracture incidence has been found to be increased in those individuals with renal phosphate wasting (42), supplementation with oral phosphorus (associated with calcitriol) appears logical, although it has not yet been proven efficacious in specific clinical trials.

Management of endocrine dysfunctions

The peripheral nature of precocious puberty arising with MAS precludes the use of GnRH analogues alone. Aromatase inhibitors have been used to diminish sex steroid production. Testolactone has been the first drug used in this indication, but has been replaced recently by the more convenient letrozole (43). Some other aromatase inhibitors, such as anastrazole, however, do not seem to be effective (44). The combination of letrozole and GnRH analogues is also possible. In boys, the combination of an anti-androgen with an aromatase inhibitor is a classical approach.

In adults, hyperthyroidism and acromegaly are the most common endocrine complications of MAS. Adults with MAS should be followed up for early detection of mild acromegaly, for example with IGF-1 annual monitoring.

Surgery

Surgery is indicated for the correction of deformities, the prevention of fracture in patients with threatening osteolytic lesions, the management of fractures and transformation of lesions into either benign (i.e., bone cysts) or malignant tumors. In polyostotic FD, the bones are often thin and weak, so the choice of technique must be considered carefully before the intervention. Autograft is contraindicated (as it contains mutated cells that will promote relapse) and a cancellous bone graft should not be used. Excising and removing a dysplastic lesion is useless because all the disease cannot be removed. Plates and screws should be avoided. Deformities should not be allowed to become severe and several operations are generally necessary to solve the problem. Intramedullary rods are the technique of choice. In children, adaptative length rods should be used. Corrective osteotomy may be used for deformities.

Therapeutic perspectives

In FD, the hyperosteoclastic component is driven by increased osteoblastic IL-6 secretion. Consequently, inhibiting IL-6 might be an attractive treatment option for those individuals who do not respond to bisphosphonate therapy or who relapse while on bisphosphonate treatment. Tocilizumab is an anti-IL-6 receptor human monoclonal antibody that is available in the treatment of rheumatoid arthritis (RA). In patients with RA, it has been shown to reduce bone resorption, as assessed with biochemical markers of bone resorption such as ICTP and CTX (45). In the future, this therapeutic possibility will be studied further.

If a gene therapy were to be considered, it would have to selectively silence only the mutated allele, because the mutated gene is indispensable in all tissues and the mutations are dominant and gain-of-function. It has been shown recently (11)
that lentiviral vectors encoding the R201C mutation could be effectively transferred to human skeletal progenitors. In addition, RNA-interfering sequences have been introduced in human skeletal progenitors using lentiviral transduction, with effective mutated Gsα silencing as a result. cAMP production could also be returned to normal, with normal differentiation of the osteoblastic cells bearing the mutated Gsα lentiviral knockdown. In the long-run, this could be the basis for the development of a gene therapy.

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