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Acute unilateral hip pain in fibrodysplasia ossificans progressiva (FOP)

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ABSTRACT

Background: Flare-ups of the hips are among the most feared and disabling complications of fibrodysplasia ossificans progressiva (FOP) and are poorly understood. In order to better understand the nature of hip flare-ups in FOP, we evaluated 25 consecutive individuals with classic FOP (14 males, 11 females; 3–56 years old, median age, 17 years old) who presented with acute unilateral hip pain.
Results: All 25 individuals were suspected of having a flare-up of the hip based on clinical history and a favorable response to a four day course of high-dose oral prednisone. Ten individuals (40%) experienced rebound symptoms of pain and/or stiffness within seven days after discontinuation of prednisone and all ten subsequently developed heterotopic ossification (HO) or decreased mobility of the affected hip. None of the 14 individuals who experienced sustained relief of symptoms following a course of oral prednisone experienced HO or decreased mobility. Incidental radiographic findings at the time of presentation were multifactoral and included osteochondromas of the proximal femur (18/25; 72%), degenerative arthritis (17/25; 68%), developmental hip dysplasia (15/25; 60%), previously existing heterotopic ossification (12/25; 48%), intra-articular synovial osteochondromatosis (8/25; 32%) or traumatic fractures through pre-existing heterotopic bone (1/25; 4%).
Conclusions: Developmental joint pathology may confound clinical evaluation of hip pain in FOP. The most useful modality for suspecting an ossification-prone flare-up of the hip was lack of sustained response to a brief course of oral prednisone. Evaluation of soft tissue edema by ultrasound or magnetic resonance imaging showed promise in identifying ossification-prone flare-ups and warrants further analysis in prospective studies.

1. Introduction

Fibrodysplasia ossificans progressiva (FOP; MIM#135100), the most catastrophic form of extraskeletal bone formation in humans, is caused by a recurrent heterozygous missense gain-of-function mutation in Activin receptor A type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor in all classically-affected individuals [1–3]. The complex phenotype of FOP results from dysregulated BMP signaling caused by the mutation and its interaction with ligands and inflammatory stimuli [3,4].

Historically, much attention has been directed to the natural history of flare-ups in FOP, but little attention has been directed to the cause of emerging symptoms at various anatomic locations [5–7]. Flare-ups of the hips are among the most feared and disabling complications of FOP and are poorly understood. Unlike flare-ups at other anatomic sites, flare-ups of the hips do not present with early clinically visible soft tissue swelling due to the deep and often retroperitoneal location of the involved tissues and the constraining nature of the deep fascial planes. Rather, flare-up of the hip often presents insidiously with mild unilateral groin pain and stiffness at rest that often feels like "a pulled muscle," but that escalates in intensity over 1–2 days. Corticosteroids, specifically high-dose oral prednisone, have been used empirically to control the painful symptoms of early flare-ups and are most effective if administered in the first 24 h of a new flare-up [8,9]. Over the past decade, individuals with FOP have been instructed to be vigilant to increasing discomfort, pain or stiffness in the groin region as a cardinal symptom of a suspected flare-up involving the hip.

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In order to better define the scope of symptomatic hip pathology in FOP, we retrospectively reviewed the cases of 25 consecutive individuals with classic FOP who presented with acute unilateral hip pain over a two year period.

2. Methods

In this retrospective analysis, we reviewed the reported symptoms, physical findings, plain radiographs of the hip, ancillary radiographic studies, management and outcome of acute unilateral hip pain in 25 consecutive individuals with classic FOP as part of routine clinical care. All individuals were established patients of the first author (FSK).

In all cases, the clinical diagnosis of FOP was confirmed by the presence of congenital malformations of the great toes and by progressive heterotopic ossification of soft tissues in characteristic anatomic patterns. The clinical diagnosis of classic FOP was previously confirmed by molecular genetic analysis in all individuals. Plain radiographs of the pelvis and hips were obtained on all patients as part of routine clinical care. The evaluation was approved by the institutional review board of The University of Pennsylvania.

3. Results

3.1. Patient demographics

Twenty-five consecutive individuals with classic FOP reported hip pain between January 2013 and December 2015. Eleven individuals were female (44%) and 14 were male (56%) and ranged in age from 3 to 56 years (median, 17 years) [Fig. 1].

