Pain in fibrous dysplasia: relationship with anatomical and clinical features

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Background and purpose — Fibrous dysplasia (FD) is a rare bone disorder associated with pain, deformities, and pathological fractures. The pathophysiological mechanism of FD-related pain remains ill-understood. We evaluated the degree of pain and the potential contributory factors in 2 patient cohorts from Austria and the Netherlands.

Patients and methods — 197 patients (16–85 years) with FD (Graz n = 105, Leiden n = 92) completed a survey concerning the presence and severity of pain at their FD site. Sex, age, type of FD, and localization of FD lesions were examined for a relationship with the presence and severity of pain.

Results — Of 197 patients from the combined cohort (61% female, mean age 49 (SD 16) years, 76% monostotic) who completed the questionnaires, 91 (46%) reported pain at sites of FD lesions. Severity of pain was higher in patients with lesions of the lower extremities and ribs compared with upper extremity or craniofacial lesions. Severe subtypes of FD (polyostotic/McCune–Albright syndrome) were more often associated with pain, often severe.

Interpretation — Our data suggest that almost 50% of patients with FD report pain at FD sites, thus representing a major clinical manifestation of the disorder, importantly also in patients with monostotic lesions. Lesions in lower extremities and ribs were more painful.

Fibrous dysplasia (FD) is a congenital, non-inherited rare bone disorder, characterized by replacement of healthy bone by fibrous tissue limited to one bone (monostotic FD) or extending to multiple bones (polyostotic FD). Bony lesions may be single, asymptomatic, and accidentally detected at routine radiological examination, but may also be present in multiple skeletal sites and responsible for a wide range of clinical symptoms, predominantly bone pain, bone deformities, and pathological fractures (Harris et al. 1962). In severe cases skeletal manifestations may also be associated with extraskeletal manifestations in the form endocrinopathies or café-au-lait skin patches in McCune–Albright syndrome or intramuscular myxomas in Mazabraud's syndrome.

In a previous study we have shown that pain is a major determinant of impaired quality of life in patients with FD (Majoor et al. 2017c). It has also been shown that FD pain is negatively age-related, suggesting that FD lesions may undergo age-related changes with less prevalence and less severity of pain, as a patient gets older (Kelly et al. 2008 , Robinson et al. 2016). This notion is further supported by studies reporting lower fracture rates, denser and more sclerotic changes on plain radiography of FD lesions, and fewer characteristic histologic features of FD such as fibrotic changes and ill-woven bone texture in older patients (Leet et al. 2004, Kuznetsov et al. 2008). Despite this tendency for FD to become more quiescent as a patient ages, pain has also been reported to increase over time in some patients, possibly due to secondary arthritic changes in adjacent joints (Kelly et al. 2008). Management of pain remains problematic, as its underlying mechanism is unknown.

We examined the prevalence and severity of pain in a combined cohort of 197 patients with FD from 2 specialized bone centers in Austria and the Netherlands. A further aim of the study was to examine the relationship between a

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number of clinical and demographic factors and the presence and severity of pain.

Patients and methods

Study design

This study addresses the prevalence and severity of pain in FD and was conducted using a cross-sectional study design, including all patients with an established diagnosis of FD seen at the Medical University of Graz (MUG) between 1984 and 2016 and at the Leiden University Medical Center (LUMC) between 2012 and 2015 as identified from the respective centers' hospital registries. The diagnosis of PFD was established on the basis of clinical and radiological features, with occasional histological and genetic confirmation. All identified patients were invited to take part in the study either by means of an interview (Graz cohort) or by completing a validated questionnaire (Leiden cohort). Additional demographic, clinical, and radiologic data were retrieved from the patients' medical records and the 2 cohorts were combined into 1 large single cohort before analysis of data.

Patients and methods

146 patients who were evaluated and treated at the MUG between 1984 and 2016 were approached by phone for an interview on the presence of pain on the basis of the validated Pain Numeric Rating Scale (PNRS), a standardized 11-step pain score validated for use in the assessment of pain in clinical trials (Hartrick et al. 2003).

138 patients who were seen at the outpatient clinic of the LUMC over a period of 3 years before the start of the study were invited by mail to complete the Brief Pain Inventory (BPI) questionnaire as previously described (Majoor et al. 2017c). Patients who did not respond to the questionnaires by mail were contacted by phone, with a maximum 2 attempts in case of no answer.

Of 146 patients from the MUG cohort who were contacted by phone, 105 (72%) agreed to be interviewed by phone and of the 138 patients from the LUMC cohort who were invited to take part in the study by mail, 92 (67%) returned a completed BPI, resulting in a combined cohort of 197 patients in whom data on pain was available for analysis.

