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Medical Therapy of Children With Fibrous Dysplasia

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INTRODUCTION

FIBROUS DYSPLASIA (FD) is a sporadic developmental disorder characterized by expanding fibrous lesions throughout the skeleton. On X-rays, the dysplastic lesions frequently have a lytic or cystic appearance. At the tissue level, the lesions consist of abnormal fibrous tissue in the marrow space intertwined with poorly defined and irregular trabeculae reminiscent of woven bone.[1] Bone scans usually show increased radiolabel uptake in the affected areas. Biochemical indices of bone turnover are usually high (particularly serum tissue nonspecific alkaline phosphatase activity) and correlate with the extent of the lesions. Hypophosphatemia is a common finding, probably caused by a circulating phosphaturic factor.[2–5]

The sites involved are typically the long bones and the skull. They are often unilateral. In some cases, a single lesion is present (monostotic form). Polyostotic (more than one site) forms are the most frequent, with, in rare instances, FD involving the whole skeleton (panostotic form).[6] When bone lesions are associated with various endocrinopathies (mostly precocious puberty) and skin lesions (café-au-lait-spots), it is referred to as the McCune-Albright syndrome (OMIM #174800).[7]

PATHOPHYSIOLOGY

FD is caused by a somatic activating mutation of the α subunit of the GS protein (GSα). The gene encoding GSα is located on the chromosome 20q13. Activating missense mutations consist of single base substitutions at codon R201 in exon 3. Such mutations induce a constitutive activation of adenylate cyclase, resulting in constitutive elevation of cAMP levels. The effects of hormones using cAMP as a second messenger therefore occur without regulation.[8] The distribution of the mutation in the body follows a mosaic pattern and probably depends on the stage of embryologic development at which the mutation arose.[9] The mutation has been detected in a number of tissues and cell types, such as bone, skin, endocrine tumors, kidney, and others, which explains the manifold manifestations of the McCune-Albright syndrome.[5,10–13]

BONE STRUCTURE

In bone mesenchymal cells, the downstream effects of the mutation include increased production of c-*fos* protein and interleukin-6.[14,15] Histologic examination of the bone lesions shows spindle-shaped cells, which have been recently identified as incompletely differentiated osteoblasts.[16–18] They produce a matrix of randomly distributed collagen fibers and islands of woven bone.[16,18,19] There is also evidence for increased bone resorptive activity. The number of osteoclasts within the lesions is slightly higher than normal and the number of nuclei per osteoclast seems to be increased.[15–17] Presumably, osteoclasts are part of the mechanism responsible for the spread of the lesions through normal adjacent bone. Overall, bone tissue organization is disturbed in FD. It is akin to that of woven bone with poor or absent lamellation in the calcified matrix and accumulation of unmineralized osteoid. The latter has been referred to as "focal osteomalacia." Interestingly, its severity is not influenced by the often observed hypophosphatemia.[20] The marrow space is filled with fibrotic tissue containing the abnormal cells described above. It is noteworthy that the margin between normal and abnormal tissue is clearly delineated (Fig. 1). This is in line with the concept that clones of cells derived from either normal or mutant cells have developed side by side.

CLINICAL FINDINGS

Symptoms include bone pain, fracture, bone deformities, and neurological deficits, especially when there are large lesions in the skull. The typical time of presentation is the second or third decade for the monostotic form and before 10 years of age for the polyostotic form. It has been estimated that precocious puberty affects ~20% of girls and a smaller percentage of boys with polyostotic FD.[3,19] In children, FD can be associated with hypophosphatemic rickets.[21,22] This could be related to the finding that the *Gsα* mutation can be present in kidney cells, which might cause phosphate wasting through increased adenylate cyclase activity.[7–10,23]

Radiological signs of FD consist mainly of lytic and cystic lesions, with reduction of cortical thickness, and sometimes, widening of the diaphysis. The lesion is typically described as being of ground glass appearance, but can also be translucent, depending on the relative amount of mineralized trabeculae within the lesion.[19]

The natural evolution of FD is highly variable, but spontaneous regression of lesions does not occur.[3,19] Lesions may remain stable for decades, but can also progress relentlessly, leading to multiple fractures and severe bone deformities. The risk of bone malignancies seems to be

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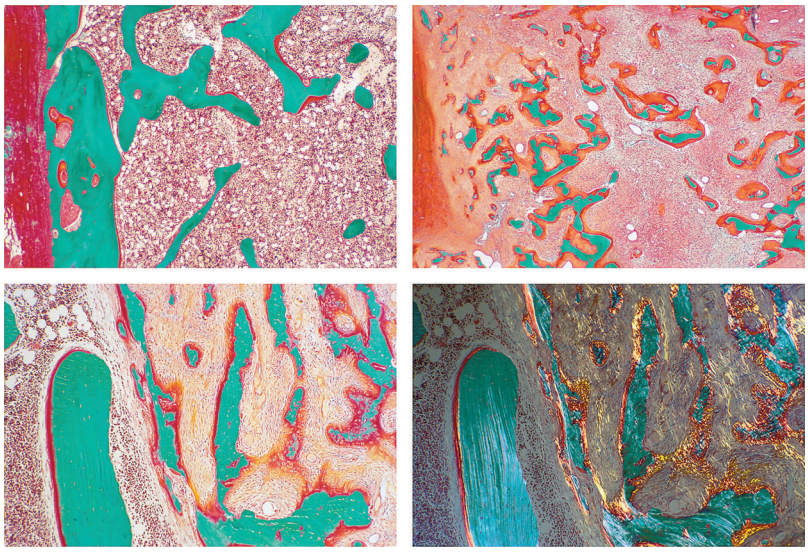

