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Improving patient outcomes in fibrous dysplasia/McCune-Albright syndrome: an international multidisciplinary workshop to inform an international partnership

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Abstract

Summary—To develop consensus on improving the management of patients, we convened an international workshop involving patients, clinicians, and researchers. Key findings included the diagnostic delay and variability in subsequent management with agreement to develop an international natural history study. We now invite other stakeholders to join the partnership.

Purpose—The aim of this study was develop a consensus on how to improve the management of patients with fibrous dysplasia and prioritize areas for research

Methods—An international workshop was held over 3 days involving patients, clinicians, and researchers. Each day had a combination of formal presentations and facilitated discussions that focused on clinical pathways and research.

The authors are grateful to all clinicians, researchers, and key patient representatives of the FD/MAS partnership for their contributions to this paper.

Compliance with ethical standards

Conflicts of interest None.

Results—The patient workshop day highlighted the variability of patients' experience in getting a diagnosis, the knowledge of general clinical staff, and understanding long-term outcomes. The research workshop prioritized collaborations that improved understanding of the contemporary natural history of fibrous dysplasia/McCune-Albright syndrome (FD/MAS). The clinical workshop outlined the key issues around diagnostics, assessment of severity, treatment and monitoring of patients.

Conclusions—In spite of advances in understanding the genetic and molecular underpinnings of fibrous dysplasia/McCune-Albright syndrome, clinical management remains a challenge. From the workshop, a consensus was reached to create an international, multi-stakeholder partnership to advance research and clinical care in FD/MAS. We invite other stakeholders to join the partnership.

Keywords

Fibrous dysplasia; McCune-Albright syndrome; Patient-centered care; Epidemiology

Introduction

Fibrous dysplasia (OMIM # 174800) is a rare disease affecting the bone and is sometimes associated with endocrine dysfunction and skin pigmentation as part of McCune-Albright syndrome [1]. Fibrous dysplasia is due to a mosaic mutation during embryogenesis leading to constitutive activation of the G-protein alpha subunit in affected tissues including the bone, endocrine glands, and skin [2]. Both children and adults report poor physical function and pain, but preliminary data suggests that they maintain emotional and social function [3, 4]. The aims of management are to ensure patients realize their highest quality of life. A number of recommendations for the diagnosis [5, 6] and management [6] of patients have been published. Management focuses on confirming the diagnosis, determining the extent of disease, providing appropriate interventions, and monitoring for complications. This requires involvement of a multidisciplinary team across the lifetime of the affected individual. The major challenge is to ensure all patients consistently receive high quality care with minimal variation.

The aim of this initiative was to develop a global strategy for future research and clinical guidance for improving patient outcomes. To facilitate this, we engaged with the Fibrous Dysplasia Support Society UK, and the Skeletal Rare Disease Working Group of the International Osteoporosis Foundation (SRD-IOF). The SRD-IOF is an international working group which focuses on mentoring and knowledge sharing, networking opportunities, developing bone-related projects, and initiating advocacy activities and integration of skeletal rare diseases of the bone into the general bone.

Method

In order to achieve the aim, a 3-day workshop was convened in conjunction with UK patient support society, the Fibrous Dysplasia Support Society (FDSS), the Oxford National Institute for Health Research (NIHR) Musculoskeletal Biomedical Research Unit, and the NIHR Musculoskeletal Rare Diseases Translational Research Collaboration. The workshop

was structured into 3 days: patients with few clinicians on the patient workshop (day 1), both patients and clinicians/researchers on the research workshop (day 2), and only clinicians/researchers on the research workshop (day 3) (agenda in supplementary materials).

Before the meeting, registered participants were sent a brief questionnaire to elicit their research priorities across diagnosis, prognosis, and treatment as well as to suggest up to three questions for research.

An update on the biology and clinical management for adults and children with fibrous dysplasia/McCune-Albright syndrome (FD/MAS) was presented, and patients and their family members were invited to comment and discuss their issues either within the wider group or in a one-to-one setting with either Dr Collins or Dr Boyce.

For the research workshop, there were presentations of a literature review of all publications in PubMED with the MESH term “Fibrous Dysplasia of Bone,” clinical assessment of bone pain, health-related quality of life, and costs in patients. The current and proposed activity of the International Osteoporosis Foundation Skeletal Rare Disease Clinical Scientific Advisors was presented followed by the research activity and key research questions from National Institute of Health (NIH), Leiden, Turin, Lyon, Florence, and Oxford. The results from the participant survey were next presented. This was followed by a discussion of the priorities for research using expert opinion. The final clinical workshop was introduced by state-of-the-art presentations on pediatric, adult, and surgical management of patients with FD/MAS followed by case presentations to stimulate discussion from the experts present on developing a global clinical pathway.

