The Predictive Factors of Fracture in Patients with Fibrous Dysplasia of Proximal Femur

Wenzheng Liu
Shandong University of Traditional Chinese Medicine

Xiuchun Yu (13969132190@qq.com)
Department of Orthopedics, the 960th Hospital of the PLA Joint Logistics Support Force

Ming Xu
Department of Orthopedics, the 960th Hospital of the PLA Joint Logistics Support Force

Research Article

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Abstract

Objective

To explore the influencing factors of fracture in patients with fibrous dysplasia (FD) of proximal femur.

Methods

Retrospective clinical observational study. A total of 49 patients with fibrous dysplasia of proximal femur who were examined and diagnosed at Department of orthopaedics of the 960th Hospital of the PLA Joint Logistics Support Force between January 2016 and January 2021 were included in the study. Among these patients, 27 were male and 22 were female. The average age was 30.8 years. There were 19 cases of monostatic fibrous dysplasia(MFD), as well as 35 cases of polystatic fibrous dysplasia(PFD) and McCune-Albright syndrome. All patients were examined by body mass index(BMI), bilateral hip X-ray film, femoral neck shaft angle measurement and bone metabolism, including N-terminal propeptide of type 1 procollagen (PINP), type 1 collagen carboxyl terminal peptide(β-CTx) and osteocalcin(OST). We divided the clinical and anatomical classification of all patients, and they were divided into fracture group and non fracture group according to whether they were fractured or not. Clinical data and imaging characteristics were analyzed retrospectively.

Results

In univariate analysis, there were statistically significant in clinical classification, anatomical classification, femoral neck shaft angle and osteocalcin (P 0.01). In multivariate logistic analysis, there were statistically significant in anatomical classification, femoral neck shaft angle and osteocalcin (P 0.05).

Conclusions

Anatomical classification, femoral neck shaft angle and osteocalcin are the important predictive factors of fracture in patients with fibrous dysplasia of proximal femur. We may effectively predict and prevent the fracture of patients with fibrous dysplasia of proximal femur through the examination of anatomical classification, femoral neck shaft angle and osteocalcin. In order to improve the accuracy and robustness of the conclusions and provide better clinical guidance, we need to conduct more comprehensive research in the subsequent clinical work.

1. Intruduction

Fibrous dysplasia (FD) is a benign intramedullary fibro-osseous lesion originally. This rare non hereditary benign bone lesion was described by Lichtensteinl in 1938 and by Lichtenstein and Jaffe in 1942,

accounting for 2.5% of all bone injuries and 7% of benign bone tumors[1]. Most of them come on in adulthood, and the disease basically stops progressing in adulthood, and a few may continue to progress, with a similar proportion of men and women[2]. At present, it is considered that FD is caused by the sporadic post-zygotic activating mutations in GNAS, resulting in dysregulated GαS-protein signaling in affected tissue[3]. This leads to the defect of osteoblast differentiation, and fibrous tissue replaces normal bone[4]. The disease can be divided into monostatic fibrous dysplasia (MFD), polystatic fibrous dysplasia (PFD) and McCune-Albright syndrome (MAS), which is PFD with endocrine system diseases. The clinical manifestations are mainly pain, deformity and fracture, while patients with MAS are often accompanied by endocrine diseases and skin coffee milk spots[5–6]. The diagnosis of this disease mainly depends on imaging and clinical manifestations. Fibrous dysplasia is radiologically characterized by homogeneous diffuse radiopacity with a ground glass appearance in continuity[7]. For patients who are difficult to be diagnosed by imaging, puncture biopsy can be carried out with the help of pathological results. Fibrous dysplasia of bone may occur in all bones of the body. In MFD,the most common sites are maxilla, proximal femur, tibia, humerus, ribs, skull, radius and iliac. And in PFD, proximal femur is most often involved[8]. Pathological fracture is one of the most common complications of fibrous dysplasia of the proximal femur. Due to the particularity of the anatomical structure of the proximal femur, the stress is highly concentrated here, so the proximal femur is the most prone site to fracture. At present, it is difficult to predict the probability of fracture in patients with fibrous dysplasia of the proximal femur, which affects the formulation of treatment plan. Therefore, in this study, we made a retrospective clinical observational study of the patients with FD of proximal femur, hoping to find out the predictive factors, which can effectively predict and prevent their fractures, so as to comprehensively treat the patients with FD of proximal femur.

