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Clinical staging of Fibrodysplasia Ossificans Progressiva (FOP)

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic condition of heterotopic ossification (HO) that results in progressive loss of joint function, ultimately rendering movement impossible. Death is most commonly the result of thoracic insufficiency syndrome, or complications related to recurrent respiratory infections. There are no current treatments for FOP, but early and emerging clinical trials offer hope for this devastating disease. With the recent reporting of a comprehensive global natural history study, scales to assess joint dysfunction, and a more accurate prediction of joint survival, it is now possible to construct a conceptual framework for the clinical staging of FOP. Based on assessment of FOP features in seven areas, it is possible to assign five clinical stages. FOP features include flare-up activity, body regions affected, thoracic insufficiency, other complications, activities of daily living (ADLs), ambulatory status, and the cumulative joint involvement scale (CAJIS) score. Assessments of these features assign an individual with FOP to early/mild, moderate, severe, profound, or late-stage disease. These criteria seek to be flexible enough to be used by clinicians without reliance on advanced imaging or specialized testing, as well as by investigators involved in research or clinical trial studies who would have these tools available. These staging measures for FOP assess the influence of HO and accelerated joint dysfunction (due to congenital abnormalities) on the ability to perform common functional activities, and thus a delay or lack of progression from one stage to the next represents the ultimate test of efficacy for drug trials. This framework will serve both as a prediction tool for FOP progression as well as a critical opportunity to substantiate therapeutic interventions. The staging system proposed here will permit an accurate assessment of severity to appropriately develop or revise clinical plans of care, define operational research criteria, and identify the effectiveness of interventions. Ultimately, this clinical staging will aid the field in moving toward earlier intervention at a stage where disease-modifying therapies may be most efficacious.

1. Introduction

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare and disabling genetic condition of congenital skeletal malformations and progressive heterotopic ossification (HO) [1,2]. A recurrent mutation in activin receptor IA/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor, is the cause of all sporadic and familial cases of classic FOP [3]. Progression of FOP, as quantified by the cumulative number of functionally ankylosed body regions, is essentially unabated throughout the course of the condition [4]. Most body regions are affected before the third decade of life [4–6].

Recent reporting of a comprehensive global natural history study, scales to assess joint dysfunction, and more accurate prediction models of joint survival have allowed the construction of a conceptual framework for the clinical staging of FOP. A comprehensive natural history study on FOP flare-ups revealed both generalized patterns of joint involvement as well as information regarding the onset and ultimate functional ankyloses of affected joints [4]. Using the same dataset generated by the FOP natural history study on flare-ups, current estimates of age- and joint-specific risks of new joint involvement were also calculated [6]. Two scales to evaluate joint dysfunction, a physician-assessed cumulative analogue joint involvement scale (CAJIS) and a patient reported mobility assessment (PRMA) provided key insight into mobility changes and functional status [5,7]. The CAJIS gave accurate and reproducible snapshots of total body and regional mobility burden of FOP that correlates with age and functional status [5]. The longitudinal PRMA confirmed the episodic and regional mobility changes first demonstrated in previous cross-sectional studies [7]. The PRMA is highly correlated with physician-reported CAJIS evaluations [7].

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The staging system proposed here will permit an accurate assessment of severity to appropriately develop or revise clinical plans of care, define operational research criteria, and identify the effectiveness of interventions.

2. Features of FOP defining clinical stages

On the basis of FOP features related to joint dysfunction (flare-up activity, body regions affected, thoracic insufficiency syndrome, other complications) and its consequences (impairments in activities of daily living [ADLs] and ambulation, increasing cumulative analog joint involvement scale [CAJIS] score), five clinical stages of FOP were defined (Table 1).

2.1. Flare-up activity and affected body regions

There are generalized patterns of flare-up activity which begin in the scalp, neck and back early in life and then proceed from these axial body regions to appendicular regions, usually the upper limbs and then the lower limbs [4,6]. The progression of flare-ups from mostly axial regions to appendicular regions is a natural distinction between early/mild and moderate severity FOP. The progression of moderate disease to severe disease, in terms of flare-up activity, is marked by the possibility of exacerbations at any location, but now specifically includes the jaw. Severe weight loss following ankylosis of the jaw is common. In the profound and end stages, flare-up activity proceeds proximally to distally (e.g., wrists and ankles) to result in ankyloses of most or all joints, respectively.

2.2. Thoracic insufficiency syndrome

Thoracic insufficiency syndrome (TIS) may be first manifested by limited chest expansion in moderate stage disease, and later characterized in severe disease by a rigid chest wall without expansion and exclusively diaphragmatic breathing [1,8]. Symptomatic TIS presents with clinical features associated with pulmonary hypertension and right-sided heart failure, which are common in profound and end-stage FOP. Features of FOP that contribute to TIS include costovertebral malformations with orthotopic ankylosis of the costovertebral joints, ossification of intercostal muscles, paravertebral muscles and aponeuroses, as well as progressive spinal deformity including kyphoscoliosis or thoracic lordosis [8,9]. Symptoms of TIS may present in younger individuals when severe scoliosis is present or when chest expansion is restricted by congenital or early fusions of the costovertebral joints.

