Atypical femoral fractures: a rare complication possibly due to the accumulation of rare genetic variants

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Antiresorptive drugs, such as bisphosphonates and denosumab, are very effective in reducing the risk of vertebral and non-vertebral fractures in patients with osteoporosis. They can be administered conveniently, are generally well tolerated and the side effects are mild and infrequent. Occasionally, however, some patients may present complications peculiar to the treatment, such as atypical femoral fractures (FFA) and maxillary osteonecrosis. These complications occur very rarely, but are potentially serious and difficult to manage, so they are a source of concern for some doctors and many patients. This fear seems to have a negative influence, although not justified, on therapeutic compliance. Therefore, it would be extremely useful to identify the rare patients who are at risk of developing these complications.

FFA is a particularly paradoxical case, since it involves fractures that appear associated with treatments that are given precisely to reduce the risk of fracture. The ASBMR (American Society for Bone and Mineral Research) has developed criteria to identify atypical fractures, which include a subtrochanteric or diaphyseal location, an origin in the outer cortex and a transverse or slightly oblique path, a minimal or absent comminution, a thickening Periosteal in the external cortex and the absence of high-impact trauma as a trigger[1]. FFA has been related mainly to bisphosphonates, but cases associated with other antiresorptive drugs have also been reported[2]. Likewise, the appearance of fractures with characteristics similar to FFA has been described in patients with some monogenic skeletal diseases, such as osteogenesis imperfecta, pycnodysostosis, osteopetrosis, hypophosphatemic rickets or hypophosphatasia, even without having received antiresorptive drugs[3,4].

The frequency of FFA varies markedly from one study to another. Estimates range from 3 to 50 cases per 100,000 patient-years of bisphosphonate treatment. Prolonged treatment, for more than 5 years, seems to be associated with an increased risk, with the incidence reaching, in these cases, about 130 cases per 100,000 patient-years[5]. In several studies, clinical factors associated with FFA have been explored. Among them, treatment with glucocorticoids together with bisphosphonates is the one that has been associated with an increased risk of FFA in a more consistent manner[5,6].

As FFA is a complication that appears very rarely, only in a minority of patients treated with antiresorptives, it is thought that individual predisposition must be a significant factor. In favor of this is the fact that with a certain frequency the fractures are bilateral in the affected patients. Hence, several authors have analyzed whether these patients have any predisposing genetic characteristics. In this line, the work of Roca-Ayats et al.,[7] published in this issue of the journal, is particularly interesting because it includes three sisters with FFA. The family association reinforces the notion of genetic predisposition. The authors sequenced the exome, that is, the DNA coding regions. Most inherited diseases are due to mutations in these regions, although they only account for about 1% of the DNA. Roca-Ayats et al. They found several mutations in the 3 sisters studied, including some in genes that encode enzymes of the mevalonate pathway. These mutations are particularly interesting because this pathway is target of bisphosphonates, which gives biological plausibility to the causal relationship between these variants and the FFA associated with these antiresorptive drugs. However, the authors could not confirm that these mutations were involved in FFA suffered by other patients unrelated to the previous ones. In the Roca-Ayats study it was also observed that some patients had a mutation in the CYP1A1 gene, which metabolizes various hormones, eicosanoids and exogenous agents. Other studies have found mutations in genes that encode bone proteins such as alkaline phosphatase or collagen in some patients isolated with FFA. But in most of the cases analyzed, these mutations were not found[4].

These results suggest that there is genetic heterogeneity, that is, the susceptibility genes vary from one patient to another. *In silico* analyses and some functional experiments suggest that these muta-

tions have a deleterious effect on the function of proteins[8]. However, it must be taken into account that mutations have not yet been shown to be directly related to FFA risk.

Another issue that is not definitively clarified is whether FFAs respond to a monogenic or polygenic pattern, that is, if they are determined by a single variant in a given gene (although different from one patient to another) that causes a serious defect in bone biology, or if they are due to the accumulation of variants with negative effects in several genes, each of them with a limited impact. In a previous study of genotyping of patients with FFA using an exon-chip technology, which analyzes rare variants in the exome, we found that patients tended to accumulate variants not present in control subjects[9]. This supports the idea of a polygenic susceptibility. However, these results have yet to be confirmed in other groups of patients.