2. Materials And Methods

2.1 General materials and data

This was a retrospective clinical observational study. The study was approved by the Institutional Ethics Committee of the 960th Hospital of the PLA Joint Logistics Support Force (approval No.2021-148). 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. A total of 49 patients with fibrous dysplasia of proximal femur who were examined and diagnosed at department of orthopaedics of the 960th Hospital of the PLA Joint Logistics Support Force between January 2016 and January 2021 were included in the study. Among these patients, 27 were male and 22 were female. The age ranged from 12 to 74 years, and the average age was 30.8±14.7(mean±SD) years. All patients were examined by BMI, bilateral hip X-ray film, femoral neck shaft angle measurement and bone metabolism, including PINP, β-CTx and OST. We divided the clinical and anatomical classification of all patients, and they were divided into fracture group and non-fracture group according to whether they were fractured or not.

2.1.1 Inclusion criteria: (1)Diagnosed as FD; (2)The lesion area involved the proximal femur; (3)The follow-up time was more than 12 months.

2.1.2 Exclusion criteria: (1)Combined with other bone tumor diseases; (2)Patients who have received systematic treatment or surgical treatment; (3)Patients who couldn't cooperate to complete the complete data collection.

2.2 Observation indicators

2.2.1 Basic observation indicators: The age, gender, BMI, clinical classification of the two groups.

2.2.2 Anatomical classification: All patients were admitted to hospital with bilateral hip joint anteroposterior X-ray films. According to Guille's classification[9], we were divided into type A: the lesion covered the whole proximal femur (Fig. 1a). Type B: the lesion only involves the femoral neck (Fig. 1b). Type C: lesions involving femoral neck and intertrochanteric region (Fig. 1c). Type D: lesions only involve the intertrochanteric area (Fig. 1d). In order to facilitate observation and due to the small sample size of type B, type C and type D, We divided the patients into two groups according to anatomical classification. Type A patients (involving the whole proximal femur) were divided into type 1. Type B, C, and D patients (involving part of proximal femur) were divided into type 2.

2.2.3 femoral neck shaft angle: All patients were examined by X-ray films of the hip joint and femoral neck shaft angle was measured.

2.2.4 Bone metabolic index: PINP,β-CTx and OST. The OC value was measured by radioimmunoassay.

2.3 Statistical Analysis

All statistical analysis were performed using SPSS26.0 software. The t-test and $\chi 2$ test were used for the comparison between the two groups. $P \leq 0.05$ indicates that the difference is statistically significant.

3. Results

3.1 The baseline of basic clinical characteristics of patients

A total of 49 patients met the inclusion criteria in this study. The baseline of basic clinical characteristics of these patients are shown in table 1. The age, gender and BMI in fracture group and non fracture group had no statistical significance (P 0.05). The clinical classification had a statistical significance (P 0.01).

3.2 The other factors of patients

Comparison of anatomical classification, femoral neck shaft angleand bone metabolic index in table 1. Comparison of anatomical classification: type 1 in fracture group was significantly higher than that in non fracture group. Anatomical classification was statistically significant(OR=8.622, P 0.05). In other words, the risk of type 1 was 8.622 times that of type 2. Comparison of femoral neck shaft

angle: (OR=0.961, P 0.05), which was statistically significant. That is to say, the femoral neck shaft angle is the protective factor. For each additional unit, the risk increases by 0.961. PINP andβ-CTx had no statistical significance (P 0.05), while osteocalcin was statistically significant (OR=0.006, P 0.05).

3.3 Multi factor Logistic analysis of possible predictive factors of fracture.

As table 2, The dependent variable is whether the fracture is or not, and the independent variable is the influencing factors (clinical classification, anatomical classification, femoral neck shaft angle and OST) that may affect factors of fracture in patients with fibrous dysplasia of proximal femur for multi factor Logistic analysis. The anatomical classification, femoral neck shaft angle and osteocalcin were statistically significant(P 0.05). Anatomical classification, femoral neck shaft angle and osteocalcin are the important predictive factors of fracture in patients with fibrous dysplasia of proximal femur.

