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ORIGINAL RESEARCH

"I Can't Take off My Shirt or Do My Own Hair"—A Qualitative Investigation of the Symptoms and Impact Experience of Children and Adolescents with Fibrodysplasia Ossificans Progressiva (FOP)

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ABSTRACT

Introduction: Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling, autosomal dominant, congenital disease characterized by progressive multi-focal heterotopic ossification (HO) of skeletal muscle, ligaments, tendons, and fascia. Past FOP studies have focused on the clinical aspects of the disease; therefore, there is a paucity of qualitative research on the patient experience. Our objective was to better understand the experience of children and adolescents living with FOP from their and their parents' perspectives.

Methods: We conducted a qualitative research study comprising in-depth, open-ended interviews with children and adolescents with FOP and their parents. Semi-structured interviews were conducted via phone call or Microsoft Teams with parent-child dyads (n = 11), adolescents (n = 6), and two clinicians. Children/adolescents and their parents were asked open-ended questions to elicit their daily experience of FOP.

Results: Concepts were organized into two major themes: symptoms of FOP and the impact of FOP on daily life. Symptoms of FOP reported by children/adolescents, parents, and clinicians were pain, swelling, redness, and stiffness. Functional impacts of flares and FOP in general included accommodations, mobility, activities of daily living, daily activities, and social activities. Impacts were attributed to the difficulties children and adolescents faced living with a disease that prohibited common activities.

Conclusions: This research documented the experience of children and adolescents with FOP and its effects on their daily lives. It provides a conceptual model for further exploration of the symptoms and impacts important to children and adolescents with FOP and their parents. Children and adolescents and their parents offered novel insights into life with the disease that have not previously been discussed

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in published literature. Future studies should build upon our conceptual model to create a holistic view of the patient experience of FOP, to inform clinical practice, and the assessment of the patient experience in clinical trials for the disease.

Keywords: Fibrodysplasia ossificans progressiva; Children and adolescents; Patient-reported experience; Qualitative research

Key Summary Points

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling, autosomal dominant, congenital disease characterized by progressive multi-focal heterotopic ossification of skeletal muscle, ligaments, tendons, and fascia.

Very little is known about the experience of people living with FOP, especially children and adolescents.

This research documented the seldom-represented patient-reported experience of FOP and its physical and emotional effects on their daily lives, and provided a conceptual model for further explorations of the symptoms and impacts of the disease.

Future studies should build upon our conceptual model to both create a holistic view of the patient experience of FOP and ensure their needs are being addressed.

INTRODUCTION

With an estimated global prevalence of less than one birth per million[1, 2], fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, severely disabling, autosomal dominant, congenital disease characterized by progressive multi-focal heterotopic ossification (HO) of skeletal muscle, ligaments, tendons, and fascia. Patients with FOP experience "flare-ups," which are sporadic, painful episodes of rapidly progressive soft tissue swelling that can be caused by falls or injury or occur spontaneously. While these swellings may resolve, they may also result in bone forming in places throughout the body where bone should not be. Over time, people with FOP experience significant disability, as mobility becomes more restricted because of bone growth [3].

Historically, FOP has been investigated through a clinical lens, with little attention paid to the patient's experience of the disease. Consequently, little is known about the experience of FOP from the perspective of the people living with the disease—especially children and adolescents. To explore what information might be available in published research, we conducted a targeted literature review in July 2020 (updated in June 2021) and found only two qualitative research papers describing the patient experience of FOP: a case report [4] and a paper about the development of a patient-reported outcome instrument in adults with FOP [5], which included limited qualitative research. Unfortunately, neither publication focused on the pediatric perspective of FOP, and even the case report—which covered psychological adaptations of children with FOP—gave limited insight into the child's experience of living with the disease. While anecdotal reports regarding the patient experience of FOP exist [6, 7], our literature review found there have been few to no scientific qualitative inquiries into the pediatric patient-reported experience of FOP.

The dearth of patient voices in the FOP literature is unfortunate; patient perspectives often extend beyond clinical outcomes and illuminate concepts that would otherwise be overlooked [8]. Moreover, families, providers, regulatory agencies, and professional organizations now place considerable emphasis on the value of patient-centered treatment assessment [9–11]. The lack of published research required that we turn to the active online FOP community to identify and investigate the aspects of their lives most affected by living with this rare disease. These included concepts related to FOP impacting children's physical mobility, daily activities, recreational activities, relationships with others, and overall health.

In this context, the objective of this current study aimed to expand upon the literature regarding the symptom and impact experience of children and adolescents with FOP, and to develop a conceptual model of these experiences, informed by qualitative interviews with children and adolescents with the disease and their parents.