Results

Patient workshop

Thirty-seven patients and 33 family members attended the patient workshop with 3 doctors present. Following the presentations from doctors, the patients were able to reflect on the day and ask questions. The theme of the comments by the patients and family was focused on the lack of information for both patients and clinicians and included:

> “How do I know what is the right and wrong information on the web?”
>
> “My doctor did tell me I also had FD in the lower arm as well as humerus and was told it did not hurt and not to worry about it.”
>
> “Who is going to look after her when she turns 17?”
>
> “The doctor looked at my x-ray of my head and got very excited and said he had not seen this before. I felt a bit like a prize cow and the doctor did not want to let me go so had to fight to get referred to a Doctor who had seen fibrous dysplasia before.”

Following the open session, a series of one-to-one consultations between patients and MTC/AMB were undertaken. The feedback from these sessions was wholly positive. Patients were encouraged to give details of their case histories and examined when necessary. Some were then given suggestions for further diagnostics and treatments.

Research workshop

Eight patients and 20 academics/clinicians were present. Following short updates on the current evidence informing clinical management of fibrous dysplasia, mechanisms of pain in the bone, and value of economic assessments, the current and proposed activity of the International Osteoporosis Foundation Skeletal Rare Disease Clinical Scientific Advisors (website) was presented. The current research activity and key research questions from the representative institutions identified a number of existing cohorts as well as two pilot studies of denosumab and tociluzimab. The Lyon-developed diagnostic pathway [5] and details about the National Institute of Health/National Center for Advancing Translational Sciences (NIH/NCATS) Global Rare Diseases Patient Registry Data Repository/GRDR^{SM} were also presented.

Ten patients/carers and nine clinicians/researchers responded to the survey. While both ranked research into treatment as the highest priority (55 and 65 %, respectively), clinicians/researchers ranked prognosis (20 %) while patients ranked diagnosis (35 %) as the next highest priority.

Several research priorities were identified (Table 1). The highest priority research was improving our understanding of the natural history of FD. The method proposed to achieve this was aggregation of cohort data already collected in tandem with the development of a prospective cohort. The key outputs of the cohort would be to (a) define the natural history, (b) determine additional surrogate markers for clinical outcomes (to skeletal disease burden score [7] and phosphaturia [8]) and treatment response, and (c) understand the mechanism of fibrous dysplasia-related bone pain. From existing datasets, work is needed to identify common questions as well as address ethical and governance issues for pooling information between countries and working with the GRDR. Of note, the patients' present felt issues around data access were surmountable and were willing to support any ethical issues. One of the statements from the patients was their wish for their information to be used for research. This was juxtaposed with the researchers concerns not to contravene national data protection regulations, and the group felt this had to be carefully balanced lest we overlook the right for the patients and their wishes to have their experience shared for the wider good.

An opportunity was identified to learn from existing international consortia that share data, such as the international disorders of sex development [9] or the Brittle Bone Disorders Consortium (https://www.rarediseasesnetwork.org/cms/BBD). For the prospective cohort, key aspects would include tools for pain assessment, fracture history, quality of life (both generic and explored disease-specific tools), costs (healthcare, informal, productivity losses, social care), standardized radiological imaging, biomarkers for disease activity, and standardized tissue biosample-operating procedures. It was recognized that if appropriately consented, the cohort could also be offered participation in international clinical trials. The group also expressed the need to establish novel research and analytical methodology appropriate for rare diseases.

From the post meeting feedback form, 100 % were willing to attend the event again, and 14/15 thought the format could work for other diseases. In more detail, what can be improved: more structured input from patients/have a patient representative speak at the

research workshop; representation from orthopedics, craniofacial surgeons, radiologists, neurosurgeons, dentists, specialist nurses, geneticists, basic researchers, and radiologists; pre-meeting circulation of revised timetable; specific discussion on fertility; and provision of a microphone. Other comments included “As a patient it has been humbling to see the level of knowledge, skill and passion being directed into FD” (from patient) and “How will the international database be used by pharma” (from patient).

Clinical workshop

Fourteen clinicians/clinician scientists and one researcher attended the clinical workshop. The rationale and content for the NIH guidance were presented followed by a discussion on key orthopedic issues. From the orthopedic presentation (FM), the following concepts were discussed: operative and non-operative interventions to improve function, role of prophylactic stabilization, bone grafting, assessment of vascularity, and choice of fixation. The subsequent discussion was split into pediatric vs. adult and along four themes: diagnostics, assessment of severity, treatment and monitoring, and the key issues (Table 2).

From the post meeting feedback, 100 % were willing to attend the event again and thought the format could work for other diseases. In more detail, what worked well: clinical cases, post lecture discussions/interaction; what could have been improved: communications about timing, more cases; other aspects that should have been covered included: indications for surgery in adult patients, specialist pain assessment and management, include more orthopedic, craniofacial, neurosurgeons and ENT surgeons.

Engagement and communication strategy

It was recognized that a number of centers and clinical specialties were not present, and a key next step is to ensure they are invited to join the group. Other aspects of the engagement strategy are shown in Table 3.