3.2. Acute unilateral hip pain

All 25 individuals reported acute unilateral onset of symptoms that began as groin pain, “stiffness” or “a pulled muscle” that rapidly escalated to more severe discomfort over 12–18 h. All 25 individuals were initially suspected of having a flare-up of the hip based on clinical history and a favorable response to a four day course of high-dose oral prednisone, the standard of care for acute FOP flare-ups involving a major joint. All experienced transient relief of symptoms (Table 1).

3.3. Rebound symptoms following prednisone use

Ten individuals (40%) experienced rebound symptoms of pain and/or stiffness within seven days after discontinuation of prednisone and all ten subsequently developed heterotopic ossification (HO) or decreased mobility of the affected hip. None of the 14 individuals who experienced sustained relief of symptoms following a course of oral prednisone experienced HO or acute decreased mobility.

3.4. Incidental radiographic findings

Incidental radiographic findings at the time of presentation were multifactorial and included osteochondromas of the proximal femur (18/25; 72%), degenerative arthritis (17/25; 68%), developmental hip dysplasia (15/25; 60%), previously existing heterotopic ossification (12/25; 48%), intra-articular synovial osteochondromatosis (8/25; 32%) or traumatic fractures through pre-existing heterotopic bone (1/25; 4%) [Figs. 2–3].

3.5. Supplementary imaging findings

In two patients (cases 17 & 20), we obtained supplementary imaging modalities, specifically magnetic resonance imaging (MRI) or ultrasound (US) on a diagnostic basis where patients experienced refractory hip pain after several rounds of corticosteroids. Interestingly, in each case, the MRI or US study revealed massive edema in the deep muscles compatible with a severe flare-up (Fig. 4).

4. Discussion

Flare-ups of the hips are among the most feared and disabling complications of FOP and are poorly understood. In the real-world management of these 25 FOP patients, we assumed that all who experienced acute, escalating, unilateral groin discomfort and stiffness had a flare-up of the hip. Fifty-six percent of patients in our retrospective analysis responded symptomatically to a brief course of high dose oral glucocorticoids and did not develop HO and/or decreased mobility as a result of the suspected flare-up. However, 40% of patients developed rebound symptoms after discontinuation of prednisone and all ten developed HO of the hip and/or decreased hip motion as a result of the suspected flare-up. Therefore, lack of sustained response to a brief course of oral prednisone was an excellent predictive factor for an ossification-prone flare-up of the hip. As all patients who lacked a sustained response to an acute course of oral prednisone had a poor outcome and none of the patients who had a sustained response to oral prednisone had a poor outcome, both the sensitivity and selectivity of the response approached 100%. More importantly, these findings suggest that there

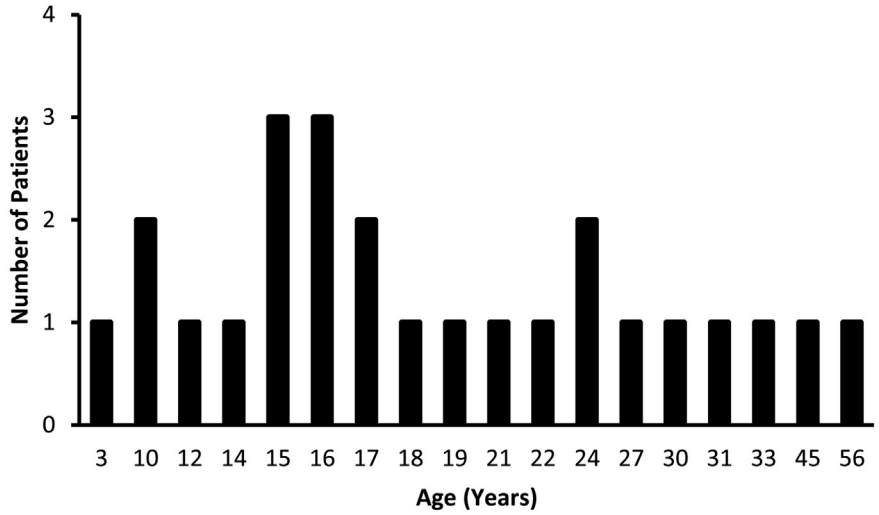

Fig. 1. Age distribution of 25 consecutive FOP patients with hip pain.

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