METHODS

This qualitative research study employed semi-structured interviews with children and adolescents with FOP and their parents to document the symptom and impact experience. We also interviewed two clinicians to gain insight into the patient experience to inform the development of the interview guides. Interviews were conducted September–November 2020. Methods followed the FDA's patient-focused drug development guidances [10, 12].

Study documents, including the protocol, demographic and health information form, interview guide, screener, and informed consent and assent forms, received ethical approval from Advarra IRB (IRB #00,046,227). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided informed consent/assent to participate in this study; written consent and assent were obtained from both patients and their parents before proceeding with the interviews.

Participants

Our participant sample was recruited through a collaboration with the International Fibrodysplasia Ossificans Progressiva Association (IFOPA; www.ifopa.org); participants were recruited in the US, UK, and Canada. The sample comprised 17 children and adolescents with FOP and their parents. Participants were included if they provided assent and informed consent signed by a parent or legal guardian, were male or female aged 4–17 years at time of consent, had a parent-reported diagnosis of FOP, and had parent-reported FOP disease activity within 1 year of the screening call. We defined FOP disease activity as self- or parent-reported pain, swelling, stiffness, warmth, redness, or other signs and symptoms associated with FOP flare-up, or worsening of joint function, or radiographic progress of HO [(increase in size or number of HO lesions) with/without being associated with flare-up episodes]. Participants were excluded if they did not speak English fluently or if they were currently participating in a clinical trial for FOP. The target recruitment was 20 child/parent dyads to achieve conceptual saturation, i.e., the point at which no new information emerges from additional interviews [13, 14]. Two clinicians who regularly treat children and adolescents with FOP were also interviewed.

Interview Conduct

Sixty-minute interviews were conducted virtually using Microsoft Teams by experienced qualitative researchers who received specific training for the current project. A semi-structured interview guide was used to elicit the child/adolescent and parent experience of FOP, including symptoms and impacts on daily life. For children aged 4–7 years, the child participated in a short interview with the parent present, and most of the interview was conducted with the parent alone; for children aged 8–11 years, the child participated in an interview alone and the parent participated in an interview alone; and for adolescents aged 12–17 years, the adolescent interviewed alone, without parents present. These age groupings were based on recommendations from the ISPOR task force report on good practices for patient-reported outcomes assessments in children and adolescents [15]. During the interview, open-ended questions were asked first, followed by specific probes as needed to gather more details. Examples of questions included: "Can you tell me what it is like for you to have FOP?" "What is it like when you have a flare-up?" "Are there things you can't do because of FOP? Can you tell me about them?"

Two clinicians with expertise in FOP were interviewed separately in the fall of 2020. Each interview lasted approximately 1 h. Clinicians

were asked to describe symptoms and impacts associated with flare-ups.

Interviews were recorded, professional transcribed, and anonymized.

Data Analysis

All transcripts were coded in ATLAS.ti software [16], using a data-driven approach and open inductive coding [13, 14, 17, 18]. As this is applied qualitative research, it was focused on a specific issue (symptoms and impacts of FOP) and did not follow a particular theoretical orientation [19]. Researchers developed the initial coding template after reviewing a subset of transcripts. This coding template was applied to two identical transcripts by two independent researchers. Any discrepancies or inconsistencies between the two researchers were resolved through discussion. The coding template was revised throughout the coding process to reflect the evolving understanding of the researchers of symptoms and the impact experience. This coding template laid the basis for developing a conceptual model. A conceptual model is a visual representation of aspects of patients' experiences, including their symptoms and their associated impacts on daily functioning. The model was developed using standard analytical techniques [13, 17].

The adequacy of the sample size was assessed by saturation analysis performed on each group of five interviews to determine how much new information about the patient experience of flare-ups was obtained in each group. Saturation analysis was conducted at the code level with child/adolescent and parent data combined on flare-related symptoms and impacts. We chose to conduct saturation only on flare-related symptoms and impacts because this is a discrete context.

RESULTS

Overview

Interviews were conducted with 2 clinicians, 11 parent/child dyads, and 6 adolescents (demographic data other than age were missing for $n = 1$ parent/child dyad). Six children were in the youngest age group (age range 5–7 years), five were in the middle age group (age range 9–11 years), and six were in the oldest age group (age range 15–17 years). Most participants were non-Hispanic and white (children/adolescents $n = 10/16$; parents $n = 10/16$). Half of the children/adolescents ($n = 7/16$) and almost all parents were female (15/16). Most children/adolescents were diagnosed before the age of 2 years and were experiencing symptoms at the time of diagnosis ($n = 11/16$). See Table 1 for the overview of participant characteristics.