FIG. 1. (Top left) Normal bone. (Top right) FD dysplastic lesion, see description in the text. (Bottom left) Margin between normal and dysplastic bone. (Bottom right) Same section under polarized light contrasting normal lamellation on the left and absence of lamellar structure on the right.

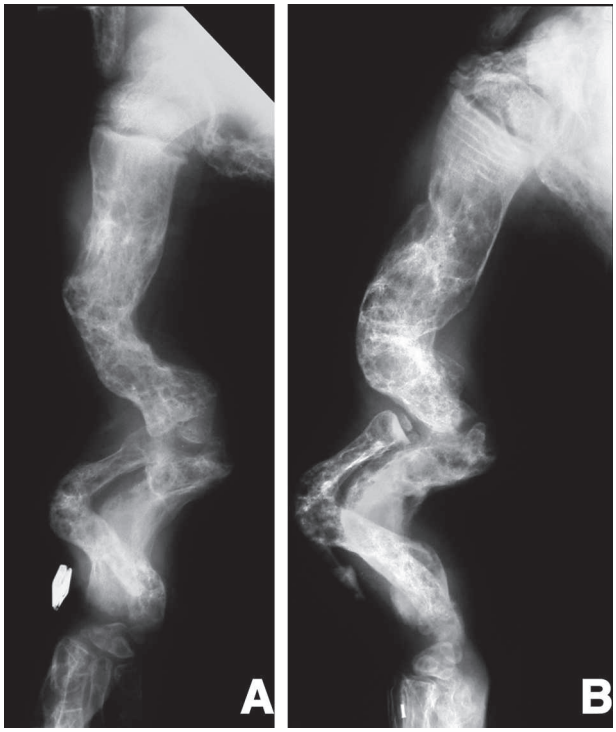

FIG. 2. Severe upper limb deformities in a 7-year-old boy with panostotic FD. (A) Before treatment. (B) After 4.6 years of pamidronate. No improvement of the lesions. The dense metaphyseal lines characterisitic of cyclical pamidronate treatment are visible under the growth plate.

slightly increased. In the largest retrospective series reported up to now, there were 28 bone malignancies in 1122 patients.[24] These malignancies were mostly osteosarcomas that developed after age 30.

DIAGNOSIS

The diagnosis of FD is usually made on the basis of clinical findings. In atypical cases, the diagnosis can be confirmed by sequence analysis of the *Gsα* gene.[13] This is best done in samples from a dysplastic bone lesion obtained during a surgical procedure. In many cases of polyostotic FD, the mutation can also be detected in peripheral blood leukocytes.[13] However, only a small proportion of leukocytes will carry the mutated gene, because the *Gsα* defect is a somatic mutation. Therefore, special enrichment techniques are necessary to detect the mutation in peripheral blood.

TREATMENT

Until recently, treatment of FD has been largely confined to orthopedic surgery, such as fracture management and nerve decompression, especially in the skull.[25] Preventive measures such as curettage of the dysplastic lesion, bone grafting, and internal fixation are sometimes performed, but bone lesions can recur after these interventions.[19,26]

Medical treatment has long been ineffective in changing

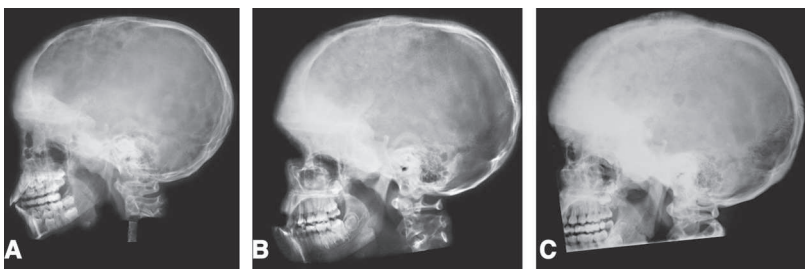

FIG. 3. Dysplastic skull lesions during pamidronate therapy in a 10-year-old girl with polyostotic FD. (Left) Before treatment. (Middle) After 3.2 years. (Right) After 6.2 years of therapy.

