Full Length Article

Longitudinal patient-reported mobility assessment in fibrodysplasia ossificans progressiva (FOP)

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ABSTRACT

Background: Fibrodysplasia ossificans progressiva (FOP) is a rare, disabling genetic disorder characterized by episodic soft tissue swelling (flare-ups) that leads to progressive heterotopic ossification and restricted joint mobility.
Methods: Here we present the first longitudinal patient-reported mobility assessment (PRMA) in FOP based on a simple evaluation tool. At initial presentation and follow-up (1–11 year span; median: 6 year span), 64 patients (36 females; 28 males) with classic FOP completed a questionnaire designed to rapidly assess mobility at 15 sites (three axial; six upper limb, and six lower limb). In order to validate this instrument, twenty-one of 64 patients (33%) underwent a cumulative analogue joint involvement scale (CAJIS) evaluation by two physicians within six months of their second self-assessment.
Results: We found that: 1) mobility changes were episodic and regional, occurring first in the neck and trunk, followed by the upper limbs and finally the lower limbs; 2) interval improvements in mobility did occur, most notably in the lower limbs (18%), and less so in the upper limbs (12%) and trunk (3%), and 3) patient-reported mobility assessments correlate highly ($R^2 = 0.81$) with physician-reported CAJIS evaluations.
Conclusion: This is the first longitudinal PRMA in FOP and provides a simple and valid tool that can be used in the design and evaluation of clinical trials in this progressively disabling disease.

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1. Introduction

Fibrodysplasia ossificans progressiva (FOP; OMIM: 135100) is a rare and disabling genetic disorder caused by heterozygous activating missense mutations of Activin receptor A type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor [1–3]. FOP is characterized by episodes of soft tissue swelling (flare-ups) that lead to progressive heterotopic ossification and restrictive joint mobility [2]. Although much progress has been made in documenting the natural history, genetics, and pathophysiology of FOP, surprisingly little attention has been devoted to patient reported outcomes in this catastrophic musculoskeletal condition [1,3–5]. Here, we present the first longitudinal patient-reported study of mobility changes in FOP based on a simple, rapid, and validated evaluation tool. Patient reported outcome studies are a cornerstone of clinical research [6] and will be a vital tool in the design and evaluation of future clinical trials.

2. Methods

2.1. Patients

All patients had classic FOP defined by confirmation of the ACVR1 (R206H) mutation. The study included English-speaking FOP patients who completed two mobility self-evaluations between 2002 and 2013.

2.2. Patient-reported mobility assessment (PRMA)

A simple mobility scale, designed to assess disease-burden at 15 anatomic locations based on the physician-reported Cumulative Analogue Joint Involvement Scale (CAJIS) was field-tested and completed by FOP patients or family members, typically in less than two minutes [7]. Axial

sites included: the neck, jaw, and chest-back. Upper limb sites included shoulders, elbows, and wrists. Lower limb sites included: hips, knees, and ankles. At each site, the patient (or a surrogate; parent or caregiver) was asked to assess whether movement or function was normal (score of 0), partially impaired (score of 1), or completely restricted (score of 2). Self-assessments were conducted at time of initial presentation and at follow-up. Scores were tabulated for the entire body and for individual regions (axial, upper limbs, lower limbs).

2.3. Patient-physician correlation of functional outcomes

A subset of patients was assessed by two physicians (FSK and RJP) in order to determine the correlation between patient-reported and physician-evaluated functional outcomes using the same 30-point CAJIS scale [7]. At each site, joint function was assessed as normal (<10% deficit; score of 0), partially impaired (10%–90% deficit; score of 1), or functionally ankylosed (>90% deficit; score of 2). Patients were included only if there was no reported exacerbation, progression, or documented disease flare-up between the time that the patient had completed their second assessment and the time they were seen by the physicians for the correlative examination. Patient evaluations were completed first and the physicians were blinded to the assessments. Physician evaluations were performed within six months of survey completion. All assessments were part of routine patient evaluations and were approved by the Investigational Review Board of the Perelman School of Medicine of the University of Pennsylvania.

2.4. Data analysis

Descriptive statistics were performed using Microsoft Excel software. The rate of progression of joint involvement was calculated as $PRMA_2 - PRMA_1/Age_2 - Age_1$, where $PRMA_2$ is the score at the second self-assessment, $PRMA_1$ the score at the first self-assessment, Age_2 the age at the second self-assessment, and Age_1 the age at the first self-assessment.

