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Disease severity and functional factors associated with walking performance in polyostotic fibrous dysplasia

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ABSTRACT

The purpose of this study was to determine the association between measures of disease severity, impairment, and ambulation ability in persons with polyostotic fibrous dysplasia (PFD). A cross-sectional sample of 81 patients (ages 5–57) with polyostotic fibrous dysplasia was evaluated as part of an ongoing study. Subjects were scored on the Skeletal Disease Burden Score (SDBS), completed a 9-minute walk test (9MW), manual muscle testing (MMT), and measurements of range of motion (ROM). Correlations between continuous variables were calculated using the Pearson correlation coefficient and ordinal variables by Spearman correlation coefficient. It was found that subjects with more severe disease walked slower than those with less skeletal disease, with the exception of the youngest subjects. Walking velocity was faster in subjects with better hip strength and range of motion and slower in those with bilateral coxa vara. Those subjects with more severe disease had less range of motion, were weaker at the hips, and more likely to have leg length discrepancy. Skeletal disease severity was associated with hip weakness, leg length discrepancy, and loss of range of motion. In most cases, findings did not differ in the presence or absence of associated endocrinopathies. Skeletal disease severity, MMT and ROM each has an impact on walking efficiency in persons with PFD. These findings suggest that treatment focused on strategies to improve or, at least, maintain hip strength and range of motion, correct leg length discrepancies and hip malalignment may help preserve ambulation ability in persons with PFD and that treatment should begin at a young age.

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Introduction

Polyostotic fibrous dysplasia (PFD) is a disorder that derives from a mutated skeletal stem cell resulting in the replacement of normal bone by a benign fibrous connective tissue formed as a consequence of the proliferation of undifferentiated cells of osteogenic lineage [1–5]. It is due to post-zygotic, missense, activating somatic mutations occurring in the *GNAS* gene, which codes for the α subunit of the stimulatory G protein ($G_s\alpha$)[6,7]. These mutations result in the upregulation of cAMP, causing defects in osteoblast differentiation and production of an abnormal bone [4]. Additionally, an increased production of IL-6 is found in bones with PFD, which may contribute to osteoclastogenesis and resorption of adjacent normal bone [8]. PFD presents as a mosaic disorder in some but not all bones in a given person and can exist as an isolated skeletal finding or may be coupled with endocrine abnormalities as the McCune–Albright Syndrome (MAS)[9]. MAS is characterized by café-au-lait pigmentation on the skin, hyperfunctioning endocrinopathies such as precocious puberty, hyperthyroidism, and fibrous dysplasia of the bone (FD)[10]. The spectrum of involved bones is broad, from a single asymptomatic site detected incidentally, to total skeletal involvement associated with marked morbidity [9,11]. PFD/MAS is a rare disease. While the precise prevalence is unknown, estimates of the prevalence of MAS range between 1/100,000 and 1/1,000,000 [10].

The diagnosis of PFD is usually made on clinical grounds, by some combination of medical history, radiographic evaluation, and radionucleotide bone scan [12]. Occasionally, histopathological and/or molecular confirmation are needed [11,13,14]. Clinical manifestations

Abbreviations: 9MW, 9-minute walk; CP, cerebral palsy; EHL, extensor hallucis longus; GM, gluteus minimus; GX, gluteus maximus; IRB, institutional review board; MMT, manual muscle testing; MAS, McCune–Albright Syndrome; MRC, Medical Research Council; NIDCR, National Institute of Dental and Craniofacial Research; NIH, National Institutes of Health; PFD, polyostotic fibrous dysplasia; ROM, range of motion; SDBS, Skeletal Disease Burden Score.

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of FD of the proximal femur, one of the most commonly affected sites, lead to the pathognomonic finding of the "shepherd's crook" deformity [15]. Common findings in the craniofacial and axial skeleton include facial asymmetry and progressive scoliosis, respectively [16–19]. FD is often associated with pain [20]. In MAS, endocrine abnormalities can exacerbate the disease [17,21–24]. Even children who initially present with a great amount of disease on imaging are quite functional in mobility and daily life skills. However, these abilities frequently show significant decline in the progression to adulthood [25].

Treatment with bisphosphonates has provided pain relief for some patients but has no overall or long-term effect on disease progression or function [26–30]. Surgical management of PFD is challenging, particularly because of growth and development through childhood into adolescence. Little has been published with respect to everyday functional capabilities of persons with FD [31–34]. Understanding of the spectrum of impairment and disability in persons with PFD is important for treatment planning and counseling of families. Information about the relationships between disease severity and function may further assist with rehabilitation and surgical treatment planning to optimize the quality of life for persons with PFD.

The goals of this study were to (a) determine the relationship between extent of PFD and the functional skill of ambulation, (b) determine the relationship between extent of PFD and measures of musculoskeletal impairment, and (c) determine the relationship between measures of impairment and ambulation ability.

