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Risk factors for fracture in patients with fibrous dysplasia of the proximal femur

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Abstract

Objective: The primary aim of this retrospective observational clinical study was to explore the risk factors for fracture in patients with fibrous dysplasia (FD) of the proximal femur.

Methods: We investigated body mass index, bilateral radiographs on both sides, femoral neck shaft angle measurements, and markers of bone metabolism in patients with FD of the proximal femur according to whether or not they had sustained a hip fracture. Nine clinical parameters (age, sex, clinical classification, anatomic classification, femoral neck shaft angle, and procollagen type I N-terminal propeptide, C-terminal telopeptide of type I collagen, and osteocalcin levels) were selected for univariate analysis. Factors that were significant in univariate analysis were then subjected to multivariate logistic analysis.

Results: Clinical classification, anatomic classification, femoral neck shaft angle, and the osteocalcin level were identified to be statistically significant risk factors for fracture in univariate analysis. Anatomic classification, femoral neck shaft angle, and the osteocalcin level remained significant risk factors in multivariate analysis.

Conclusions: Anatomic classification, femoral neck shaft angle, and the osteocalcin level are important risk factors for fracture in patients with FD of the proximal femur and could be used to guide implementation of a fracture prevention strategy in these patients.

Keywords

Fibrous dysplasia, proximal femur, fracture, risk factor, anatomic classification, femoral neck shaft angle, osteocalcin

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Introduction

Fibrous dysplasia (FD) is a rare, non-hereditary, benign intramedullary fibro-osseous lesion that was first described by Lichtenstein in 1938 and accounts for 2.5% of all bone injuries and 7% of all benign bone tumors.[1] Most cases of FD are diagnosed in childhood. The disease essentially stops progressing in adulthood but may continue to progress in a few patients, with both sexes equally affected.[2] At present, FD is believed to be caused by sporadic post-zygotic activating mutations in GNAS, resulting in dysregulated GαS protein signaling in affected tissues.[3] This leads to defects in osteoblast differentiation, with fibrous tissue replacing normal bone.[4] The disease can be classified as monostotic fibrous dysplasia (MFD), polyostotic fibrous dysplasia (PFD), or McCune-Albright syndrome, which is PFD complicated by endocrine disease. The main clinical manifestations are pain, deformities, and fractures, while patients with McCune-Albright syndrome present with endocrine disease and café au lait spots.[5,6] Diagnosis of FD depends mainly on imaging and clinical manifestations. The disease is radiologically characterized by homogeneous diffuse radiopacity with a ground glass appearance in continuity.[7] For patients who cannot be diagnosed by imaging, puncture biopsy can be performed with the help of pathological findings. FD may occur in any bone in the body. In cases of MFD, the most common sites are the maxilla, proximal femur, tibia, humerus, ribs, skull, radius, and iliac bone, while in cases of PFD, the most common site is the proximal femur.[8] Pathological fracture is one of the most common complications of FD at this site. Stress is highly concentrated at the proximal femur because of its particular anatomic structure. Therefore, the proximal femur is the site most prone to fracture. At present, prediction of the probability of fracture in patients with FD of the proximal femur is difficult and affects treatment planning. The aim of this study was to identify risk factors for fracture in patients with FD of the proximal femur.

Methods

Study design and patient selection. This retrospective observational clinical study included patients who were diagnosed to have FD of the proximal femur in the Department of Orthopaedics at The 960th Hospital of the PLA Joint Logistics Support Force between January 2016 and January 2021. The inclusion criteria were as follows: a radiological or pathological diagnosis of FD; lesion area involving the proximal femur; and follow-up duration longer than 12 months. Patients with concomitant neoplastic bone disease, those with incomplete case data, and those who smoked or consumed alcohol were excluded.

The study was approved by our institutional ethics committee (approval number 2021-148; date of approval, 28 December 2021). All experimental procedures were conducted in accordance with the Declaration of Helsinki (World Medical Association, as amended 2013) and the Health Insurance Portability and Accountability Act. Written informed consent was not necessary in view of the retrospective design of the study and the lack of impact on the health and financial status of patients. All patient details have been de-identified. The reporting of the study conforms to the STROBE guidelines.[9]

Information on body mass index (BMI), findings on bilateral hip radiographs, femoral neck shaft angle, and biomarkers of bone metabolism at the time of diagnosis was collected. The patients were divided into a fracture group and non-fracture group based on findings on bilateral hip radiographs and compared for age, sex,

BMI, and clinical classification (MFD or PFD).