Collected data included data on the presence of absence of pain (yes/no) and when present, the severity of current pain on a scale ranging from 0 to 10 with 0 indicating "no pain" and 10 indicating "the worst possible pain imaginable." Data on sex, age, and type of FD (monostotic/polyostotic/McCune–Albright syndrome/Mazabraud syndrome) were retrieved from the patients' medical records at the respective medical centers. Data were also retrieved on the localizations of FD lesions including the craniofacial region, upper extremity, lower extremity including the pelvis, ribs, and spine. The extent of skeletal disease, as measured by the skeletal burden score (Collins et al. 2005), was available only in one center and therefore not included in the analysis.

Statistics

Statistical analysis was performed using SPSS Statistics 23.0 (IBM Corp, Armonk, NY, USA). Results are presented as mean (SD) or as median (intermediate range) and in the case of categorical data as percentages. Difference in pain between FD localizations (e.g., craniofacial, upper extremity, lower extremity, ribs, and spine) was assessed using the ANOVA test. Only monostotic patients were included in this sub-analysis in order to evaluate a potential difference in pain symptoms between different FD localizations. 5 patients with monostotic disease of the spine were excluded from this analysis due to low numbers. Other potential risk factors (e.g., sex, age, type of FD) were analyzed using logistic regression analysis (results presented as OR, p-value) for the presence of pain (yes/no), and with linear regression analysis (results presented as B-coefficient per degree of pain on VAS, p-value) for the extent of current pain on a scale from 0 to 10. Both analyses were primarily performed using univariable analysis followed by a multivariable analysis.

Ethics, funding, and potential conflicts of interest

Ethical approval was obtained from the Medical Ethics Committee of both centers participating in the study. This research was funded by a research grant from the Bontius Foundation of the Leiden University Medical Center for research into Fibrous Dysplasia. The authors have declared that they have no conflict of interest.

Results

Patient characteristics (Table 1)

Women predominated (120 women vs. 77 men). The majority of the patients (98%) were adults and all patients were skeletally mature (range 16–85 years). Mean age at the time of pain assessment was 49 years (SD 16), and mean overall follow-up was 16 years (SD 11). The majority of patients (76%) had monostotic FD, 20% had polyostotic FD, 5% had McCune–Albright syndrome, and 3% had Mazabraud's syndrome. In the whole cohort, the lower extremity was the most common localization of FD (52%), followed by the craniofacial region (26%), ribs (19%), upper extremity (16%), and spine (11%). Data on medical and surgical treatment were not used in the analysis of factors potentially affecting presence or severity of pain, due to the heterogeneity in agents, doses, schedules, and duration of use of these agents in this combined FD cohort.

Differences between the Dutch and Austrian FD cohorts (Table 1)

Patients from the LUMC cohort were younger compared with patients from the MUG cohort. The LUMC cohort also

Table 1. Cohort characteristics and differences between the two cohorts. Data pertaining to localization of FD lesions included the multiple lesions of polyostotic patients

	Austrian	Dutch	P-value	Total
Invited patients	146	138		284
Included patients	105	92		197
response rate (%)	71.9	66.7		69.4
Women/men	60/45	60/32	0.2	120/77
Age [a]	51.5 (16.4)	46.1 (15.3)	0.02	49.0 (16.1)
Follow-up [a]	15.1 (7.8)	16.7 (14.1)	0.3	15.8 (11.3)
Type of FD, n (%)				
Monostotic	90 (86)	58 (63)	< 0.001	149 (76)
Polyostotic	12 ()	26 (28)	< 0.001	39 (20)
McCune-Albright	1 (1)	8 (9)	< 0.001	9 (5)
Mazabraud's syndrome, n (%)	1 (1)	5 (5)	0.1	6 (3)
Localization of FD, n (%)				
Craniofacial	29 (28)	22 (24)	0.6	51 (26)
Upper extremity	24 (23)	8 (9)	0.1	32 (16)
Lower extremity	63 (60)	40 (45)	0.004	103 (52)
Ribs	27 (26)	11 (3)	0.003	38 (19)
Spine	11 (11)	11 (13)	0.9	22 (11)

[a] Mean (SD) years

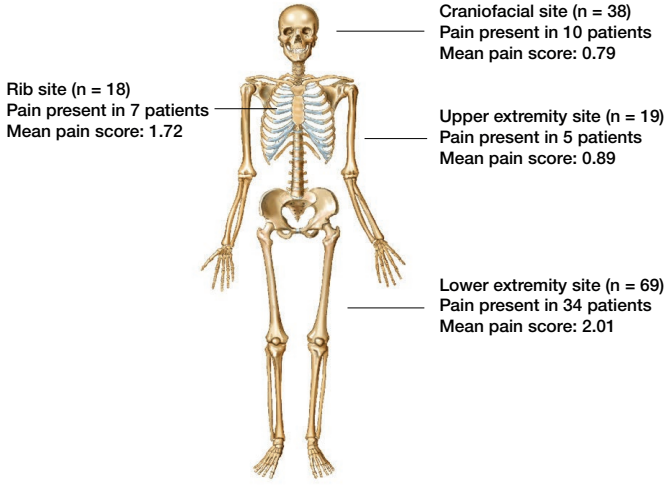

Figure 1. Presence and severity of pain in monostotic FD sites (n = 144). The presence of pain (yes/no) and the mean pain scores in the group of monostotic patients is highest in patients with lesions of the lower extremity and lowest in patients with craniofacial FD.