3.4 The presentation of the results of clinical examinations of two patients in this study

Figure 2 showed the imaging changes of proximal femur case 1. A 12-year-old girl accompanied by right thigh pain for 3 years. On examination, the lesions only involved the intertrochanteric area and her osteocalcin level was within the normal range. The imaging examinations and pathological results indicated the FD of proximal femur of case 1.

Figure 3 showed the imaging changes of proximal femur of case 2. A 56-year-old women accompanied by left femoral pain for 10 month. On examination, the lesions covered the whole proximal femur and her osteocalcin level was above the normal rang. The imaging examinations and pathological results indicated the FD of proximal femur of case 2.

4. Discussion

Fracture is one of the serious complications of fibrous dysplasia. Because of the particularity of its anatomical position, proximal femur is easy to occur deformities and fractures[10]. Many FD patients couldn't predict whether they will have a fracture or not, and they are often hospitalized after a fracture occurs, so they will miss the best opportunity for treatment. Therefore, early prediction of the incidence of fractures in patients with fibrous dysplasia involving the proximal femur, so as to formulate better treatment strategies, which will help to reduce the incidence of fractures. At present, scholars at China and abroad mainly focus on the treatment of proximal femoral fibrous dysplasia. However there are no case reports on the predictive factors of fracture in patients with fibrous dysplasia of proximal femur, so there is no clear standard about it. Majoor BCJ reviewed of 32 patients with FD in the proximal femur. They investigated the surgical treatment methods and efficacies, but did not discuss the the predictive factors of fracture in patients with fibrous dysplasia of proximal femur[11]. In a retrospective analysis of 26 children with proximal femoral FD, Bian investigated the surgical treatment, clinical effect and revision reasons, but did not introduce a clear standard about fracture factors[12]. Therefore, we need to analyze the influencing factors of fractures in patients with proximal femoral fibrous dysplasia to predict the

incidence of fractures. And we formulate corresponding intervention programs to reduce the incidence of fracture.

In order to facilitate the research, scholars at home and abroad have classified FD of proximal femur. At present, the mainstream is the following three types: Guille's classification[9], Ippolit classification[13], Zhang's classification[14]. In this study, we chose Guille's classification, which is simple to operate and convenient for clinical application. We found that most patients are type A FD of proximal femur, and the number of type B, type C and type D cases is less. We divided the patients into two groups according to anatomical classification. Type A patients(involving the whole proximal femur) were divided into type 1. Type B, C, and D patients(involving part of proximal femur) were divided into type 2. In the fracture group, there were 14 patients with type 1 FD of proximal femur In multivariate logistic analysis, there was statistically significant in anatomical classification (OR value=8.622, P 0.05). Type 1 FD of proximal femur is causing extensive bone destruction due to its wide range of lesions. At this time, the supporting force of the proximal femur decreases, which makes it difficult to support the weight of upper body, so it is easy to fracture.

As an important anatomical marker of the proximal femur, femoral neck shaft angle can increase the range of motion of the lower limbs and transmit the strength of the trunk to the wide base. At present, there are few studies on the relationship between femoral neck shaft angle and fracture in fibrous dysplasia of proximal femur.In addition, it is considered that hip varus is easy to lead to proximal femoral fractur[15]. In a study of 37 cases of femoral neck fracture, it was found that FNSA could serve as a predictive factor for the risk of femoral head stress fracture[16]. In our study, all patients received X-ray examination of hip joint and measured the femoral neck shaft angle. Among the 17 patients in the fracture group, there were 13 patients with the femoral neck shaft angle were less than normal (P 0.05). Therefore, we think that among the patients with fibrous dysplasia of proximal femur, the patients with femoral neck shaft angle less than the normal value are more prone to fracture than the patients within the normal range. And the smaller the femoral neck shaft angle, the greater the risk of fracture.

