Fibrous dysplasia

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Chapter 13

General discussion

The findings from this thesis were instrumental in shedding new light on various important aspects of the rare bone disease fibrous dysplasia (FD). The role of *GNAS*-mutations in the development of pathologic changes in tissues other than the skeleton was explored, current treatment modalities, both medical and surgical, were evaluated and discussed, and the impact of fibrous dysplasia on the quality of life of patients affected with this disorder was systematically addressed. This Discussion chapter addresses remaining knowledge gaps, new questions generated by our findings, as well as future research perspectives.

Pitfalls and challenges in the diagnosis of fibrous dysplasia

An important challenge in the management of FD is the avoidance of delayed diagnosis. As nearly universal in the case of rare diseases, there is a lack of knowledge about the clinical presentation of fibrous dysplasia among non-specialists in the field of bone diseases, and among general practitioners. This often leads to problems in recognizing the manifestations of the disease resulting in diagnostic delay.[1] The wide clinical spectrum of fibrous dysplasia and heterogeneity of disease manifestations represent an even greater challenge for early diagnosis.[1-4] Early recognition of fibrous dysplasia in primary care and in secondary non-bone specialised care institutions may be very difficult. Case examples are that of an elderly patient with a pathological fracture of the humerus, but without ever having had complaints; a young patient with facial deformities, precocious puberty and GH-excess in the context of McCune-Albright syndrome, or a patient with a shepherd's crook deformity of the femur and severe mobility problems which all have fibrous dysplasia but associated with very different clinical presentations. In order to prevent diagnostic delay, specialist centres should aim at increasing awareness not only among general practitioners which are likely to be the first health care professionals to see the patient at presentation, but also among colleagues not familiar with rare bone diseases such as endocrinologists, rheumatologists, ENT surgeons, ophthalmologists and orthopaedic surgeons. Information about fibrous dysplasia should be made available and be easily accessible to both treating physicians and patients on reliable websites in order to facilitate a shorter diagnostic process. Guidelines should also be developed for further investigation of the extent and severity of the skeletal and non-skeletal manifestations of FD, and for best standard of care in its management.

Another pitfall in the early diagnosis of fibrous dysplasia is the variation in diagnostic approach between institutions, and also between different specialisms. Fibrous dysplasia represents the multidisciplinary disease par excellence, but it remains to

date often diagnosed and treated by a single medical specialty. Historically, fibrous dysplasia has been diagnosed on the basis of clinical and radiographic features, but today we have access to a wide range of diagnostic tools to aide this process. Clinical presentation remains, however, the most important tool for diagnosis, with the classical skeletal manifestations of fibrous dysplasia consisting of pain at the site of a lesion, deformity of affected bones and pathological fractures. In case of the McCune-Albright syndrome, these symptoms are usually more severe and associated with endocrinological abnormalities such as precocious puberty, GH-excess or hyperthyroidism. Next to evaluation of clinical characteristics, conventional X-rays should be evaluated for the characteristic features of fibrous dysplasia such as a ground glass effect, endosteal scalloping, well-circumscribed borders, possible cortical thinning and absent periosteal reaction, and the pathognomonic shepherd's crook deformity in severe cases of fibrous dysplasia of the proximal femur.[3-6] Evolution of fibrous dysplasia lesions has been reported on radiographic imaging, with lesions observed to become more sclerotic and less homogenous over time.[4,7] A technetium-99 skeletal scintigraphy should be performed to establish the extent and type of FD (monostotic vs. polyostotic, and craniofacial involvement), and skeletal burden scores (SBS) should be calculated.[8-10] The use F-NaF bone PET/CT scanning appears promising,[11-13] with possible advantages over technetium-99 skeletal scintigraphy including a more quantitative evaluation of the activity of fibrous dysplasia lesions and readily available 3D images that may aid in determining fracture risk and help with planning of surgical interventions. The evaluation of the potential of F-NaF bone PET/CT scanning in fibrous dysplasia represents an interesting topic for future research in this field.