2.3. Other complications

In profound and end-stage FOP, pneumonia and pressure ulcers are common secondary to TIS and immobility, respectively. Recurrent respiratory infections are common in end-stage disease.

2.4. Functional assessments

Three functional measures are used to assess progression across clinical stages, including ability to perform basic activities of daily living (ADLs), ambulatory status, and CAJIS score.

In early stage disease, no or minimal assistance with ADLs is required due to mild joint limitations or physical delays in developmental milestones. Some assistance with ADLs is required in moderate stage disease, and assistance is needed for most activities in the severe stage. In profound and end-stage disease, patients are dependent for all ADLs.

In early/mild FOP, ambulation is unaffected or cannot be evaluated due to very young age. In moderate stage disease, patients are usually capable of walking, but may use a wheelchair in extenuating circumstances (e.g., long distances). In severe stage disease, a patient commonly requires an assistive device for walking and/or uses a wheelchair. An individual with FOP is typically wheelchair-bound or bed-bound in profound and end-stage disease, respectively.

The CAJIS was recently described and validated [5]. Briefly, the CAJIS is a simple, rapidly-administered assessment of mobility limitation at 15 anatomic locations. It can be performed in less than 2 min and can be adapted to any clinical setting. CAJIS scores are tabulated for the entire body (out of 30) and for individual regions [axial (out of 6), upper limbs (out of 12), lower limbs (out of 12)]. Upper extremity CAJIS

Table 1
Clinical stages of FOP.

		Clinical stages				
		Early/mild	Moderate	Late/severe	Profound	End-stage
Features*	Flare-ups	No history of flare-ups, or if present, limited to scalp, neck, or back	History of flare-ups mostly limited to axial regions and upper limbs	History of flare-ups in any location	History of flare-ups in any location	History of flare-ups in any location
	Body regions affected	Neck, back, upper limbs	Neck, back, chest, upper and lower limbs	Neck, back, chest, upper and lower limbs; jaw	Neck, back, chest, upper and lower limbs, jaw and distal limbs (wrists and ankles)	Ankyloses of most or all joints
	Thoracic insufficiency		Limited chest expansion	Rigid chest wall; no chest expansion; diaphragmatic breathing	Symptomatic thoracic insufficiency syndrome (pulmonary hypertension and right-sided heart failure)**	Symptomatic thoracic insufficiency syndrome (pulmonary hypertension and right-sided heart failure)**
	Other complications				Pneumonia; pressure ulcers	Recurrent respiratory infections
	ADLs	No or minimal assistance required due to mild joint limitations or physical delay in developmental milestones	Some assistance required	Assistance needed for most activities	Dependent for all ADLs	Dependent for all ADLs
	Ambulation	Unaffected or cannot evaluate due to very young age	Walks; May use wheelchair in extenuating circumstances (e.g., long distances)	Walks with assistive device and/or uses wheelchair	Wheelchair-bound	Mostly bed-bound
	CAJIS	≤4	5–18	19–24	≥24	≥28

* Features may appear at any stage, but are presented in a typical or common sequence. Features for any stage are assumed to also include those of the preceding stage(s).
** When symptomatic thoracic insufficiency syndrome is present in a younger individual (e.g., in the case of substantial scoliosis or poor chest expansion for any reason) criteria for ADLs, ambulation, and CAJIS score may not apply.

predicts ability to perform ADLs and lower extremity CAJIS predicts ambulatory status. ADLs and ambulation are self-reported, or in the case of younger patients, reported by parents or care-givers. In early stage FOP the total CAJIS score is usually ≤4, in moderate stage 5–18, severe stage 19–24, profound stage ≥ 24, and end-stage ≥28.

3. Assigning a clinical stage

A clinical stage is assigned independent of age. The stage is dictated by the most severe FOP feature. Functional status should be in agreement with the clinical stage assigned when the most severe feature is based on flare-up activity, affected body regions, thoracic insufficiency syndrome, or other complications.

Among patients with FOP-like HO and/or toe malformations, a small number of patients have clinical features unusual for FOP [10]. These atypical FOP patients are categorized as having classic defining features of FOP (abnormal great toes and HO) plus one or more atypical features (e.g., mild cognitive impairment) or as having major variations in one or both of the two classic defining features of FOP, such as normal great toes or severe reduction deficits of digits [10]. The staging system proposed here should also be applicable to phenotypic variants of FOP, with or without the classic ACVR1 mutation.

4. Discussion

The first conceptual framework for clinical staging is presented here based on evaluation of hallmark FOP features in seven areas, assigning five clinical stages. These staging measures assess the influence of HO and accelerated joint dysfunction (due to congenital abnormalities) on the ability to perform common functional activities, and thus a delay or lack of progression from one stage to the next represents the ultimate test of efficacy for drug trials.

Future modifications of this framework should be undertaken as more clinical data regarding FOP is collected. To vigorously test the staging system outlined here, it should be applied to subjects with carefully curated longitudinal information about their disease progression, perhaps using data that will be collected in the current FOP natural history study (www.clinicaltrials.gov; Identifier NCT023322255).

