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ORIGINAL ARTICLE

Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions

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Abstract
Summary To determine the prevalence, distribution, age-related changes and treatment of pain in fibrous dysplasia, we studied 78 children and adults. Pain was common, more prevalent and intense in adults, sometimes requiring narcotic analgesia. It was often untreated, especially in children, and surprisingly severity did not correlate with skeletal disease burden.
Introduction Pain is common in fibrous dysplasia (FD), but relatively unstudied. We studied a well-characterized population of patients with a spectrum of disease.
Methods Thirty-five children (16 male, 19 female, mean age 11.4 (range 5–18)) and 43 adults (15 male, 28 female, 23–62 yrs, mean age 40.3 (range 23–62)) were studied. Bone scans were used to identify the location and extent of disease. The Brief Pain Inventory was used to determine severity.
Results Pain at sites of FD was common, reported by 67% of the population, but more prevalent and severe in the adult group than the children (81% and 49%, respectively $p<0.005$, severity 4.1/10, and 2.8/10, respectively, $p<0.01$). Surprisingly, there was no correlation between pain severity and skeletal disease burden. Children were more likely than adults to be untreated for pain (44% vs. 26%).
Conclusions Pain, which was sometimes severe, was common in subjects with FD. It was often un- or under-treated, especially in children. The prevalence and severity of pain was greater in the adult group, but unrelated to the burden of FD.

Keywords Analgesia · Biophosphonates · Fibrous dysplasia · Gs alpha · McCune-Albright syndrome · Pain

Disclosures: none

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Introduction

Fibrous dysplasia of bone (FD) is a congenital, non-inherited skeletal disorder which is usually diagnosed in childhood [1, 2]. In FD, normal bone and bone marrow are replaced by an accumulation of fibrous tissue composed of masses of pre-osteoblastic cells [2, 3]. The etiology of the disease is somatic activating mutations in the cAMP-regulating protein, $G_S\alpha$, which is coded for by the *GNAS* gene [4–6]. The extent of the disease can vary greatly, from a single skeletal site (monostotic FD, MFD), or multiple sites (polyostotic FD, PFD), to essentially the entire skeleton (panostotic FD) [7, 8].

PFD is frequently seen with some combination of cafe-au-lait skin pigmentation, and/or hyperfunctioning endocrinopathies, such as gonadotropin-independent precocious puberty [9], peripheral hyperthyroidism [10], growth hormone excess [11], and/or renal phosphate wasting [12]. When FD presents with these skin or endocrine findings, it

is known as McCune-Albright syndrome (MAS) [13, 14]. FD can be associated with multiple skeletal complications, including fractures, limb length discrepancy and bowing, and rarely, malignant transformation [15].

Pain is a common occurrence in FD [16, 17]. Indeed, pain is often the presenting symptom of the disease [18, 19]. When the health-related quality of life was assessed in FD subjects, both adults and children had significantly more pain than the U. S. population [20]. Yet, it is a common misconception that pain, like the fracture rate, which is lower in adult patients with FD [15], dissipates into adulthood. Pain can at times be severe and requires the use of narcotic analgesics for adequate control. Lack of recognition by the medical community that pain severity in FD can be great and require treatment with narcotics, and that pain can persist into adulthood, has led many patients to be labeled as "drug seeking" and inadequately treated. Adequate pain management has been made a health care priority by patients and by the Agency for Health Care Policy and Research, the Joint Commission on Accreditation of Health Care Organizations, and the American Medical Society [21]. Yet in patients with FD, pain prevalence, its association with skeletal sites and/or severity of FD, and its treatment are poorly understood. By studying a relatively large population of patients with FD, we sought to answer these questions.

Methods and patients

Patients

All subjects enrolled in a National Institutes of Health Institutional Review Board-approved study of FD and MAS were invited to complete the self report Brief Pain Inventory (BPI) [22] and a demographic data questionnaire during their initial evaluation at NIH between July 2000 and July 2005. Ninety-one subjects were enrolled during that period, and 78 (86%) completed the pain form and had a ^{99}Tc-MDP bone scan. Written informed consent was obtained from each subject or from a parent of minor participants. The diagnosis of FD was established in all patients based on clinical history, histopathological findings, radiographic findings, and when necessary, an analysis of the *GNAS* gene for R201 mutations.