3. Results

There were 64 patients from 11 countries and five continents (28 males; 36 females). At initial self-evaluation, patients were three months- 53 years of age (median: 12 years). The total PRMA scores were 0–28/30 (median: 6). Median regional joint involvement scores were: axial 2/6; upper limb 3/12; lower limb 2/12. At the second self-evaluation, patients were 3–62 years of age (median: 19 years) and the total PRMA scores were 2–30/30 (median: 11). Median regional joint involvement scores were: axial 3/6; upper limb 4/12; lower limb 2/12. The interval between the initial and second self-assessments was 1–11 years (median: 6 years; Fig. 1).

In the 64 patients who completed an initial and follow-up PRMA, progression was episodic and regionally variable. Disease progression followed an axial > upper limb > lower limb pattern although interval improvements were noted in many (Fig. 2A–D), with the greatest overall progression occurring before the age of 30 years (Fig. 3).

Forty-five/64 patients (70%) reported an overall worsening of mobility between the initial and follow-up PRMA, while 9/64 patients (14%) reported no change and 10/64 patients (16%) reported an interval improvement. The greatest self-reported worsening of mobility and the smallest self-reported improvement in mobility occurred in the axial region while the smallest self-reported worsening of mobility and the greatest self-reported improvement in mobility occurred in the lower limbs. Overall, about 40% of patients reported no interval changes in mobility among the axial, upper limb or lower limb sites (Table 1).

Twenty one/64 patients (33%) had a physician-reported CAJIS evaluation within six months of the second PRMA without any history of intervening flare-up or reported worsening of their condition. In this cohort, there were nine males and twelve females with an age-range
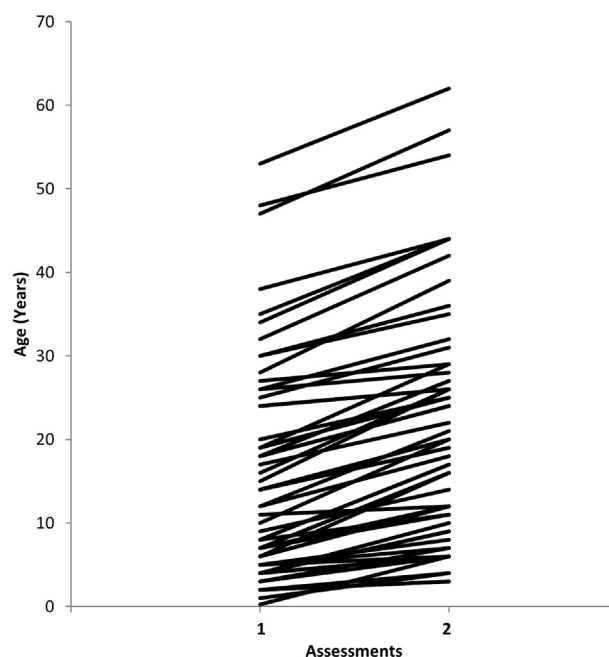

Fig. 1. Interval between first and second patient self-assessments. The interval between the first and second assessment was 1–11 years (median: 6 years).

of 3–54 years (median: 12 years). Patient self-assessments (PRMA) correlate highly ($R^2 = 0.81$) with physician-reported CAJIS evaluations and the discrepancy between PRMA and CAJIS was 0–9/30 (median: 1/30; 5%; Fig. 4). CAJIS scores were more severe than the PRMA scores in 9/21 cases (43%), identical to the PRMA scores in 5/21 cases (24%), and less severe than the PRMA scores in 7/21 cases (33%).

4. Discussion

This is the first longitudinal PRMA in FOP and provides a simple and valid tool that can be used to inform the design and evaluation of clinical trials in this progressively disabling disease. There were three major findings of the study: 1) mobility changes were episodic and regional, occurring first in the neck and trunk followed by the upper limbs and finally the lower limbs; 2) interval improvements in mobility can occur, most notably in the lower limbs (18%), and less so in the upper limbs (12%) and trunk (3%), and 3) PRMAs correlate highly ($R^2 = 0.81$) with physician-reported CAJIS evaluations.

Within a span of 1–11 years (median: 6 years), patients reported disease progression at almost all sites, but with great variability. Disease involvement was greater at axial than appendicular sites at all ages, reflecting the earlier involvement of axial sites in nearly all individuals. Axial and upper limb involvement preceded lower limb involvement at all ages. We found that more severe mobility loss occurred at axial sites and in the upper limbs during childhood, most likely due to the robust disease activity at those sites during childhood, coupled with the fact that anatomic targets were progressively removed from further functional involvement when a joint became ankylosed.