Bone metabolic index have high reference value for the impact of fracture risk. Osteocalcin is used as an indicator of bone formation and absorption. Osteocalcin is the most abundant non-collagenous protein in bone and is specifically expressed in osteoblasts[17]. It plays an important role in regulating bone calcium metabolism. It is a new biochemical marker to study bone metabolism. It can maintain normal bone mineralization, inhibit abnormal hydroxyapatite crystallization, and directly reflect the activity of osteoblasts and bone formation[18]. Osteocalcin is closely related to bone mineral density[19], and it is an important marker of hip fracture risk[20–21]. Although osteocalcin is a marker of bone formation, it may also be released from the bone matrix during bone resorption. Therefore, serum osteocalcin can also be regarded as a marker of bone turnover, not just a marker of bone formation[22]. In a study, osteocalcin deficient mice developed rich bones. Therefore, it is considered that the lack of osteocalcin is related to the improvement of bone functional quality, which indicates that osteocalcin is a negative regulator of bone formation, and the expression of osteocalcin in fibrous dysplasia is generally higher than that in

other lesions, so it may inhibit bone formation with poor bone fiber structure[23]. Therefore, the higher the osteocalcin index, the lower the quality of bone at this time, and the risk of fracture will increase accordingly. In the fracture group, there were 16 patients' osteocalcin was higher than normal (P 0.05). Therefore, the higher the osteocalcin value, the greater the risk of fracture. At this time, we need to formulate corresponding intervention programs to prevent the occurrence of fracture.

In a study, there were 172 fractures in 35 patients with FD were followed up for 14.2 years. They believed that the peak of fracture rate was 6 to 10 years old, and then decreased with age[24]. In a retrospective study, Han thought that the peak age of fractures in patients with proximal femoral fibrous dysplasia was bimodal. The first peak is between 6 and 10 years old, and the second peak is after 36 years old[25]. However, there was no significant correlation with age in our study. Perhaps due to the small number of samples, age did not become a predictive factor of fracture in patients with fibrous dysplasia of proximal femur. Now there is a lack of corresponding research on the impact of gender factors on fractures in patients with proximal femoral fibrous dysplasia, so it is not used as an influencing factor. The incidence rate of MFD is 8 to 10 times that of PFD. In a multicenter study of 14 patients with MFD of the proximal femur, half of these patients eventually developed disease and fracture progression[26]. In many studies, BMI is considered to be closely related to fracture. They believe that low BMI is a risk factor for fracture[27–28], and there was few study on the relationship between fibrous dysplasia fracture of proximal femur and BMI. In our study, the p-value of clinical classification and BMI were more than 0.05, and there were no statistical significance.

In other studies, the risk of fracture was significantly increased in patients with endocrine diseases. Hyperthyroidism can increase the loss of bone mass and destruction of bone structure, so it will increase the risk of fracture[29–30]. However, we did not choose to include patients with endocrine diseases. This study also has some limitations. Firstly, the number of patients smoking and drinking is small, so they are not included in the study. Meanwhile, the fracture rate will also be affected by external factors (including environment, behavior,etc). In addition, because some patients failed to follow up on time and the clinical data were incomplete, the sample size of this study is insufficient. Large sample cost research is needed in the future. We also need to study the pathophysiology of FD of proximal femur deeply, and make timely and comprehensive therapeutic regimen for patients to prevent the occurrence of fractures.

5. Conculsion

In conculsion, anatomical classification, femoral neck shaft angle and osteocalcin are the important predictive factors of fracture in patients with fibrous dysplasia of proximal femur. We should analyze the incidence of fracture according to various examination indexes of patients, so as to formulate the next treatment plan and prevent the occurrence of fracture.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of the 960th Hospital of the PLA Joint Logistics Support Force (approval No.2021-148). 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. Since this study is a retrospective study and has no impact on the health and economic status of patients. The institutional ethics committee of the 960th Hospital of the PLA joint logistics support force has signed the application for "exemption from informed consent".

Consent for publication

Not Applicable

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.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

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

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Anatomical classification of FD of proximal femur according to X-ray films.