Clinicians interviewed reported that pain and swelling are among the most common symptoms that patients with FOP report; secondary symptoms include loss of movement, redness, tenderness, and stiffness. Clinicians also report that when assessing patients, they focus on restriction in movement and pain.

Patients and parents reported various symptoms and impacts of FOP, which were reported in relation to a flare-up or FOP more generally. All concepts emerged in the first 13 interviews, with no new flare-related concepts emerging in interviews 14–17. Thus, conceptual saturation was achieved for flare-related symptoms and impacts.

Table 1 Participant demographics

Variable	*N* (%)
Gender	
Female	7 (44)
Male	9 (56)
Ethnicity and race	
White (English/Welsh/Scottish/Northern Irish/British)	2 (13)
Hispanic/Latino and White/Caucasian	2 (13)
Hispanic/Latino and Black/African American	1 (6)
Non-Hispanic/Non-Latino and White/Caucasian	10 (63)
Non-Hispanic/Non-Latino and Biracial	1 (6)
Age of diagnosis	
< 1 year	6 (38)
1–2 years	5 (31)
2–5 years	2 (13)
5–7 years	2 (13)
12 + years	1 (6)
Age at signs or symptoms	
< 1 year	9 (56)
1–2 years	1 (6)
2–5 years	2 (13)
5–7 years	1 (6)
12 + years	3 (19)
Other chronic diseases	
Hearing loss	6 (38)
Anxiety	4 (25)
Breathing problems	4 (25)
Dental issues	2 (13)
Depression	2 (13)
Weight loss	2 (13)
Joint disease	1 (6)
Cognitive problems	1 (6)
Swollen glands	1 (6)
Autoimmune disease	1 (6)
Other (urticaria)	1 (6)
Other (restricted lung)	1 (6)
Hair loss, disease of nervous system, endocrine disorder, blood disease, cancer, heart disease, kidney disease, amenorrhea	0
Methods to manage FOP symptoms	
Nonsteroidal anti-inflammatory medication	13 (81)
Glucocorticoids	12 (75)
Occupational therapy	7 (44)
Mast cell inhibitors and leukotriene antagonists	6 (38)
Active respiratory activities	6 (38)
Cannabinoids	4 (25)
Biophosphonates	3 (19)
Selective tyrosine kinase inhibitor	3 (19)
Other (palovarotene)	1 (6)
Other (IV/IG therapy)	1 (6)
Other (mobility)	1 (6)
Other (psychotherapist)	1 (6)
Other (acetaminophen)	1 (6)

Children, adolescents, and parents reported various symptoms and functional impacts of FOP, and these were spontaneously reported in relation to a flare-up or FOP more generally. The conceptual model of symptoms and functional impacts can be found below in Fig. 1.

Symptoms

Symptoms of FOP reported by children/adolescents, parents, and clinicians were pain, swelling, redness, and stiffness. When describing their FOP symptoms, one adolescent stated:

> "It feels really big. I think it feels bigger than it is, and just very

Symptoms of FOP	
Pain[1,2,3]	Swelling[1,2,3]
Redness[1,2,3]	Warmth[1,2]
Stiffness[1,2,3]	Feels sick / Fever / Flu-like symptoms[1,2]
Tired[2]	Tingling[2]
Itchy[2]	Strong smelling urine[2]
Twitching in eyes[2,4]	Migraine[2,4]

Functional impacts of FOP	
Accommodations[1,2]	Mobility[1,2]
ADLs[1,2]	Daily activities[1,2]
Social activities[1,2]	School[2]
Mental health[2]	Medical[2]

Fig. 1 Conceptual model of symptoms and functional impacts of FOP: [1]child reported; [2]patient reported; [3]clinician reported; [4]specific to flare location. Note: ADLs refer to basic self-care tasks such as bathing or brushing teeth; daily activities refers to other activities that people do on a daily basis

uncomfortable because of the swelling mostly." (15 years old)

While these symptoms were distinct, children/adolescents and their parents often reported experiencing multiple symptoms at the same time, such as this adolescent complaining of pain, redness, and swelling (which are all related to inflammation):

"Pain—a lot of pain. And then it turns red. Usually the area's red or hot, and it starts swelling." (17 years old)

Additional symptoms reported by both children/adolescents and parents included feeling sick, having flu-like symptoms, or being tired. Parents alone reported the most variation in symptoms related to flares for their child, including the child feeling tired, tingling, or itchy, having a veiny pattern on the skin, and having strong-smelling urine. Two other symptoms, twitching in eyes and migraine, were also reported by parents but were specific to a flare location (back and neck) and not general symptoms.