The findings in this study were consistent with those of previously-reported cross-sectional natural history studies [8–10]. However, in analyzing longitudinal data on individual patients, we were surprised to find improvements in PRMAs, most notably in the lower limbs in some individuals. The exact cause of this interval improvement in PRMA is unknown, but might possibly be related to resolution of edema following acute flare-ups or functional adaptation to mobility restriction. Lower limb involvement most often occurs at or following skeletal maturity, so relative change in position of non-bridging heterotopic bone with growth is an unlikely explanation.
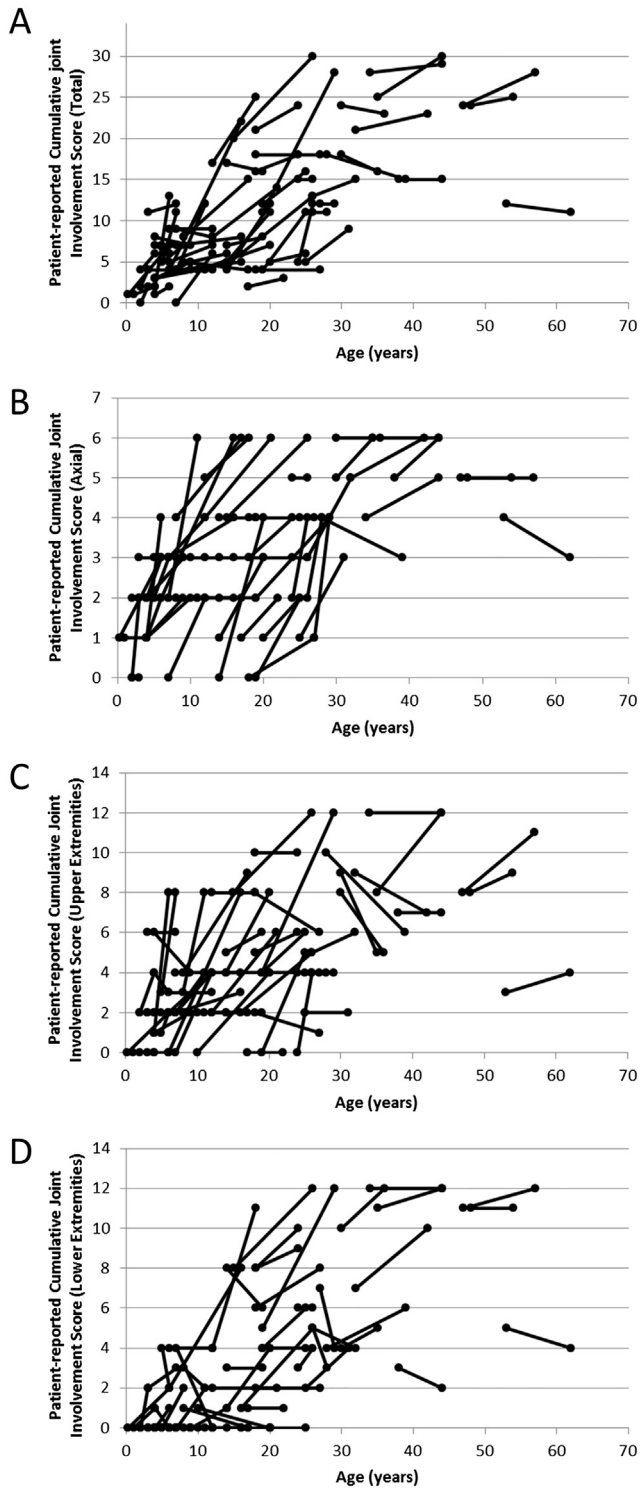
A

B

C

D

Fig. 2. Longitudinal patient-reported cumulative joint involvement scores: A) total body; B) axial; C) upper limb; D) lower limb.

It is reasonable to conclude from data in cross-sectional natural history studies that patients with classic FOP have normal mobility at birth with the possible exception of variably decreased mobility of the neck from congenital orthotopic fusions of the subaxial cervical vertebra [1–3]. Our data on individuals less than two years of age strongly support this conclusion. Importantly, our study reveals that while FOP is overwhelmingly progressive, there are periods when the disease is likely quiescent without additional flare-ups or mobility loss; and during these periods, mobility lost during previous flare-ups may, in fact, improve.
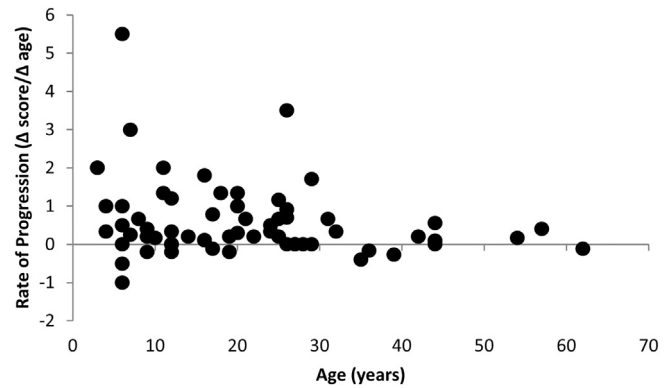

Fig. 3. Rate of progression of joint involvement. Note that the greatest overall progression occurs before the age of 30 years.