Next to plain radiography and whole body scan imaging, computed tomography scans (CT-scans) of FD lesion(s) can be a helpful tool for orthopaedic surgeons to plan an intervention and for the development of a custom-made implant as demonstrated in Chapter 5 of this Thesis.

Magnetic Resonance scanning (MR-scanning) is also valuable in the evaluation of fibrous dysplasia.[14-16] It has been shown in this thesis that cystic changes represent a risk factor for fractures in FD of the humerus, thus providing the rationale for an increased role for MR-imaging in FD at this localisation as cystic changes are most sensitively assessed using MR-imaging. The advantage of MR-scans over conventional radiographs or CT-scans is their detailed imaging of soft tissue. MR-scans are thus also indicated in case of suspicion for intramuscular myxomas in the context of Mazabraud's syndrome, especially in the presence of unexplained complaints of the upper leg.[17]

Both CT-and MR-scans may be used to assess a rare possible malignant transformation of an FD lesion.[18] Both CT- and MRI-scans are important imaging techniques to evaluate the extent of affected bone in patients with craniofacial FD, as well as to assess the risk of compression of cranial nerves.[19,20]

Currently, bone markers such as ALP, P1NP and CTX are mostly used to monitor disease activity and response to medical therapy in a variety of bone diseases, including osteoporosis. It would be of interest to investigate a potential role for these markers in the diagnosis and differential diagnosis of FD, for instance simple bone cysts or a Paget lesion, which may present with similar radiographic features as an FD lesion.[21-24] Serum levels of FGF-23, that are often increased in polyostotic fibrous dysplasia, and shown to be related to extent and severity of FD lesions, could also help to discriminate fibrous dysplasia from other bone disorders, although little is so far known about levels of FGF-23 in simple bone cysts, morbus Paget or osteosarcomas.[25,26]

Next to bone markers, serum levels of calcium, phosphate, vitamin D, and intact PTH should be determined in patients with FD as these are known to be associated with mineralisation defects and are at risk of further impairment in mineralisation of bone in case of vitamin D deficiency or hypophosphatemia, which would in turn increase the risk of pain, deformity and fracture.[27,28] Extraskeletal manifestations of FD should be evaluated by an endocrinology screen in which serum levels of growth hormone and IGF-1 (especially in craniofacial FD), prolactin, TSH, cortisol are elevated. Serum levels of FGF-23 and phosphate should also be determined and TMP/GFR calculated to screen for possible renal phosphate wasting. Non-endocrine manifestations of FD, such as intramuscular myxomas, should be screened for on the basis of symptoms. Lastly, an increased risk of developing breast cancer in relatively young women with fibrous dysplasia was demonstrated in this thesis, as described in Chapter 3. On the basis of these findings early screening for breast cancer from the age of 35 was recommended in women with FD, particularly those with thoracic FD lesions.

In case the diagnosis of FD is still in doubt, especially in case of a possible malignant bone tumour, it is advisable to perform a biopsy of the lesion with additional *GNAS*-mutation analysis.[29-31] It is important to realize, however, that a *GNAS*-mutation might not be identified in all patients with FD, as identification rates vary widely, even in patients with evident polyostotic distribution of FD lesions.[32-34] These false negative results might be at least partially related to the mosaic distribution of the GNAS-mutation, which can lead to sampling errors. However, an important further factor for false negative results is the type of mutation analysis conducted on the

pathologic specimens. Next-generation sequencing is thus more likely to accurately identify a mutation in mosaic disorders than Sanger sequencing, and would provide more information about the frequency of the mutation in the sampled region. The process of decalcification of the samples also appears to play a role in the reliability of the outcomes of genetic analysis in FD.[35]

Impaired Quality of Life in fibrous dysplasia

The wide clinical spectrum in FD translates in a wide spectrum of impairment in QoL among patients with FD. Although we have shown that extensive disease and the presence of endocrinopathies are associated with more severe impairment in quality of life and negative illness perceptions, it is critical to realize that a number of additional factors may play a negative role on QoL in an FD patient.