"We had migraines, and then we had a twitching issue that was happening, and they felt that that was happening because there's no place for the inflammation to go, so it was going to his brain and causing the migraines and causing an issue with his eyes." (Parent of a 9-year-old)

In the supplementary materials, Online Appendix A provides a list of illustrative quotes from children/adolescents and parents to provide further insight regarding the child/adolescent and parent experience of symptoms.

Additionally, children/adolescents and parents reported that the duration of flare-ups varies significantly. Some participants reported that they come in cycles, while others complained of difficulty determining the end of a flare-up. When a flare-up ends, patients report that they feel *back to normal*, the *pain subsides*, *swelling goes down*, and *redness goes away*. Similarly, the frequency of flare-ups varies, with children/adolescents and parents reporting *pretty often*, *once or twice a year*, *every week or every month*, *continuous*, and *once every 4 to 5 months*. The size of flare-ups and severity of pain also vary; patients and parents report that the larger flare-ups are the ones that hurt more. Some flare-ups result in new bone growth, while others do not. This information is consistent with what was reported in Pignolo et al. (2015), which reports on the results of a global survey of the natural history of flare-ups in FOP [20].

Impact

Functional impacts of flares and FOP in general were also described by children/adolescents and parents, including accommodations, mobility, activities of daily living (ADLs), daily activities, and social activities. Impacts were attributed to the difficulties children and adolescents faced living with a disease that prohibited common activities. Children/adolescents and parents

alike described the challenges in daily life, saying:

> "Sometimes getting dressed, it's kind of hard to do it on my own." (16 years old)
> "I do also have to help her with her toiletry like in the restroom to make sure her hygiene is good, because she cannot reach behind her back or reach down." (Parent of a 5-year-old)
> "There's been times when he has felt left out because he couldn't—he wasn't allowed to do things for safety reasons, like bounce houses at birthday parties and those kinds of things." (Parent of a 5-year-old)

Impact concepts described only by parents included school, mental health, and medical impacts. For example, one parent said:

> "Again, he's had a really good year, but previously there have been times where he's missed a lot of school due to pain, and that was really difficult for him, too, just socially—anything at school that he had to do differently, like not participating in gym or doing it differently or special equipment in the classroom, stuff like that." (Parent of an 11-year-old).

Other impacts reported included a limitation in mobility, difficulty focusing on anything else, and problems with sleep, moodiness, and appetite being affected. One adolescent commented:

> "Well, it's like when I sleep, it's a lot of pain, and I'm awfully—mostly uncomfortable a lot of the time. Sleeping, I end up turning a lot." (17 years old)

Some of these concepts were further broken down into sub-concepts; supplementary details and illustrative quotes can be found in Appendix B in the supplementary materials.

DISCUSSION

Our main objective for this study was to gain an in-depth understanding of the experience of children and adolescents living with FOP from their perspective and that of their parents. We positioned the patient's voice at the forefront of our investigation to reveal emotional and physical effects that may not be as detailed in quantitative studies. As there is a paucity of qualitative, patient-reported information in the literature, our study contributes new perspectives on the experience of living with FOP including the symptom experience and functional impacts of accommodations, school, mental health, ADLs, social activities, and medical impacts to complement existing quantitative research with patients and parents [21, 22].

Through our interviews, we were able to elicit important concepts that describe the experience of children and adolescents with FOP, which contributed to our development of a conceptual model of their experience of the disease. Notably, we found that children and adolescents with FOP and their parents described the experience of FOP regarding symptoms and functional impacts of the disease. In addition, some concepts were specifically related to flare-ups (e.g., swelling), while others were related to the disease experience more generally (e.g., impact on social activities).

These findings add to the understanding of the experience of children and adolescents with FOP and can help inform the assessment of this population in a clinical or research setting. By prioritizing the patient perspective as a necessary tool, researchers and clinicians ensure that the concepts important to patients are represented. Moreover, the data uncovered in this study could potentially be used to develop a conceptual model of the adult experience of FOP, further expanding clinical understanding of what is important to patients with this rare disease.