The demographics of those enrolled are shown in Table 1. All patients underwent an endocrine and metabolic evaluation to assess gonadal function, phosphorus metabolism, thyroid function, growth hormone (GH)/insulin-like

Table 1 Demographic and health data

	Studied		Not studied*	
	Adults	Children	Adults	Children
Number of cases	43	35	4	9
Mean age (range)	40.3 (23–62)	11.4 (5–18)	46.3 (21–80)	8.3 (3–17)
Gender				
Male	30%	46%	25%	78%
Female	70%	54%	75%	22%
Race				
Caucasian	84%	83%	100%	89%
Black	2%	6%	0	0
Hispanic	5%	9%	0	11%
Asian	9%	3%	0	0
Endocrinopathies				
Prec. puberty	51%	57%	0	33%
Hyperthyroid	23%	46%	0	56%
Growth hormone excess	21%	17%	0	0
Three endocrinopathies	2%	17%	0	0
Two endocrinopathies	26%	23%	0	44%
One endocrinopathy	30%	30%	0	33%
FD only - no endocrinopathies	42%	26%	100%	22%
Monostotic FD	9%	3%	50%	11%
Phosphaturia	47%	37%	12%	22%

*Twelve subjects were not included in the study due to lack of pain reporting form and one due to lack of bone scan. Prec. = precocious, FD = fibrous dysplasia, phosphaturia = renal tubular reabsorption of phosphate below the age- and gender-matched lower limit.

growth factor-1 (IGF-1) axis, and vitamin D status. The diagnosis of GH excess was established when the serum GH concentration was >1.0 ng/dl at 120 minutes on a standard oral glucose tolerance test. The diagnosis of phosphaturia (renal phosphate wasting) was established if the tubular maximum of phosphate reabsorption relative to glomerular filtration rate (TmP/GFR) was below the age- and gender-specific range.

Bone scans were assessed for sites of FD involvement, which were identified as areas of non-physiologic tracer uptake, and disease severity was determined using a validated scoring tool [23]. The fact that tracer uptake sites represented FD was confirmed by radiograph and/or CT.

Pain was assessed using a human figure drawing and the numeric rating scale (NRS) of the Brief Pain Inventory (BPI). The BPI is a short, self-administered questionnaire developed to assess the severity and impact of pain primarily in cancer patients [22]. It has been shown to be valid and reliable in adults when used to assess cancer pain (ibid), chronic and acute nonmalignant pain [24, 25] and pain in osteoarthritis patients [26]. The human figure drawing and the NRS were used for this analysis because these have proven to be reliable and valid to assess pain in children as young as five years old [27–29]. The NRS is a horizontal line with word anchors of "no pain" and "pain as bad as you can imagine" at the extremes and the numbers 0 to 10 equally distributed over the line. Subjects mark the line to indicate their pain. Since the intent of the analysis was to measure pain associated with FD, the presence of pain in any body compartment of the human figure drawing of the BPI was recorded only if there was evidence of FD in that compartment on the bone scan. The goal was to assess pain "intrinsic" to the FD and not pain that occurred in relation to a fracture. Therefore, acute or healing fractures were excluded from the analysis (i.e., >6 months since radiographic evidence of complete healing at a site at which there had been a recent fracture). Analgesic use and perceived relief information was obtained as part of the questionnaire, and confirmed during patient interviews. Some patients were receiving more than one category of treatment, in which case they were included in both categories. The approach to pain relief was to start with non-steroidal anti-inflammatory drugs (NSAIDS), and when these were inadequate, start treatment with bisphosphonates. If these were inadequate, narcotic analgesics was added to the regimen.

Statistical analysis

Data are presented as means unless otherwise specified. Non-parametric analyses were used throughout. Means were compared using Fisher's exact tests and Mann Whitney Tests, and performed with GraphPad Instat software (version 3.0, San Diego, CA). Correlations were determined using logistic regression for analysis of effects, and performed using SAS software (version 8.2; SAS Institute, Cary, North Carolina).

Results

The study population was made up of a group of subjects with a broad spectrum of disease, from isolated monostotic FD, to total skeletal involvement. The distribution of the disease burden of all subjects enrolled (both those studied and those excluded from the analysis) is shown in Fig. 1. The lower extremities were the sites most likely to be affected by FD (86% of adults, 97% of children, p = NS for differences between adults and children). The head was also commonly affected (86% of adults, 94% of children, p = NS). FD lesions were found less frequently in the upper extremities (72% of adults, 89% of children, p = NS), the ribs (72% of adults, 57% of children, p = NS) and the spine (72% of adults, 46% of children, $p<0.05$). The spine was the only site at which there was a significant increase in FD involvement over time (Fig. 3).