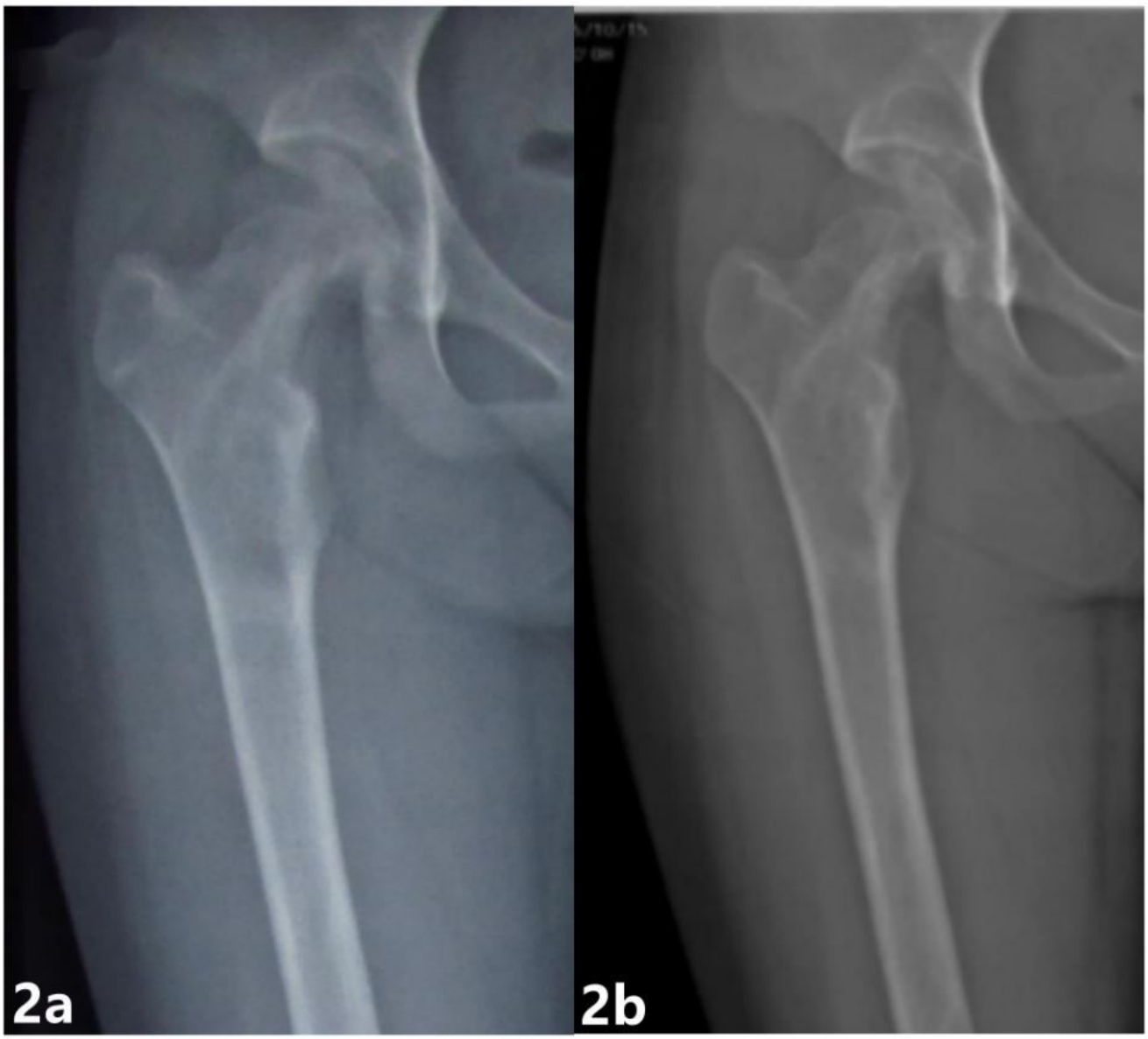

Figure 2

The X-ray film of FD patient without fracture.

Figure 3

The X-ray film of FD patient with fracture.

Supplementary Files

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- Table2.pdf