Table 2. Factors that may contribute to pain in a combined cohort of 197 patients with FD. Possible risk factors for the presence pain were analyzed with logistic regression analysis (odds ratio, OR) and for the severity of pain with linear regression analysis (B-coefficient (B) per 1 degree of pain on VAS score)

	Sex		Age		Type of FD	
	OR/B	p-value	OR/B	p-value	OR/B	p-value
Pain (yes/no) (OR)						
Univariable analysis	0.57	0.06	0.99	0.5	0.36	0.001
Multivariable analysis	0.56	0.06	0.99	0.6	0.36	0.001
Severity of pain (B)						
Univariable analysis	0.67	0.08	0.003	0.8	1.07	0.002
Multivariable analysis	0.65	0.08	0.000	1.0	1.05	0.002

included more patients with polyostotic FD and McCune–Albright syndrome than the MUG cohort. Other demographic or clinical features were similar between the 2 cohorts.

Differences between responders and non-responders

Distribution of age, sex, and type of FD was similar between responders and non-responders from the MUG cohort. Within the LUMC cohort, type of FD and age distribution were similar between responders and non-responders. However, there was a greater proportion of women who completed the questionnaire in the LUMC cohort.

Prevalence and severity of pain

Of the 197 survey responders, 46% reported having pain at the site of their FD lesions (Figure). In the group of patients reporting having pain at the time of the survey, the median pain score was 4 (1–9). A higher proportion of patients with monostotic lesions of the lower extremity (49%) or ribs (39%) reported having pain (yes/no) compared with patients who had monostotic lesions of the upper extremity (26%) or craniofacial region (26%), although these differences in prevalence of pain were not statistically significant (p = 0.09). In contrast, there was a statistically significant difference (p = 0.05) in severity of pain between monostotic lesions depending on their localization. Pain was thus reported to be most severe in patients with monostotic lesions of the lower extremity, mean 2.0 (SD 2.7), followed by ribs, mean 1.7 (SD 2.5), upper extremity mean 0.9 (SD 2.0), and lastly craniofacial lesions, mean 0.8 (SD 1.7).

Potential risk factors for pain in fibrous dysplasia (Table 2)

Univariable regression analysis showed that only the more severe types of FD were predictive for both the presence (OR 0.36, p = 0.001) and severity of pain (B-coefficient 1.07, p = 0.002). There was no relationship observed between sex or age and the presence or severity of reported pain. After correction for age and sex, the severe type of FD remained a statistically significant risk factor for the presence and severity of pain in multivariable analysis (respectively OR 0.36, p = 0.001 and B-coefficient 1.0, p = 0.002). This difference is clinically relevant, as patients with polyostotic FD are at risk of scoring 1 degree higher on VAS compared with patients with monostotic disease, as are patients with McCune–Albright of scoring 1 degree higher compared with polyostotic patients.

Discussion

This survey on the prevalence and severity of pain in patients with FD from a large combined cohort from Austria and the Netherlands highlights the importance of this clinical manifestation of FD, with nearly half of the patients reporting having pain at the site of their FD lesions with a mean score of 4 out of a maximum of 10. In patients with monostotic lesions, pain was more often present and was more severe when the FD lesions were localized in the lower extremities or ribs compared with lesions localized in the craniofacial region or upper extremities. Severity of type of FD was predictive for the presence of pain and for its severity as expressed by higher pain scores.

An 81% prevalence of pain has been reported among adult patients with FD, although a lesser prevalence of 49%, similar to our prevalence, was reported in a more recent study (Kelly et al. 2008, Benhamou et al. 2016). This discrepancy in findings might be explained by the composition of our combined cohort in which a high proportion of patients had monostotic FD (76%). 2 studies addressing Quality of Life (QoL) in FD have shown that patients with FD have lower scores in the bodily pain domain of the SF-36 compared with the general population (Kelly et al. 2005, Majoor et al. 2017c). We hypothesized that patients with limited monostotic FD would report less pain than those with more extensive polyostotic disease, or those with the more severe McCune–Albright syndrome. Similarly to previous reports, we found a prognostic value of type of FD (polyostotic/McCune–Albright syndrome) as regards quality of life and severity of pain.