Although this study did reveal unique, rich, and detailed insight into the patient experience, it did have some limitations. First, study participants were recruited via convenience sampling, which can limit the ability to generalize our findings to all people living with FOP; however, larger quantitative studies have reported findings that are consistent with what we heard from patients [20, 22]. Second, we conducted this study during the COVID-19

pandemic, a challenging environment for qualitative study. As a result of COVID-19 restrictions, interviews could only be conducted via phone or internet. In addition, the immediate daily experiences of the participants were limited because of COVID restrictions, which may have affected the topics they discussed. As the pandemic wanes, additional research should consider in-person interviews to ensure accessibility and the collection of additional data. Finally, for children under the age of 7 years or those requiring assistance, their parents were present during the conduct of the interview, which may have biased their responses. However, this is a recommended practice in qualitative research with young children [15].

CONCLUSION

This qualitative research documented the seldom-represented patient-reported experience of children and adolescents with FOP and its physical and emotional effects on their daily lives. It provides a conceptual model for further exploration of the symptoms and impacts important to children and adolescents with FOP and their parents. Patients and their parents offered novel insights into life with the disease that have not surfaced in previous qualitative research. Moreover, children/adolescents and their parents reported the dynamic nature of flare-ups, confirming the variability of their intensity and duration. Future studies should build upon our conceptual model to both create a holistic view of the patient experience of FOP and ensure their needs are being addressed.

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Compliance with Ethics Guidelines. Study documents, including the protocol, demographic and health information form, interview guide, screener, and informed consent and assent forms received ethical approval from Advarra IRB (IRB #00,046,227). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided informed consent to participate in the study. Consent and assent via written consent forms were obtained from both

patients and their parents before proceeding with the interviews.

Data Availability. All data generated or analyzed during this study are included in this published article.

REFERENCES

1. Liljesthröm M, Pignolo R, Kaplan F. Epidemiology of the global fibrodysplasia ossificans progressiva (FOP) community. J Rare Dis Res Treat. 2020;5(2):31–6.

2. Pignolo RJ, et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in the United States: estimate from three treatment centers and a patient organization. Orphanet J Rare Dis. 2021;16(1):1–8.

3. International Fibrodysplasia Ossificans Progressiva Association (IFOPA). What is FOP?. https://www.ifopa.org/what_is_fop. Accessed 10 July 2020.

4. Jha MS, Shanker RV, Kumar A, Singh TB. Psychological interventions in a case of fibrodysplasia ossificans progressiva: A case report. Int J Case Rep Images (IJCRI). 2013;4(2):115–9.

5. Mattera MS, Kaplan FS, Pignolo RJ, Grogan D, Revicki DA. Patient-reported physical function outome measure for adults with fibrodysplasia ossificans progressiva: intelligent test design based on promis item banks. Value Health. 2015;18(3):A65.

6. Zapata-Whelan C. Finding magic mountain: life with five glorious kids and a rogue gene called FOP. Da Capo Lifelong Books; 2006. p. 320.

7. Cali IL, Rossano L. Fibrodysplasia ossificans progressiva: the patient voice. Bone. 2018;109:291–4.

8. Perfetto EM, et al. Value to whom? The patient voice in the value discussion. Value Health. 2017;20(2):286–91.

9. Dean S, et al. "The patient is speaking": discovering the patient voice in ophthalmology. Br J Ophthalmol. 2017;101(6):700–8.

10. US Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. 2020. https://www.fda.gov/media/139088/download.

11. US Food and Drug Administration. Roadmap to Patient-Focused Outcome Measurement in Clinical Trials 2015. https://www.fda.gov/media/87004/download.

12. US Food and Drug Administration. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. 2019. https://www.fda.gov/media/131230/download.

13. Bowling A. Research methods in health: investigating health and health services. 3rd ed. Maidenhead: Open University Press; 2009.

14. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–90.

15. Matza LS, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013;16(4):461–79.

16. Friese S. ATLAS. ti 7 User Manual Updated for program version: 7.5. ATLAS. ti, Berlin. 2014.

17. Bryman A, Burgess B. Analyzing qualitative data. New York: Routledge; 2002.

18. Thomas DR. A general inductive approach for analyzing qualitative evaluation data. Am J Eval. 2006;27(2):237–46.

19. Qualitative research in health care. In: Mays N, Pope, C. editors. BMJ Books; 2000.

20. Pignolo RJ, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): a comprehensive global assessment. J Bone Miner Res. 2016;31(3):650–6.

21. Al Mukaddam M, et al. Caregiver support in fibrodysplasia ossificans progressiva. J Rare Dis Res Treat. 2021;6(1):6–12.

22. Pignolo RJ, et al. Self-reported baseline phenotypes from the International Fibrodysplasia Ossificans Progressiva (FOP) Association Global Registry. Bone. 2020;134:115274.