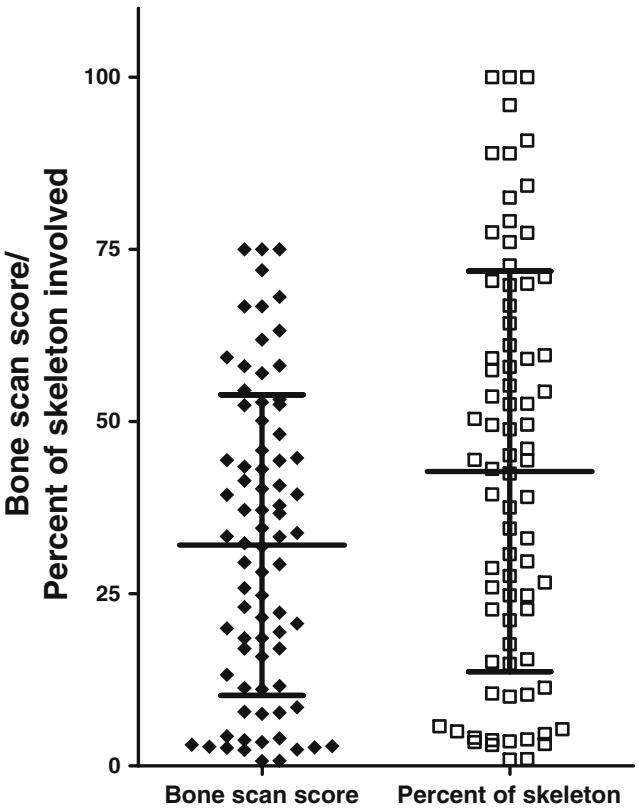

Fig. 1 Distribution fibrous dysplasia disease burden. The skeletal disease burden of fibrous dysplasia (filled diamonds) and the percent of the skeleton that this represents (open squares) in the population studied are shown. The mean and ± 1 SD are indicated. The population studied included a well-distributed group of patients in terms of degree of disease severity

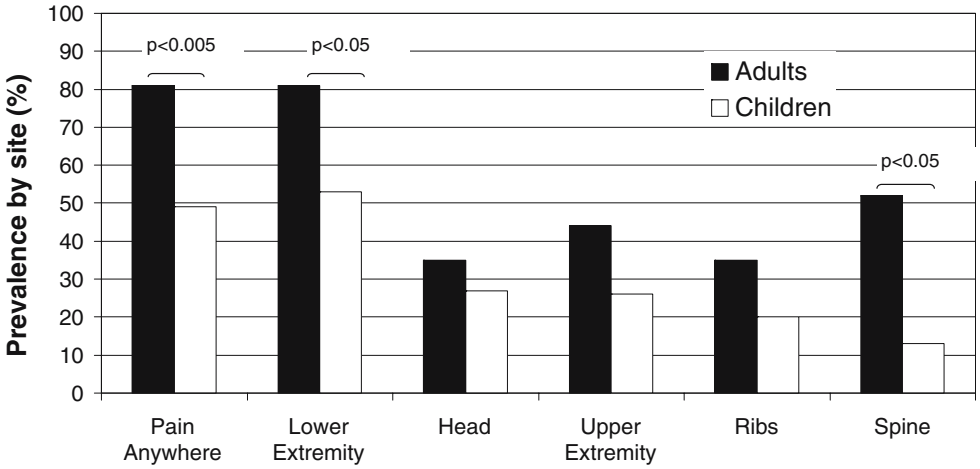

Fig. 2 Prevalence of pain at skeletal sites involved with fibrous dysplasia in adults and children. Adults had significantly more pain than children in general ($p<0.005$), and at both the lower extremity and the spine ($p<0.05$ for both)

Pain was prevalent in the FD population; 67% reported pain at FD sites. Pain was more prevalent in the adult group than the group of children, and was reported by 81% of adults and 49% of children ($p<0.005$) (Fig. 2). Adults reported significantly more pain than children in both the lower extremities (adults 81%, children 53%, $p<0.05$) and the spine (adults 52%, children 13%, $p<0.05$) (Fig. 3). The degree of pain reported was considerable, but quite variable. The mean pain score (on the 0 to 10 pain scale) for adults was 4.1 (range 1 to 8, ± 1.8), and 2.8 for children (range 1 to 7, ± 1.8) (Table 2). Adults had significantly more pain than children ($p<0.01$). In an effort to assess if