Monostotic patients with lesions of the lower extremities demonstrated the highest prevalence and severity of pain compared with lesions localized elsewhere in the skeleton as also reported by Kelly et al. (2008). Weight-bearing forces acting on the lower extremities combined with the poor quality of FD bone may result in deformities and pathological fractures, and thus a higher prevalence and severity of pain, particularly in the case of the femur (Nakashima et al. 1984, Leet et al. 2004, DiCaprio and Enneking 2005, Benhamou et al. 2016). FD lesions in bones of the lower extremities are also less likely to benefit fully from surgical interventions compared with lesions of non-weight bearing bones (DiCaprio and Enneking 2005, Majoor et al. 2017a). Although severe pain has been described in patients with craniofacial FD, we found a low prevalence and severity of pain in patients with craniofacial FD as reported by others (Chao and Katznelson 2008, Kelly et al. 2008, Makitie et al. 2008).

Extensive skeletal involvement of FD, as measured by the Skeletal Burden Score, has been reported to be associated with high circulating levels of bone turnover markers and of FGF-23 and with impaired QoL, including pain, in a number of studies (Collins et al. 2005, Kelly et al. 2008, Majoor et al. 2017b). This suggests that the extent of FD lesions would be a major cause for the presence and severity of pain in patients with demonstrated high skeletal burden scores as seen in polyostotic FD and McCune–Albright syndrome. However, Majoor et al. (2017c) found no association between skeletal burden scores and pain. Other factors than extent of FD lesions, such as anatomical location and age-related changes, may also be responsible for the prevalence and severity of pain in patients with FD, also in those with the milder monostotic types, particularly of the lower extremities (Kelly et al. 2008). Indeed, we found that localization of FD lesions was a main determinant of the presence and severity of pain. Whereas the precise mechanism of pain in FD remains elusive, extra-skeletal factors may also play a role, as observed in patients with McCune–Albright syndrome, who report more pain than patients with polyostotic FD but with no extra-skeletal manifestations of FD. Neurogenic involvement may also play a role as alluded to by Chapurlat et al. (2012). These results imply that small, monostotic lesions may be associated with severe pain depending on their anatomical location. For example, a patient with a small monostotic lesion of the proximal femur may experience more pain than a patient with extensive disease of the humerus. The potential contributory role of extra-skeletal factors in the pathogenesis of pain in FD may help explain non-response or poor response to treatment with bone-modifying agents such as bisphosphonates.

In our patients, age did not appear to influence the prevalence and severity of pain. However, Kelly et al. (2008) showed a higher prevalence and severity of pain in adults than in children with FD. The difference in prevalence and severity of pain before and after growth is completed suggests a contributing role for factors associated with growth in the pathophysiology of pain in FD.

Women are generally believed to experience more pain than men (Berkley 1997). Similar to the report by Kelly et al. (2008), we found no sex difference in the severity of pain, although female FD patients in our cohort did report a higher prevalence of pain.

Strengths and limitations

One of the main strengths of our study is the inclusion of patients with different types of FD from 2 relatively large cohorts from different countries in whom data on the prevalence of pain and its severity were specifically and individually collected by interview or questionnaire. A further strength of the study is the predominance of patients with monostotic FD, compared with earlier studies including a lesser proportion of these patients, which allowed us to determine the relevance of anatomical localization of isolated FD lesions in the prevalence and severity of pain.

Our study has also a number of limitations, including the use of 2 different, albeit comparable questionnaires, to calculate pain scores and the single time-point measurement of pain, as opposed to repeated measurements, which might have

allowed us to demonstrate a time pattern for the pain. Because we included patients from two specialized bone-tumor centers, there might be a selection within our cohort towards the more severely affected FD patients and thus the patients with more pain. The hypothesis that the majority of monostotic FD patients have asymptomatic disease and will therefore never consult a physician, in combination with the possibility that painful patients are more accessible to participate in a study, might enhance this effect. However, due to the rarity of FD, this disorder is often, if not always, treated in specialized centers. Our cohort represents one of the largest cohorts of patients with FD ever reported, and more specifically the general population of FD patients that will seek counsel and/or that need treatment. Lastly, we did not include data on previous surgery and treatment with bisphosphonates in our analysis of pain in these patients.

Conclusion

We found that although the more severe types of FD (polyostotic/McCune–Albright syndrome) are predictive for presence and severity of pain, these are also determined by the localization of the lesions in the weight-bearing lower extremity and the rib lesions in patients with monostotic FD. These results have clinical implications in the management of patients with FD, as they highlight the fact that small, monostotic lesions may be the source of severe pain depending on their anatomical location.

BCJM and NMA-D were involved in acquisition, analysis, and interpretation of the data and in drafting the manuscript. ET, WM-E, AF, NAT-H, BL, PDSD, and AL were involved in acquisition and interpretation of the data and in drafting the manuscript.

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