FOP features may appear at any stage, but are presented in this conceptual framework in a typical or common sequence. Trauma, severe viral illness, or unexpected reactions to immunization may precipitate accelerated progression of FOP at any age [4], but in general there are predictable patterns of flare-up activity, joint involvement, and secondary complications which correlate with functional decline and serve to define the clinical stages proposed (Table 1). Features for any stage are assumed to also include those of the preceding stage(s) and thus the key criteria for each stage have been highlighted (Table 1).

Clinical features distinguishing profound and end-stage disease may be subtle. However, it is proposed that end-stage FOP can be distinguished from profound stage disease on the basis of ankyloses of most or all joints (CAJIS ≥28), recurrent respiratory infections, and mostly bed-bound status.

It is proposed that the most severe FOP feature be the primary basis for assignment of a clinical stage and that functional status should be consistent with that stage when based on flare-up activity, joint involvement, or complications. However, there may be exceptions to this approach. For example, some individuals with FOP can accommodate to new limitations through the use of assistive devices or by developing alternative ways to accomplish ADLs, postponing the time until they are completely dependent. Nevertheless, the accompanying assessments are designed to capture, at least in one domain (ADLs, ambulation, CAJIS score), functional decline consistent with hallmark FOP features. Another exception may present, especially in younger individuals with severe TIS, where joint function may be more relatively preserved for their clinical stage. In this case, the most severe stage should still be assigned because of the association between TIS and mortality [8].

Future iterations of this staging system may consider a scoring system based on weighted features. However, currently a score (or scoring range) is not assigned to each stage in order to emphasize the importance of defining the stage by the most severe feature, since this is most likely to influence morbidity and mortality, and with other supporting clinical features that are consistent with that stage. If scores are assigned, it might be possible to have an individual with a relatively low score, but with a feature associated with higher morbidity and mortality. As in the above example, a young FOP patient with significant scoliosis and TIS, but without other substantial impairments, might be assigned a score consistent with severe or even moderate stage disease, minimizing the life-threatening nature of TIS. One might assign a higher weight to TIS in a scoring algorithm, but this would essentially place the subject in the same stage as the framework proposed here, but with the added requirement to actually calculate a score. As a first attempt to clinical staging of FOP, a simple approach is preferable, with reference only to a table (e.g., Table 1) to facilitate the evaluation.

These criteria seek to be flexible enough to be used by clinicians without reliance on advanced imaging or specialized testing, as well as by investigators involved in research or clinical trial studies who would have these tools available. These staging measures for FOP assess the influence of HO and accelerated joint dysfunction (due to congenital abnormalities) on the ability to perform common functional activities, and thus a delay or lack of progression from one stage to the next represents a meaningful test of efficacy for drug trials. Ultimately, this clinical staging will aid the field in moving toward earlier intervention at a stage where disease-modifying therapies may be most efficacious.

4.1. Case scenarios

4.1.1. Case 1

A two-year old female has had relentless flare-ups for 12 months resulting in ankyloses of her neck, thoraco-lumbar spine, bilateral shoulders and bilateral elbows. There is limited chest expansion. According to her mother, she requires assistance with most basic ADLs and has some delayed developmental milestones, including walking. She has a CAJIS score of 11. Assessments of flare-up activity, body regions affected, TIS, and CAJIS score are all consistent with this individual having moderate stage FOP despite her very young age. Functional assessments other than CAJIS score may be obscured by her developmental delays.

4.1.2. Case 2

A 21 year-old male reports two flare-ups over the last three years, his most recent one resulting in complete ankylosis of the jaw. He admits to a 15-lb weight loss since his jaw locked. He has complete functional ankyloses of his neck, thoraco-lumbar spine, bilateral shoulders, and right elbow. He has partial ankyloses of his bilateral hips, right knee, and right ankle. He has negligible chest expansion. He requires assistance with most ADLs. He walks short distances and uses a wheel chair for longer distances. His CAJIS score is 16. His most advanced features are an affected jaw and very poor chest expansion, assigning him to severe/late stage disease. Despite a lower than predicted CAJIS score, his limited ability to perform ADLs and ambulatory status are consistent with late-stage FOP.

4.1.3. Case 3

A 49 year old female can only partially move her wrists bilaterally. She has chronic complaints of musculoskeletal pain controlled by judicious use of non-steroidal anti-inflammatory agents. She has a rigid chest wall and easily fatigues. She is dependent on all of her basic ADLs and is exclusively wheelchair-bound. In the prior year she was treated for pneumonia. These findings are consistent with profound stage FOP.

5. Conclusions

A conceptual framework for the clinical staging of FOP is proposed. Based on assessment of hallmark FOP features in seven areas, it is possible to assign five clinical stages. This framework will serve both as a prediction tool for FOP progression as well as a critical opportunity to substantiate therapeutic interventions.

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 RJP and FSK. The manuscript was written by RJP, with revisions by FSK. The manuscript was approved by both authors.

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