the natural evolution of the disease. A few anecdotal reports on therapy with calcitonin describe a decrease in biochemical markers of bone metabolism,[27,28] but little clinical benefit for the patient.[29] More recently, an observational study of treatment with the bisphosphonate compound pamidronate has yielded promising results in adults.[30] Cycles with intravenous pamidronate (60 mg/day on 3 successive days) were given every 6 months for 18 months and every 12 months thereafter. The follow-up time ranged from 18 to 64 months. Overall, there was a decreased intensity of bone pain, a decreased number of painful sites, a decrease in biochemical markers of bone turnover, and a radiographically apparent "refilling of osteolytic sites" in about one half of the patients. Similar observations have also been made in several smaller series of adult patients.[31,32]

It seems counterintuitive that an osteoclast inhibitor such as pamidronate should be effective in FD, a disease that is caused by a mutation in cells of the osteoblast lineage. However, as discussed earlier, the fibrotic lesions produce substances that stimulate bone resorption, leading to expansion of the lesion. Pamidronate could interfere with this process.

The published pediatric experience on the use of bisphosphonates in FD is very limited.[31,33,34] All studies used cyclic intravenous pamidronate infusions that were given every 6 months. A decrease in bone pain and in markers of bone metabolism was universally reported. No improvement in radiographic or bone scintigraphic parameters was found in the nine FD children reported by Lala et al.[33] However, in two girls reported by Pfeilschifter and Ziegler,[31] the density of bone lesions appeared to increase, as judged from standard X-rays. In our own experience, "refilling" of lesions rarely, if ever, occurs in growing individuals. We have evaluated the effects of cyclic pamidronate administration in 18 children and adolescents with polyostotic FD[35] who received treatment for 1.2–9.1 years (median: 3.8 years). Dosage was 3 mg/kg/3-day-cycle repeated every 4 months. Within 1–4 months after the first cycle, bone pain decreased and sometimes disappeared, and the patient experienced a sense of well-being and increased stamina. There was, however, no radiographic evidence of filling of lytic lesions or thickening of bone cortex. Limb deformities did not regress (Fig. 2). Only in one 10-year-old girl did dysplastic skull lesions appear to improve mildly (Fig. 3). In the 13 patients with well-delimited lesions, there was a significant increase in lesion width even after correction for the width of the unaffected contralateral bone. In the 10 patients who had received at least 3 years of therapy (and who had no evidence of dysplastic lesions in the spine), a significant increase in volumetric BMD was observed in the lumbar spine (L_1–L_4), reaching a value 22% higher than the value expected for normal children. At the histological level, there was no obvious effect of treatment on the dysplastic lesions. In iliac crest bone samples showing no lesions, an overall decrease in bone turnover rate was evident, with no mineralization defect.

As for the side effects of treatment, the so called "acute phase reaction" with fever and increased C-reactive protein can be expected to occur in children with FD during the first infusion cycle, as it does in osteogenesis imperfecta.[36] A 13-year-old boy with polyostotic FD developed rickets and osteomalacia during pamidronate therapy,[30] which, however, is not necessarily a side effect of the drug, because rickets and osteomalacia may be associated with FD, particularly if, as in this case, the patient is hypophosphatemic. Most of the time, the mineralization defect is very mild, and long-term therapy with calcitriol and phosphate is not warranted unless overt rickets is evident.

CRITICAL EVALUATION OF BISPHOSPHONATE TREATMENT

Relief of bone pain is the most obvious benefit of pamidronate therapy in children and adolescents with FD. In our view, this by itself justifies this form of treatment in severely affected patients. Other positive effects reported in the literature require critical evaluation. Most authors interpret decreased systemic markers of bone turnover as evidence of decreased disease activity. This may be true, but it is clear that bisphosphonate treatment inhibits the turnover of both dysplastic and normal bone. It is often a matter of speculation as to whether decreased bone markers reflect more the desired outcome or a side effect (suppressed turnover of healthy bone tissue). Similarly, an increase in the areal or volumetric BMD at skeletal sites without dysplastic lesions certainly is not a sign of effective therapy but indicates a side effect (i.e., the action of the drug on healthy bone tissue).

The treatment effect on the disease process should be analyzed by actually looking at the lesions. This is not a trivial matter. Radiographic "refilling of dysplastic lesions" should be diagnosed by an observer who is blinded to the treatment status of the patient. However, this is not possible in growing individuals, because bisphosphonate treatment produces unmistakable skeletal effects, such as metaphyseal bands.[36] Densitometric assessment of an involved site has been described in a case report on an adult,[37] but this is often technically difficult to do in children because of changing bone shape.[34] Thus, these indirect methods to evaluate bone are inadequate to reliably characterize the effect of bisphosphonates on the dysplastic lesions. Histologic data are needed to get a clearer picture.

CONCLUSION

There are no controlled studies to prove the efficacy of any medical intervention in children with FD. Very little is known about the effects of bisphosphonate treatment in children and adolescents with FD, and these effects are difficult to measure objectively. However, most patients report decreased bone pain after the first pamidronate infusion, which in our view justifies the use of this drug in severely affected patients. The many unsolved questions regarding this form of treatment can only be addressed when a large number of patients are treated in a standardized controlled fashion and data on the outcome are collected, an arduous task, particularly in the pediatric age group.

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