Anatomic classification. The bilateral anteroposterior radiographs of the hip joint obtained for all patients on admission to hospital were reviewed. Using Guille's classification,[10] the lesions seen were classified as type A (lesion covering the entire proximal femur, Figure 1a), type B (lesion involving only the femoral neck, Figure 1b), type C (lesion involving the femoral neck and intertrochanteric region, Figure 1c), or type D (lesion involving only the intertrochanteric area, Figure 1d). To facilitate observation and in view of the small numbers of type B, C, and D lesions, we divided the patients into two groups according to anatomic classification. Patients with type A lesions (involving the whole proximal femur) were designated as type 1 and those with type B, C, or D lesions (involving only part of the proximal femur) were designated as type 2.

Measurement of femoral neck shaft angles. The femoral neck shaft angle was measured retrospectively for all patients on bilateral anteroposterior plain radiographs of the hip joint by two radiologists with 5 and 10 years of radiology experience who were working independently and blinded to all clinical information. The normal range of femoral neck shaft angle values is from 120° to 140° in adults and from 135° to 145° in children.

Measurement of bone biomarker levels. Procollagen type 1 N-terminal propeptide (P1NP), C-terminal telopeptide of type I collagen (β-CTx), and osteocalcin levels were measured by an electrochemiluminescence method using a Cobas e601 analyzer (Roche, Berlin, Germany). The following normal reference values were used:

P1NP: premenopausal women, 8.53 to 64.32 μg/L; postmenopausal women, 21.32 to 112.8 μg/L; men, 9.06 to 72.24 μg/L
β-CTx: premenopausal women, 0.068 to 0.68 μg/L; postmenopausal women, 0.131 to 0.9 μg/L; men, 0.043 to 0.783 μg/L
OST: premenopausal women, 11 to 43 μg/L; postmenopausal women, 15 to 46 μg/L; men aged 18 to 30 years, 24 to 70 μg/L; men aged 31 to 50 years, 14 to 42 μg/L; men aged 51 to 70 years, 14 to 46 μg/L.

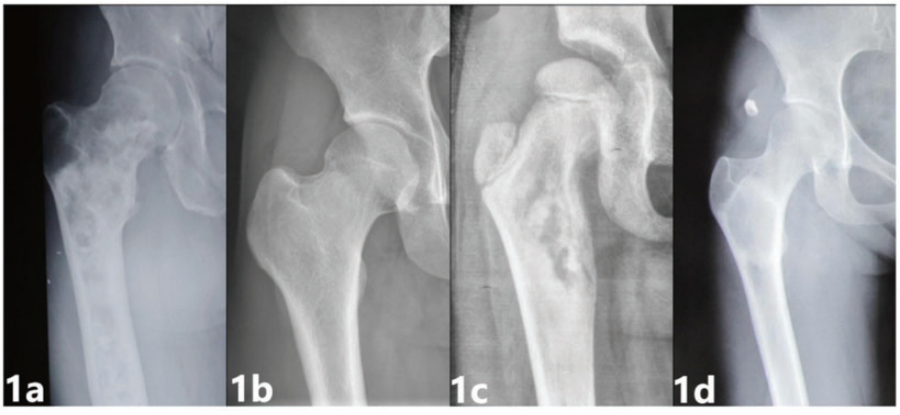

Figure 1. Anatomic classification of fibrous dysplasia of the proximal femur based on findings on radiographs. (a) Type A: the lesion covers the entire proximal femur. (b) Type B: the lesion only involves the femoral neck. (c) Type C: the lesion involves the femoral neck and intertrochanteric region and (d) Type D: the lesion involves only the intertrochanteric area.

Statistical analysis

Continuous variables were compared between groups using the Student's *t*-test and categorical variables using the chi-squared test. First, potential risk factors were analyzed by univariate analysis. Factors that were significant in univariate analysis were then analyzed by multivariate logistic analysis. All statistical analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). A *P*-value ≤ 0.05 was considered statistically significant.

Results

Patient demographic and clinical characteristics

Forty-nine patients (27 male, 22 female) were diagnosed to have FD of the proximal femur during the study period. The mean patient age was 30.8 ± 14.7 years (range 12 to 74). Twenty-seven patients had MFD and 22 had PFD. In patients who experienced fractures, the mean duration of follow-up after the most recent fracture was 32.41 ± 15.81 months (range 10–60). The patient demographic and clinical characteristics are shown in Table 1. There was a statistically significant difference in the clinical classification between the fracture group and the non-fracture group ($P < 0.01$) but not in age, sex, or BMI.