Definition of disease activity in FD

One of the as yet to be unravelled aspect of FD is how to define disease activity. Pain is believed to be associated with active disease and it has been suggested that the latter may be associated with increased bone turnover as identified by increased circulating levels of bone turnover markers, but this premise remains to be conclusively established. Notwithstanding, the presence of pain symptoms and/or increased bone turnover markers have been used as indications for treatment with antiresorptive agents, in the hope that decreasing bone turnover would be associated with a decrease in pain symptoms as a result of decreasing FD disease activity. However, in two of our studies addressing pain in patients with FD (Chapter 9 and 10), none of the bone markers studied was associated with pain levels, and this was also true for serum levels of FGF-23. This finding suggests that a metabolically active lesion is not necessarily painful. It has also been suggested that some radiographic features may suggest activity or quiescence of a fibrous dysplasia lesion. Sclerotic rimming is thus believed to reflect quiescence of a lesion, typically in older patients with an incidental diagnosis of FD, whereas cortical thinning and a ground glass appearance are believed to be associated with active disease and also with a risk of developing deformities and pathological fractures.[4,7,36] Whereas extent and metabolic activity of FD lesions can be assessed by skeletal scintigraphy, activity of these lesions does not appear to change significantly over time, even after intensive treatment with antiresorptive agents and significant decreases in bone turnover, precluding the use of this imaging technique for monitoring changes in disease activity. The ability of NaF-PET scans to demonstrate reliable changes following treatment remains to be established.

The need for a multidisciplinary approach in the management of fibrous dysplasia

In this thesis the benefits and limitations of a number of available surgical and medical options for the treatment of FD have been discussed. The surgical treatment of FD has historically focused on lesions of the lower, weight-bearing extremities as these have the higher likelihood of being associated with pain, deformities and (recurrent) fractures, with resulting impairment of function and associated impairment in quality of life.[37-39] In contrast to fractures of the lower extremities, fractures of the upper extremities tend to be more forgiving and heal properly in the majority of cases after conservative treatment with immobilization of the fracture site with a cast or sling as has demonstrated in Chapter 6.[38] In Chapter 5 of this thesis an individualized, patient-tailored approach is proposed for the management of FD of the proximal femur, based on our own experience and that reported in published literature. The proposed algorithm should be considered as best clinical practice surgical treatment strategy based on our clinical experience and that of others, rather than being a strict guideline on the basis of hard evidence, which remains to date rather scarce. Well-established (international) studies conducted in a large number of patients and addressing outcome of various available interventions are required to confirm the validity of the proposed algorithm in the management of FD of the proximal femur. Although surgery has been the main treatment option for patients with FD until the early nineties, medical treatment options using antiresorptive agents such as bisphosphonates and more recently denosumab and tocilizumab are gaining increasing popularity, although opinions are still divided on indications for treatment and type, optimal dose and interval of use of these agents, mainly as existing studies have largely been conducted in small and heterogenic cohorts, and relatively low administered doses, raising questions about the reliability of reported outcomes and the implication of these results for current clinical practice.[21-24,40-44] In Chapter 7 of this thesis treatment with mainly the oral bisphosphonate olpadronate was evaluated in patients with polyostotic FD and various disease severity and activity as evaluated by serum levels of bone turnover markers and calculated skeletal burden score (SBS). Our data from this study suggest that whereas the majority of patients responded to a certain extent to treatment with bisphosphonates, a high SBS was associated with relative resistance to treatment. Interestingly, the majority of patients who had an incomplete response to long-term treatment with bisphosphonates, demonstrated a surprisingly swift and complete response to treatment with the RANK-Ligand antibody denosumab with normalisation of bone turnover markers and disappearance or significant decrease in pain levels as reported in Chapter 8. No side-effects were observed with treatment with either bisphosphonates or up to 1 year treatment with

denosumab. Our findings suggest that patients with symptomatic FD and increased bone turnover may be safely treated with bisphosphonates, also in the long-term with a potential beneficial switch to three-monthly denosumab injections in those with an unsatisfactory response to at least one year of treatment with appropriate doses of bisphosphonates. Caution should be however, exerted with the use of denosumab, based on recent reports of deleterious rebound effects on discontinuation of treatment in patients with osteoporosis as well in 2 cases of FD.[24,45-47]