Discussion

The principal agreement of the meeting was the need for international collaboration to improve the evidence base and clinical care for patients with FD/MAS. Another key component was the recognition that the current global variation in patient care from diagnostics to assessment of severity, management, and monitoring was not evidence-based and may also hinder improvement in the evidence base. Finally, the value of a single template for evidence-based diagnostic and treatment guidelines and research assessment was recognized to enable audit of good practice as well as maximizing collaboration for research.

The format of the 3 days worked well by linking a patient day, mixed patient/clinical/researcher day, and a pure clinical day. The use of clinical cases to stimulate discussion on clinical pathways was very successful. While there were specific pediatric and adult sections to the day, most attendees participated in both, allowing further sharing of experiences in both directions and recognition of the importance of FD/MAS management across the lifespan. There was a limited surgical representation and no radiological representation. Future meetings will need to address greater orthopedic, craniofacial, and radiologist

involvement as well as inviting other centers to join the group. The workshop collated opinions from the experts present, and a systematic review was not performed given the low number of trials. We also recognize that while a number of patients, family members, and carers attended, they may not be representative of the average patient with FD.

In summary, we have described the successful initiation of the international FD/MAS partnership that includes clinicians and patients and the methods and outputs from the inaugural meeting. We wish to extend the invitation for others to join this partnership to support improving outcomes for patients with FD/MAS. For more information please contact rudy@ndorms.ox.ac.uk.

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Table 1

Research topic list

Domain	Subject
Natural history/ spectrum of disease	International cohort to establish natural history and predictors of progression Mechanisms of bone pain in FD including patient assessment of pain Harmonize methods for diagnostics, demographics, biochemistry, bone sample processing, and storage Measurement of quality of life using generic and development of disease-specific tools Health, social care, and informal costs across the lifespan Define the spectrum of extraskeletal manifestations in FD/MAS including neuropsychiatric, gastro-intestinal, gynecological, and cardiac manifestations
Management	RCT of current bone therapies to confirm efficacy Novel therapies using small molecules Improving the evidence base for orthopedic and craniofacial surgical indications and techniques Management of extraskeletal manifestations including long-term gynecologic complications in adults and pancreatic involvement
Prognosis	Fertility and disease activity during pregnancy Development of tools to aid in assessment of severity and assist in prognostication

Table 2

clinical topic list

Domain	Subject	Comment
Diagnostic	Importance of isotope bone scintigraphy vs. whole body MR	Sensitivity and practicality of whole body MR When to delay scintigraphy in children without overt bone disease
	Role of biopsy and mutation analysis	Heterogeneity of lesions affects sensitivity of biopsy-based methods
	Diagnostic pathways differs between Lyon and NIH	Harmonization of diagnostic pathways with table of differential diagnoses by site of lesion
	Natural history of Mazabraud's syndrome	
Staging	Staging evaluation to determine the extent of skeletal and extraskeletal involvement should be performed in all patients with suspected disease at initial presentation	Evidence-based guidelines to be determined by review of existing literature and harmonization of the existing NIH and Lyon pathways
	Clinical assessment template differs between centers	Harmonization of NIH clinical template to develop a global clinical template tool. Identify key languages for translation
	Which diagnostic tests to assess disease severity and extraskeletal involvement	
	Long-term medical vs. surgical management of hyperthyroidism	
	Role of biochemical testing and pituitary MR in diagnosis and management of growth hormone excess	
	Value of ongoing surveillance for progression of skeletal deformities across the lifespan, including scoliosis, hearing and vision deficits, and dental complications including mal-occlusions	
Management	The group acknowledged the importance of defining appropriate indications for anti-resorptive therapy	
	The dose and timing of anti-resorptive therapy varied between sites. The group consensus was to identify the maximum dosing for induction therapy and then the rationale for the timing of maintenance therapy. Surveillance of possible side effects of anti-resorptive therapy (osteonecrosis of the jaw, atypical subtrochanteric femoral fractures, hypocalcaemia).	
	Methods for treatment of hypophosphatemia should be informed by pathways in the management of other conditions of FGF23 excess	
	Use existing guidance for typical and atypical analgesics as well as adjuvant interventions in those with chronic pain	
	Optimizing management of endocrinopathies, including the impact on skeletal disease progression and pain	Effects of uncontrolled GH excess on craniofacial disease progression. Effects of untreated or inadequately treated hypophosphatemia on pain and fracture risk. Medical therapies are effective for most endocrinopathies, and surgical management for gonadal disease is not indicated.
	Management of craniofacial FD	Importance of routine vision and hearing monitoring. Prophylactic optic nerve decompression in asymptomatic patients is contraindicated.
	The role of rehabilitation medicine and physiotherapy in management of function, deformities, and pain	
	Guidance for dental health	

Table 3

Engagement strategy

Strategy
Use the IOF to disseminate research and clinical guidelines
Update the Wikipedia pages on fibrous dysplasia and McCune-Albright syndrome
Submit publications in medical, orthopedic, and craniofacial journals
Develop an international network of patient societies and centers of excellence
Produce a patient leaflet that includes information about recommended diagnostic tests, therapies, complications, and research opportunities
Apply for external funding to support the research and clinical network
Plan a meeting for 2016/17