Anatomic classification, femoral neck shaft angle, and bone biomarker levels are shown according to fracture status in Table 1 and Table 2. The between-group difference in anatomic classification was statistically significant (odds ratio 8.622, $P < 0.05$), as was the femoral neck shaft angle (odds ratio 0.961, $P < 0.05$). There was no statistically significant between-group difference in the P1NP or β-CTx level; however, there was a significant difference in the osteocalcin level between the groups (odds ratio 0.006, $P < 0.05$).

Multivariate logistic analysis of possible predictors of fracture

Clinical classification, anatomic classification, femoral neck shaft angle, and the osteocalcin level were statistically significant prognostic factors in univariate analysis and were entered into the multivariate logistic analysis. As shown in Table 3, anatomic classification, femoral neck shaft angle, and osteocalcin level remained statistically significant In multivariate logistic analysis ($P < 0.05$).

Table 1. Demographic and clinical variables according to fracture status.

Variable	Fracture group	Non-fracture group	t or χ^2	*P*-value
n	17	32		
Age (years)	29.88 ± 13.85	31.40 ± 15.10	$t = 3.39$	0.736
Sex (male, %)	9 (52.94%)	18 (56.25%)	$\chi^2 = 0.49$	0.852
BMI (kg/m^2)	23.98 ± 3.89	22.04 ± 3.04	$t = 1.89$	0.93
Clinical classification (MFD, %)	12 (70.59%)	15 (46.88%)	$\chi^2 = 4.59$	0.014
Anatomic classification (type 1, %)	14 (82.35%)	12 (37.5%)	$\chi^2 = 7.257$	0.007
Femoral neck shaft angle (normal, %)	23.98 ± 3.89	22.04 ± 3.04	$t = 4.121$	0.009
P1NP (normal, %)	3 (17.65%)	10 (31.25%)	$t = 1.054$	0.305
β-CTx (normal, %)	3 (17.65%)	11 (34.38%)	$t = 1.522$	0.217
Osteocalcin (normal, %)	1 (5.88%)	14 (43.75%)	$t = 7.495$	0.006

β-CTx, C-terminal telopeptide of type I collagen; BMI, body mass index; MFD, monostotic fibrous dysplasia; P1NP, procollagen type I N-terminal propeptide.

Table 2. Variables identified to be significant risk factors for fracture according to sex and BMI.

	Variable	Fracture group	Non-fracture group	*P*-value
n		9	18	
Male	P1NP (μg/L)	546.72 ± 140.73	401.02 ± 106.37	0.649
	β-CTx (μg/L)	1.30 ± 0.28	1.46 ± 0.25	0.704
	OST (μg/L)	102.14 ± 11.17	85.46 ± 15.68	0.047
	Femoral neck shaft angle (°)	109.67 ± 8.27	136.11 ± 1.57	0.000
n		8	14	
Female	P1NP (μg/L)	454.76 ± 155.78	331.63 ± 93.92	0.479
	β-CTx (μg/L)	1.39 ± 0.71	1.12 ± 0.18	0.399
	Osteocalcin (μg/L)	129.91 ± 30.16	97.01 ± 23.59	0.045
	Femoral neck shaft angle (°)	105.13 ± 5.84	127.36 ± 7.63	0.031
n		6	23	
Normal BMI*	P1NP (μg/L)	388.86 ± 153.92	382.20 ± 83.87	0.971
	β-CTx (μg/L)	1.12 ± 0.27	1.40 ± 0.20	0.507
	Osteocalcin (μg/L)	95.32 ±2 2.69	96.14 ± 16.16	0.024
	Femoral neck shaft angle (°)	101.67 ± 5.36	132.13 ± 4.85	0.005
n		11	9	
Abnormal BMI	P1NP (μg/L)	565.95 ± 134.45	341.19 ± 146.03	0.273
	β-CTx (μg/L)	1.46 ± 0.25	1.09 ± 0.28	0.331
	Osteocalcin (μg/L)	126.05 ± 20.24	76.44 ± 24.39	0.036
	Femoral neck shaft angle (°)	110.73 ± 7.23	132.67 ± 0.67	0.014

*Normal BMI in China is defined as 18.5–23.9.
β-CTx, C-terminal telopeptide of type I collagen; BMI, body mass index; P1NP, procollagen type 1 N-terminal propeptide.

Table 3. Multivariate logistic analysis of risk factors for fracture in patients with fibrous dysplasia of the proximal femur.