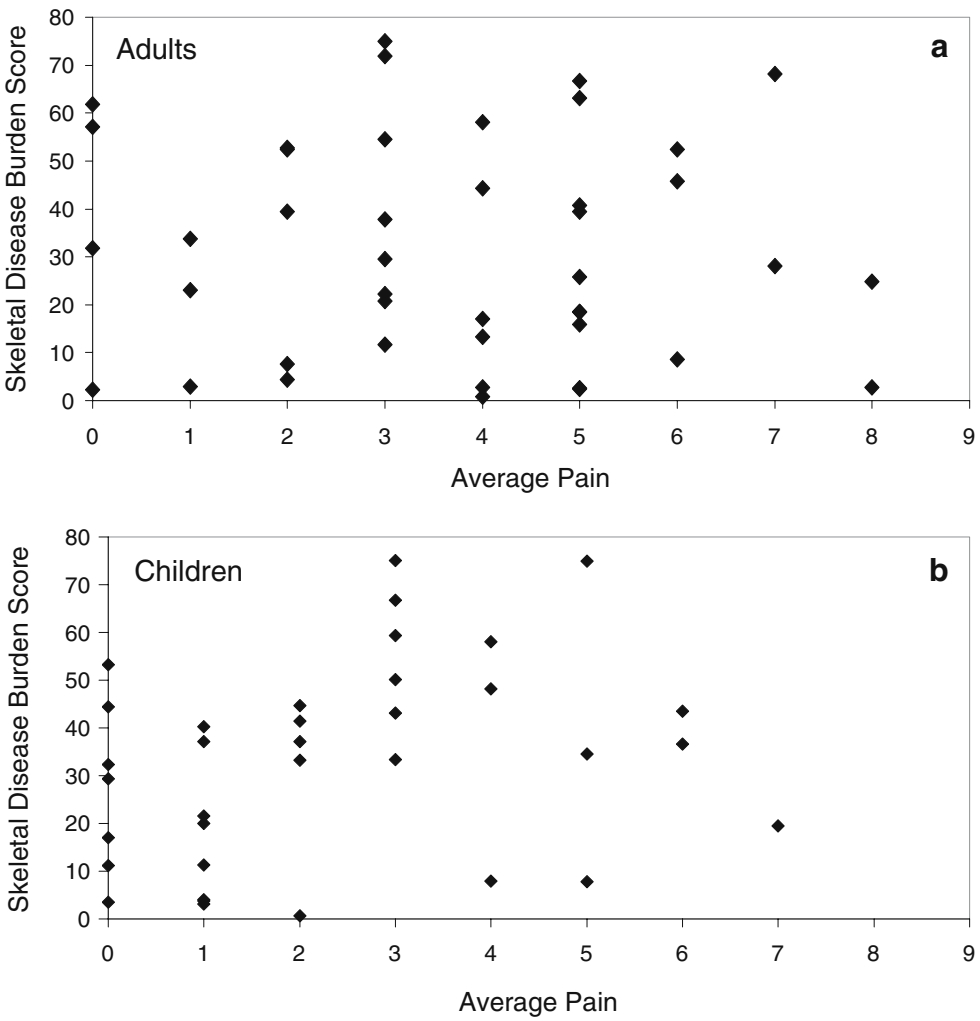

Fig. 3 Relationship between pain and the extent of fibrous dysplasia in adults and children. Adults are shown in panel **a**, and children in panel **b**. There was no relationship between the extent of FD (as assessed by the skeletal disease burden score) and the severity of pain

Table 2 Pain severity, treatment and response to treatment

	Adults		Children	
Mean pain scores				
Average pain	4.1 *		2.8	
Treatments in subjects reporting pain:	% that used treatment	% relief reported	% that used treatment	% relief reported
No treatment	26%		44%	
NSAIDs	57%	56%	56%	50%
Narcotics	26%	47%	17%	90%
Bisphosphonates/Other	26%	73%	17%	75%
Alternative Treatments	17%	52%	11%	No report

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

pain prevalence was different in different age groups, we examined the prevalence of pain in age group increments of 10 years (Table 3). No pain was reported by children less than 10 years old, while 50–60% of those age 11 through 30 reported pain and 85–100% of the patients over 31 years of age experiencing pain.

There was no correlation between pain prevalence and gender, phosphate wasting, vitamin D deficiency (serum vitamin D level <32 ng/ml was used as a cutoff for the diagnosis of vitamin D deficiency), or any endocrinopathy in children. Growth hormone excess was positively correlated with pain prevalence at FD sites in adults ($p=0.031$). Surprisingly, there was no relationship between the extent of bone involved with FD, as measured by the skeletal disease burden score, and pain severity (Fig. 3a and b).