There were several limitations to this study. First, the self-assessment instrument was not designed to record subtle changes in joint position or to distinguish between loss of movement from congenital malformation, edema, heterotopic ossification, joint dysplasia, osteochondromas, intra-articular synovial osteochondromatosis, or early degenerative joint disease - all of which can occur in FOP. Rather, the questionnaire was designed to be a simple, rapid, and assess PRMA regardless of cause.

Second, the study was not annotated radiographically, and therefore it is not possible to determine the anatomic substrates of immobility. Individuals with FOP suffer from arthropathy, especially about the hips, in addition to progressive heterotopic ossification and it is entirely possible that PRMA changes may have reflected interval changes in symptomatic joint disease as well as mobility changes from heterotopic ossification. An additional possibility is the loss of joint hypermobility, usually present in children until about the age of seven, which may explain some loss in range of motion with age, mainly in the extremities. Ongoing annotated longitudinal natural history studies of FOP will likely resolve these issues.

Third, discrepancies could have arisen if patients or parents filled out the assessments [11]. For example, PRMAs at first assessment were more likely completed by the parent (for a young child) while the PRMA at the follow-up assessment was more likely to be completed by the patient at an older age.

Patient (PRMA)-physician (CAJIS) correlation of mobility at or near the time of the second self-assessment revealed a median discrepancy of 1/30 (5%) in PRMA score. CAJIS scores were more severe than the PRMA scores in 43% of patients, and it is likely that at least part of this discrepancy may be due to physicians and patients interpreting the scoring criteria differently. As a case in point, we noted a patient-physician discrepancy of 9/30 in one patient outlier and conducted a re-evaluation with that patient in order to explore the possible source(s) of the discrepancy. The re-evaluation was instructive in highlighting ambiguities in the self-assessment tool such as determining whether limited movement of the shoulders was due to elbow involvement, whether limitations of pronation and supination of the forearm should be tabulated as wrist or elbow restriction or neither, and whether limited movement of the subtalar joints should be interpreted by the patient

Table 1

Trends in patient-reported mobility assessment (PRMA).

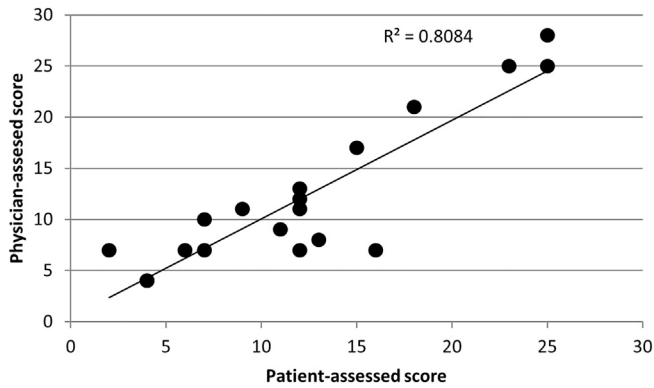| Trend	Scores-percentage (n out of 64)			
	Total	Axial	Upper	Lower
Declining	70 (45/64)	58 (37/64)	47 (30/64)	41 (26/64)
Unchanged	14 (9/64)	39 (25/64)	41 (26/64)	41 (26/64)
Improving	16 (10/64)	3 (2/64)	12 (8/64)	18 (12/64)

Fig. 4. Patient-physician correlation of joint involvement. The correlation between patient-assessed score (PRMA) and physician-assessed score (CAJIS) was high ($R^2 = 0.81$).

as loss of ankle mobility. Clarifications or modifications in the self-administration of this evaluation tool may be needed in future studies.

Despite the noted limitations of the PRMA, patient-reported mobility evaluations are vital to understanding the longitudinal natural history of FOP and will certainly become a valuable tool in the design and evaluation of clinical trials in this progressively disabling disease [12].

5. Conclusion

This is the first longitudinal patient self-assessment mobility scale in FOP and provides a simple and valid tool that can be used in the design and evaluation of clinical trials in this progressively disabling disease.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' roles

Conception and design of the work were by FSK and RJP. Collection and/or assembly of data were by FSK and RJP. The manuscript was written by FSK and RJP, with revisions by MA. Data analysis and interpretation were performed by all authors. The manuscript was approved by all authors.

Acknowledgements

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