Variable	B	SE	World	P-value	OR	95%CI
Clinical classification	−0.919	1.099	0.699	0.403	0.399	0.046–3.438
Anatomical classification	2.154	0.925	5.423	0.020	8.622	1.407–52.854
Femoral neck shaft angle	−0.40	0.18	2.525	0.026	0.961	0.928–0.995
Osteocalcin	−2.499	1.266	4.157	0.041	0.082	0.007–0.908

CI, confidence interval; OR, odds ratio.

Two representative cases

Figure 2 shows the imaging findings at the proximal femur for a 22-year-old girl who was hospitalized with a 3-year history of right thigh pain. Upon examination, the lesions only involved part of the proximal femur, the anatomic classification was type 2, and her osteocalcin level was within the normal range. The imaging examinations and pathological results indicated FD of the proximal femur. The patient had no fractures during 12 months of follow-up.

Figure 3 shows the imaging findings at the proximal femur for a 36-year-old woman who was admitted to hospital with a 10-month history of pain in the left femur. Examination revealed that the lesions covered the entire proximal femur, the anatomic classification was type 1, and her osteocalcin level was above the normal range. The imaging examinations and

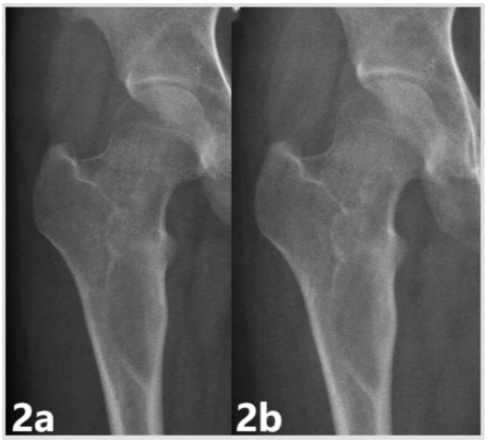

Figure 2. Radiographs for a patient with fibrous dysplasia of the proximal femur who did not develop a fracture. Radiographs obtained (a) at the time of diagnosis and (b) when the patient was rechecked. There was no fracture of the proximal femur.

pathological results indicated FD of the proximal femur. The patient sustained a fracture of the proximal femur during the third month of follow-up.

Discussion

Fracture is a serious complication of FD. The proximal femur is susceptible to deformities and fractures because of its particular anatomic position.[11] It is difficult to predict a fracture in patients with FD, and they are often not hospitalized until a fracture occurs, by which time they have missed the best opportunity for treatment. Therefore, early prediction of fractures in patients with FD involving the proximal femur is critical to be able to formulate the best treatment strategy and to reduce the incidence of the fractures that occur. Several investigators have devised treatment strategies for fractures in patients with FD of the proximal femur. However, there are no reports on risk factors for fracture in these patients with FD, so there are

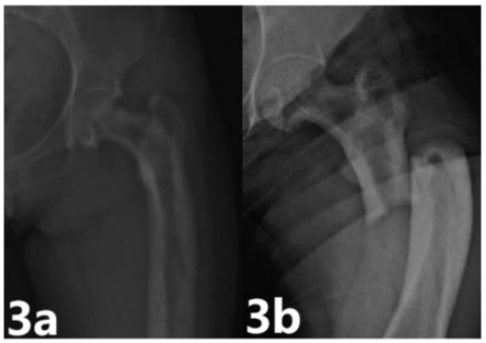

Figure 3. Radiographs for a patient with fibrous dysplasia of the proximal femur who sustained a fracture. (a) Radiograph showing that the lesion covered the entire proximal femur at the time of diagnosis. (b) Radiograph obtained when the patient was rechecked showing a fracture of the proximal femur.

no clear standards for prevention. Majoor et al. reviewed the surgical treatment methods used in 32 patients with FD of the proximal femur and their efficacy but did not discuss any risk factors for fractures in these patients.[12] Bian et al. retrospectively investigated the surgical treatment methods used, clinical outcomes, and reasons for revision in 26 children with FD of the proximal femur but did not investigate any risk factors for fracture in these patients.[13] Therefore, there is a need to identify the risk factors for fracture in these patients to be able to estimate the risk of fracture and develop preventative strategies.