Methods and materials

Subjects were chosen from a group of ninety-seven patients enrolled in an NIDCR IRB-approved natural history study of PFD/MAS. All subjects or their parents gave informed consent to participate in this study. All subjects were assessed for the presence of café au lait spots (CAL) and endocrinopathies which are associated with MAS. Functional measures obtained as part of the protocol included nine-minute walk test (9MW), joint range of motion measurements (ROM), and manual muscle testing (MMT). Imaging included ^{99}Tc-MDP bone scan. Data for analysis were chosen from the first visit during which every one of these measures was obtained for each subject.

The 9MW test is a standardized, validated measure of ambulation endurance and efficiency [35]. Patients were instructed to walk and/or run at the fastest comfortable pace that they would be able to sustain for a full nine minutes. Walking velocity was compared to age and gender adjusted norms for children under 17. Since there are no specific adult norms for the 9MW, reference values for 17 year olds were used for adult patients. Distance covered in the nine minutes was assigned a percentile according to normalized values. Percentiles were used in statistical analyses.

ROM of lower limb joints was measured by one of two examiners with a goniometer using standard technique. Bilateral lower limb ROM was measured at the hip (flexion, extension, internal rotation, external rotation, and abduction), knee (flexion and extension) and ankle (plantar flexion and dorsiflexion). In order to compare and combine different joint movements, Z-scores for each movement were calculated using published norms and standard errors [36]. Movements were then grouped by joint and mean Z-scores were calculated for each joint.

MMT of the lower limbs was performed using a standard technique scored on the Medical Research Council (MRC) ordinal scale of 0 to 5 [37]. The median for each muscle (gluteus maximus, gluteus medius, iliopsoas, quadriceps, hamstrings, and ankle plantar and dorsiflexors) was then calculated for purpose of analysis.

The presence or absence of leg length discrepancy at the time of the subject's first visit was determined by review of the physiatry clinical note associated with that visit.

The bone scan was used to calculate the Skeletal Disease Burden Score (SDBS), a validated tool developed to assess the overall disease burden of PFD [38]. This weighted measure was derived from the determination of isotopic activity in the various body segments on Tc^{99}-MDP bone scans. In addition, skeletal location of fibrous dysplasia was recorded. Hip x-rays were reviewed for neck to shaft angle and subjects were classified as normal, unilateral or bilateral coxa valgus or varus or mixed valgus/varus.

Calculations

Correlations between continuous data (SDBS, ROM) were determined using the Pearson correlation coefficient; correlations with ordinal data (9MW percentile, MMT) were found using the Spearman correlation coefficient. Correlations between SDBS and ROM were used to determine the relationship between the extent of PFD and joint mobility. To determine the relationship between the extent of PFD and strength impairment, correlations were calculated between SDBS and MMT. Correlations between MMT and ROM were calculated to determine the relationship between strength impairment and joint mobility. T-tests were also performed to examine for differences in SDBS, 9MW, MMT, and ROM between groups with or without CAL, precocious puberty, abnormal level of growth hormone, abnormal thyroid function, hypercortisolemia, presence of craniofacial, axial or appendicular fibrous dysplasia, femoral FB, or leg length discrepancy (LLD). Chi square or Fisher's exact tests were performed to look for possible associations between leg length discrepancy and either endocrinopathies or distribution of skeletal disease. Analysis of Variance with post-hoc Tukey tests were performed to examine for differences in 9MW in relation to categories of femoral alignment.

Results

Eighty-one subjects (32 males, 49 females) had data sets that met the criteria for evaluation of their records. Patients ranged in age from 5 to 57 years (mean = 25). Seventy-seven (95%) of the participants presented with both PFD and MAS. Further demographic data are summarized in Table 1. Data were extracted from the subjects' first visits at which all tests were recorded. All data were collected prospectively as part of ongoing studies. No significant differences were detected between male and female subjects for range of motion or on manual muscle testing.

Correlation between SDBS and 9MW was found to be strongly negative ($R = -0.52$, $p < 0.0001$, Fig. 1). When separated into children (age < 12), adolescents ($12 \leq$ age < 18), and adults (age $\geq$ 18), as shown in Figs. 1B–D, respectively, correlations between SDBS and 9MW were strongly negative and significant in the adolescent and adult age groups ($R = -0.78$, $p = 0.001$; $R = -0.53$, $p < 0.001$, respectively). However, correlation became insignificant for the subgroup of children less than 12 years of age.

Correlations between SDBS and MMT are shown in Table 2(a). Moderate negative correlation was found between SDBS and hip strength, including both the gluteus medius (GM) and maximus (GX).

Table 1
Patient demographics.

Gender	41% male
Age	25.03 ± 15.7 years
CAL	65.4%
PFD	97.5%
Precocious puberty	45.7%
Abnormal GH	14.8%
Thyroid	39.5%
Hypercortisolism	6.17%
Phosphate wasting	32.1%
Craniofacial FD	86.4%
Axial FD	80.2%
Appendicular FD	88.9%
Femoral involvement	81.5%
SDBS score	28.4 ± 20.0