Another suggested therapeutic agent in the management of symptomatic FD is tocilizumab, an inhibitor of IL-6, an interleukin that has been reported to be one of the driving factors for increased osteoclastogenesis in FD.[48] Apart from a single case report there are to date no reports on outcomes of treatment with tocilizumab in patients with FD.[44] Future studies are required to establish the role of each of these antiresorptive agents in the management of patients with FD, particularly addressing specific hard outcome measures such as prevention of progression of lesions, deformity and fractures, but also control of pain and improvement of function and quality of life.

In this thesis we addressed the use of both medical and surgical options but did not specifically look at the outcomes of a combined approach, which might be a particularly interesting and to date unexplored field in the management of fibrous dysplasia. As shown in Chapter 4 and 5, recurrence of activity of FD lesions is responsible for failure of a number of surgical interventions, especially relating to bone grafting interventions where grafts partially or fully resorb after implantation in the pathological FD tissue. It could be speculated that pre- and postoperative treatment with antiresorptive agents may improve outcomes of these procedures by decreasing the activity of FD lesions thus precluding recurrence of curetted lesions or resorption of implanted bone grafts. Although not specifically studied in FD, bisphosphonates have been shown to be able to reduce resorption rates of bone grafts in basic studies.[49,50] A hypothetical downside of combining bone grafting with antiresorptive treatment might be that bone grafts might take longer to anchor in healthy bone as a result of the decreased bone turnover, although this has not been studied in FD.[51,52] Lowering recurrence and resorption rates could improve the outcomes of bone graft surgery in FD, allowing for a single biological reconstruction instead of repeatedly undergoing surgery, as is now often the case in patients with severe lesions of the lower extremities, particularly of the proximal femur. Because antiresorptives agents have been suggested to have a thickening effect on the often thinned cortex of FD affected long bones, the outcome of metallic implants might also potentially improve by pre- and post-operative treatment with antiresorptive agents by decreasing the risk of (repetitive) fractures or breaking out of implants.[53,54]

Data on outcome of combined medical and surgical treatment are very scarce to non-existent in FD. One of the major reasons for the lack of studies addressing combined treatment options is probably the heterogeneity of FD phenotypes, the different types of surgery performed and the variety of medical agents administered. This makes it nearly impossible to draw any firm conclusions regarding the possible synergetic effect of antiresorptive treatment with surgical procedures on various outcomes, including pain and function, using retrospective data. Prospective studies are thus warranted but unfortunately difficult to perform in the currently sized cohorts due to the rarity of FD, especially as you would want to specifically look at subgroups of patients, surgical interventions and medication used. International collaboration would provide a basis to perform these much-needed studies to further improve and individualize the various treatment options in patients with FD.

Future perspectives in the management of fibrous dysplasia

More and more studies are now focusing on unravelling the pathophysiologic mechanism of the various manifestations of FD, aiming at developing novel approaches for its treatment with the ultimate goal being the definitive cure of the disease. Many of the limitations in current treatment options are due to our lack of full understanding the pathophysiology of FD. In spite of the discovery of *GNAS*-mutations as the cause for the development of FD, we do not as yet fully understand the mechanism by which these mutations lead to the different pathognomonic features of FD, nor do we comprehend what exactly causes the wide differences between FD phenotypes.[29,30,55,56] An example of this is our failure to understand why full excision of monostotic lesions is associated in almost all cases with recurrence of the lesions, despite securing free resection margins, suggesting that even very few residual undetected GNAS-mutated bone cells are capable of resulting in recurrence of an FD lesion.[3,57] A possible explanation for this phenomenon might lie in the mosaic pattern of the causative *GNAS*-mutation. It would be interesting to study this hypothesis by performing genetic analysis of bone biopsies of FD lesions sampled at different distances from the radiographic and histological visible margins of an FD lesion and determining the frequency of the *GNAS*-mutation in these samples using Next-Generation-Sequencing. A promising new FD mouse models could aid in answering these questions.[58,59] If we could determine what kind of resection margin would be appropriate, we could hypothetically be able to cure monostotic patients from FD by resecting the whole of FD affected bone, although we have to bear in mind that a large resection might have serious disadvantages depending on what reconstruction is possible after resection. Another interesting starting point in trying to develop a