Patients reported using a variety of treatments to control pain (Table 2). NSAIDs were most commonly used (57% of adults and 56% of children who had pain). Some subjects reported using more than one treatment. There was a trend for children who reported pain to be less likely to be treated for pain than adults ($p=0.21$). The bisphosphonate/other category includes bisphosphonates, muscle relaxants, and antidepressant drugs. The alternative medicine category includes chondroitin and glucosamine, acupuncture, transcutaneous electrical nerve stimulation (TENS), application of heat, exercise, physical therapy and stretching. There was no significant difference between the amount of relief reported from each treatment category by adults or children.

Table 3 Prevalence of pain in age groups

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

Discussion

This study was in part prompted by the frequent observation and report from patients that it is was common for children to be pain-free, but later developed pain as they transitioned into adulthood even while the disease was becoming clinically quiescent in terms of fractures. To better define this, we quantified pain at radiographically documented sites of FD involvement. As previously shown [30], we found that the lower extremities and the skull base were the sites most commonly involved with FD, but that there was a greater prevalence of FD in the spine in adults compared to children, suggesting that spine was a site for the appearance of new FD lesions. We found that pain was more prevalent at all FD sites in adults compared to children, and that the lower extremity and the spine were the sites most likely to be painful in adults. Pain was not only more common in adults, but likely to be more intense. Pain was absent below the age of ten, and quite likely to be present after the age of 30. Since pain reporting in the age group <10 was by parental proxy, and children this age often deny pain or experience pain as being "tired," it is possible that we failed to detect pain in this group. However, it has been shown that in patients with chronic pain, pain and quality of life reporting by parents of children with chronic pain is reliable [31].

While craniofacial and rib FD can often be quite painful, it was surprising that less than half of the subjects with craniofacial and rib FD reported pain at these sites. Perhaps even more surprising was the absence of any correlation between pain severity and extent of disease. In fact, of 11 patients with nearly total body disease (panostotic FD); five had an average pain score of 2 or less (on a scale of 10). What accounts for this is not known. The mechanisms of

pain are extremely complex [32]; there are psychological effects, environmental factors, and wide individual differences in the pain perception. Clearly, there is much to be learned about the mechanisms of pain in FD, and in bone pain in general. Although the pain literature suggests that women in general have lower thresholds for pain [33], there was no gender difference in pain reports of subjects in this study. The positive correlation between GH excess and the report of pain suggests that exposure to excess GH may play a role in generating pain.

This study found that in spite of clinically significant pain, 26% of the adults and 44% of the children were not treated for pain. Unfortunately, under-treatment of chronic pain is a persistent problem in health care delivery, especially in children [28, 34, 35]. Many of the subjects in this study were referred to and enrolled in a study of bisphosphonates for the treatment of FD. One of the endpoints of that study was pain control, and involved adjusting the medical regimen of the patients while on study drug (alendronate vs. placebo). Therefore, adjusting the medical regimen that subjects were on at enrollment to maximize pain control and assessment of the adequacy of pain control by medication group was not a goal of this study.

In the group studied, NSAIDs were the drugs most commonly used to treat pain, and in most cases NSAIDs alone were effective at relieving pain. Often combining NSAIDs with non-pharmacologic measures, such as heat, massage, etc., can be adequate for relief. Our approach in clinical practice, outside of the context of therapeutic trial, when NSAIDs are not adequate, is to use intravenous bisphosphonates. A number of studies have shown that the administration of intravenous bisphosphonates relieve the pain of FD [17, 36–40]. The use of bisphosphonates in this group of patients was low, in part, because many of these patients were referred for a placebo-controlled study of alendronate for the treatment of FD, and previous bisphosphonate use was an exclusion criterion.

These results must be interpreted in light of possible referral bias. Greater than 80% of the subjects in the study were self-referred via the internet. This may reflect lack of what was felt to be adequate care, and thus the need for self-referral. In addition, as a tertiary referral center, there is a bias towards seeing patients with more severe disease, both in terms of a greater burden of FD, as well as more prevalent endocrine dysfunction. Yet, as seen in Fig. 1, the spectrum of disease seen in this study was broad and included patients with little skeletal disease.

Pain is a common feature of FD that is often times untreated or under-treated. Contrary to prevailing thought, the prevalence of pain in the group of adult subjects was greater and more severe than in the group of children, and pain severity did not correlate with the burden of FD. Pain control is a priority for patients and families of children with FD, and inadequate pain control is one of the primary factors negatively affecting the health-related quality of life in both adults and children with FD[20]. A step-wise approach to pain management, starting with NSAIDS is prudent. Intravenous bisphosphonates are often useful, but some pain may also require use of narcotics. Patients frequently report under treatment and are often labeled as "drug seeking" when narcotic analgesics are necessary for pain relief. Health care professionals need to be aware of the pain their patients with FD experience, and to assess and address it at every patient interaction.

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