Several investigators have developed classification systems for FD of the proximal femur. At present, there are three such systems, namely, the classifications developed by Guille et al,[10] Ippolito et al,[14] and Zhang et al.[15] In this study, we applied Guille's classification, which is simple to use. We found that most of the patients we included were type A and that the numbers of type B, C, and D cases were low. For research and observation purposes, we divided the patients into two types according to anatomic classification: type A

(involving the entire proximal femur) were designated as type 1 and type B, C and D (involving part of the proximal femur) were designated as type 2. In multivariate logistic analysis, there was a statistically significant difference in anatomic classification between the fracture group and the non-fracture group. Type 1 caused widespread bone destruction owing to the extensive nature of the lesions, and as the bone strength at the proximal femur decreased, supporting the weight of the upper body became more difficult and the incidence of fracture increased. Therefore, a type 1 anatomic classification is an important risk factor for fracture in patients with FD of the proximal femur.

At present, there are few studies on the relationship between the femoral neck shaft angle and fracture in patients with FD of the proximal femur. Furthermore, hip varus is believed to contribute to fractures of the proximal femur.[16] In a study of 37 cases of femoral neck fracture, it was found that the femoral neck shaft angle could serve as a predictor of the risk of stress fractures of the femoral head.[17] In our study, all patients underwent radiographic examinations of the hip joint and the femoral neck shaft angle was measured. We found that patients with FD of the proximal femur whose femoral neck shaft angle was not within the normal range were more likely to sustain a fracture than those in whom this angle is within the normal range. Therefore, a femoral neck shaft angle that is not within the normal range is another important risk factor for fractures in these patients.

Indices of bone metabolism are strong predictors of fracture risk. The osteocalcin level is widely used as an indicator of bone formation and absorption. Osteocalcin is the most abundant non-collagenous protein in bone and specifically expressed in osteoblasts.[18] It plays an important role in regulating bone calcium metabolism and is a novel biomarker that can be used to study bone metabolism. It can maintain homeostasis of bone mineralization, inhibit abnormal hydroxyapatite crystallization, and directly reflect the activity of osteoblasts and bone formation.[19] Osteocalcin is closely related to bone mineral density[20] and is an important marker of hip fracture risk.[21,22] Although osteocalcin is a marker of bone formation, it may also be released from the bone matrix during bone resorption. Therefore, the serum osteocalcin level can also be regarded as a marker of bone turnover.[23] In another study,[24] *Ost*-deficient mice were observed to develop strong bones. Therefore, it is considered that low osteocalcin levels are related to improved bone function, which indicates that osteocalcin is a negative regulator of bone formation; its expression in FD is generally higher than that in other lesions, so it may inhibit bone formation and contribute to poor fibers within the bone structure. Therefore, the higher the osteocalcin level, the lower the bone quality and higher the risk of fracture.

A previous study that followed 35 patients with FD for 14.2 years reported 172 fractures and noted that the peak age for fracture was 6 to 10 years, with a decrease thereafter.[25] In a retrospective study by Han et al., the peak age for fracture in patients with FD of the proximal femur was bimodal, with the first peak at 6 to 10 years of age and the second peak after the age of 36 years.[26] In a multicenter study of 14 patients with MFD of the proximal femur, half of the patients eventually developed fractures.[27] Many studies have identified low BMI to be a risk factor for fracture.[28,29] However, BMI was not found to be a statistically significant risk factor in our study. Other studies have found the risk of fracture to be significantly increased in patients with endocrine disease. Hyperthyroidism can increase the loss of bone mass and destruction of bone structure, thereby increasing the risk of fracture.[30,31]

This study has some limitations. First, there was a small number of patients who smoked or consumed alcohol who were not included in the study. However, the fracture rate can be affected by external factors, including the environment and behavior. Research in larger cohorts is needed in the future. We also need to study the pathophysiology of FD of the proximal femur in greater detail and design a comprehensive therapeutic regimen to prevent fractures in these patients.

Conclusion

Anatomic classification, femoral neck shaft angle, and the osteocalcin level are important risk factors for fracture in patients with FD of the proximal femur. Examination of these indices would be helpful in terms of guidance regarding fracture prevention strategies in these patients.

Author contributions

W.L. and X.Y. designed the research, conducted the clinical examinations, and drafted and revised the manuscript. M.X. and X.Y. analyzed the patients' images. W.L. organized the data and generated the figures and tables. All authors contributed to the article and approved the submitted version.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declare that they have no conflict of interest.

Ethics statement

The study was approved by the Institutional Ethics Committee of The 960th Hospital of the PLA Joint Logistics Support Force (approval number 2021-148; date of approval, 28 December 2021). All experimental procedures were conducted in accordance with the Declaration of Helsinki (World Medical Association, as amended 2013) and the Health Insurance Portability and Accountability Act. Written informed consent was not necessary in view of the retrospective design of the study and the lack of impact on the health and financial status of patients.

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