cure for FD is the notion that FD can be seen as a disease of pluripotent cells mutating during embryonic development, in other words considering FD as a stem cell disease.[60] This means that the disorder could theoretically be systemically treated with a form of genetic therapy by silencing the mutated allele.[61] Ex vivo experiments have already demonstrated that it is possible to revert the FD phenotype with the use of lentivirally-expressed shRNAs.[62] However, in vivo experiments, let alone implementation of this kind of therapy in clinical practice are currently precluded by the lack of possibilities to restrict delivery of healthy stem cells to specific skeletal sites.[61]

Another potentially attractive option for the treatment of fibrous dysplasia might be local injection of anti-resorptive agents. Hypothetically, higher doses of these agents might be locally administered without an increased risk for systemic side effects. The possibility of injecting local agents has so far only been explored in cystic degeneration of humeral FD lesions, but might potentially be interesting as future treatment option of symptomatic lesions in other anatomical localisations.

While awaiting the discovery of a definitive cure for FD, which may take decades, we should continue to further explore the added benefits of a multidisciplinary approach in the management of FD.

Fibrous dysplasia as a systemic disease

Historically, FD was first described as a disease of bone. Whereas still mainly considered to be a rare disease of bone, more systemic effects of the GNAS mutation are represented in the extraskeletal manifestations of patients with FD as endocrinopathies in the context of the McCune-Albright syndrome (less than 5% of all patients with FD) or intramuscular myxomas in the context of Mazabraud's syndrome (less than 1% of all patients with FD).[4,63] Interestingly, the *GNAS*-mutation that is responsible for this disease is not only found in the bony lesions of patients with FD, but also in the thyroid tissue of patients that develop associated hyperthyroidism, in the pituitary tissue of patients with associated GH-excess or prolactin excess and in associated intramuscular myxomas.[29,64-67] It is of note that in the absence of FD, solitary pituitary adenomas, solitary thyroid adenomas and solitary intramuscular myxomas may also carry *GNAS*-mutations.[56,68-70] These findings suggest that *GNAS*-mutations do not only affect skeletal tissue but also, albeit to a lower extent, other tissue types. This might be explained by the function of the *GNAS* complex locus and its encoding of the stimulatory G protein (Gsα). Gsα plays a key role in the osteoblastic lineage and in the differentiation of bone marrow stromal cells, providing the explanation for the formation of FD lesions by

stimulation of Gsα and therefore cAMP, resulting in enhanced commitment of stromal cells but also an inhibition of their further differentiation into osteoblasts.[71,72] Next to skeletal tissue, Gsα is expressed in a large number of tissues from ectodermal, endodermal and mesodermal origin. These tissue types include the proximal renal tubules, neonatal brown fat, thyroid tissue, gonads and the paraventricular nucleus of the hypothalamus and pituitary.[64,72] The majority of these tissue types have been described as possibly malfunctioning in patients with McCune-Albright syndrome.[67]

With this knowledge we can probably explain why patients with a wide distribution of GNAS-mutations are at risk of developing extraskeletal manifestations, as they have the increased risk of these mutations being also present in tissue types other than bone. It is thus not surprising that intramuscular myxomas in the context of Mazabraud's syndrome are often found in patients with McCune-Albright syndrome, or that we found an increased risk of developing breast cancer in women with polyostotic FD, with lesions at thoracic sites.[73] It is however essential to realize that this hypothesis does not preclude the possibility of extraskeletal manifestations occurring in patients with monostotic disease. The finding of Mazabraud's syndrome related myxomas in patients with monostotic fibrous dysplasia underlines this, and it is likely that this also applies for other extraskeletal manifestations such as GH-excess, precocious puberty or even breast cancer. This also raises the possibility of the detection of (many) more *GNAS*-linked extraskeletal manifestations of FD, in the coming years, as have new extraskeletal manifestations such as thyroid carcinoma and in this thesis breast cancer been linked to FD in recent years.[66] It is therefore essential that we change the general perspective of FD from being only a disorder of bone to a broader view that the skeletal manifestations of FD may represent only part of the systemic manifestations of *GNAS* mutations and that these systematic manifestations may not be precluded by the monostotic or less severe forms of skeletal disease.

Conclusion

Fibrous dysplasia is a heterogeneous genetic but non-inherited rare bone disorder that is caused by the mosaic distribution of a postzygotic mutation of the *GNAS*-gene. Although its predominant features are the characteristic bony lesions, there is a wide spectrum of FD phenotypes that include a continuously expanding list of extraskeletal manifestations, underlining the systemic aspect of this *GNAS*-related disease. In line with its wide range of phenotypes, FD is associated with a wide clinical spectrum of symptoms, with pain, deformity, and fractures, leading not only to decreased mobility and function but also significantly impairing Quality of Life. Available surgical and

medical therapeutic options should be delivered in a patient-tailored, individualized manner, with full knowledge of their limitations and complications to ensure their most optimal outcome of the various modalities used, singly or in combination. FD is often a multisystemic disease, particularly its most severe forms, so that a multidisciplinary approach is mandatory to achieve the best life-long outcomes. The rarity of the disease dictates that all health care professionals involved in the care of FD should invest in international collaboration to provide the necessary power of numbers that can only be provided from large multicentre studies to address the several unanswered questions posed by this ubiquitous disorder, and fulfil the clinical unmet need of developing best clinical practice guidelines for its management.

Key findings

- Fibrous dysplasia is a systemic, *GNAS*-related disease, with characteristic bony lesions as its key feature.
- Pain symptoms are common in fibrous dysplasia, particularly in lesions of the weight-bearing lower extremities and ribs and generally in the more severe types of fibrous dysplasia.
- Quality of Life is impaired throughout the wide spectrum of fibrous dysplasia, including its milder forms, with severity of impairment being related to disease extent and severity as evaluated on skeletal scintigraphy by skeletal burden scores.
- Illness perceptions are altered leading to impaired Quality of Life in patients with fibrous dysplasia.
- Mazabraud's syndrome is more prevalent than previously suggested, and surgical resection of symptomatic myxomas has a good functional outcome, although recurrence may occur.
- Women with FD have an increased risk of developing breast cancer at a younger age than the general population, particularly those with thoracic FD lesions.
- Fibrous dysplasia lesions of the humerus with cystic deformation are associated with increased fracture risk, although these fractures can be safely treated conservatively in the majority of the patients.
- Cortical allografts, angled-blade plates and intramedullary nails are adequate and safe treatment options for fibrous dysplasia of the proximal femur, provided they are tailor-designed according to individual patient specifications.
- Long-term bisphosphonate therapy is associated with beneficial and safe outcomes in the majority of patients with polyostotic fibrous dysplasia, although response to therapy is limited by the higher skeletal disease burden in the more severely affected patients, particularly those with McCune-Albright syndrome.

- In patients with incomplete response or resistance to long-treatment with bisphosphonates, treatment with denosumab is associated good clinical and functional outcomes in the majority of the patients.
- FD should be treated by multidisciplinary teams in dedicated centres ideally collaborating with national and international centres with expertise in this disorder and other rare bone diseases.

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