Although the results published in this field are still very few, the absence of replication is striking. That is, the genetic variants associated with FFA, a) are different in the different studies, and b) differ among the different patients in the same study. Logically, the work of Roca-Ayats is an exception in this last aspect, since it included several members of the same family. This suggests that the variants that predispose to FFA are rare variants, very rare in the general population, probably typical of a specific population group, or even of a specific patient. If this is really the case, it will be very difficult to replicate the results in different populations.

In fact, some epidemiological studies support the importance of genetic background and race in susceptibility to FFA. Thus, this complication seems to be much more frequent among Asians than in the Caucasian population[5,10]. On the other hand, FFA may be favored by certain characteristics of skeletal development. In fact, several studies have found an association between the curvature of the femur and FFA, so that FFA would be more frequent in patients with a varus femur[11]. But this phenomenon is not universal. Some patients with FFA do not present varus of the femur and in them the susceptibility presumably is conditioned by anomalies of the remodeling or other alterations of the bone biology, more than by alterations in their geometry.

The studies of genomic scanning and exome analysis are providing the first data to shed light on the determinants of individual susceptibility to FFA. To advance in this field, on the one hand, genetic studies of much larger groups of patients are needed. On the other hand, functional studies that demonstrate the real impact of these genetic variants on bone, through the analysis of transgenic and knock-out animals and other gene editing experiments. But keep in mind that it will not be enough to analyze the skeleton of genetically modified animals under basal conditions, but it will also be necessary to determine the skeletal changes in response to the antiresorptive.

There are other aspects not yet explored and whose involvement in the FFA cannot be ruled out *a priori*. These include, for example, alterations in DNA regulatory regions (non-coding regions not included in the exome analysis) and epigenetic marks such as DNA methylation and post-translational modifications of histones.

In short, the published clinical studies suggest that there is an individual susceptibility to FFA, determined, at least in part, by genetic factors. Such aspects have not yet been identified with certainty, but they may be polygenic, related to the accumulation of rare mutations in diverse genes. The Roca-Ayats study is a very interesting contribution to a question that has still hardly been explored. In anticipation of advances in this field, which should ideally lead us to be able to identify patients at risk early, clinicians and patients should not forget that FFAs are much less frequent than fragility fractures and that the risk-benefit ratio of antiresorptive drugs is clearly favorable. It has been estimated that for every FFA that could appear related to antiresorptive treatment, more than 100 hip fractures and several hundred other fractures are prevented[12]. Therefore, a very infrequent adverse effect such as FFA should not be an impediment for patients with osteoporosis to receive antiresorptive treatment when indicated and thus benefit from the marked reduction in fracture risk achieved with these drugs.

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Bibliography

1. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29(1):1-23.
2. Thompson RN, Armstrong CL, Heyburn G. Bilateral atypical femoral fractures in a patient prescribed denosumab - A case report. Bone. 2014;61:44-7.
3. Andersen JD, Bünger MH, Rahbek O, Hald JD, Harsløf T, Langdahl BL. Do femoral fractures in adult patients with osteogenesis imperfecta imitate atypical femoral fractures? A case series. Osteoporos Int. 2018 Nov 17; [Epub ahead of print].
4. Nguyen HH, M van de Laarschot D, Verkerk AJ, Milat F, Zillikens MC, Ebeling PR. Genetic risk factors for atypical femoral fractures (AFFs): a systematic review. J Bone Miner Res Plus. 2018;2(1):1-11.
5. Starr J, Tay YKD, Shane E. Current understanding of epidemiology, pathophysiology, and management of atypical femur fractures. Curr Osteoporos Rep. 2018;16(4):519-29.
6. López-Delgado L, Riancho-Zarrabeitia L, Riancho JA. Genetic and acquired factors influencing the effectiveness and toxicity of drug therapy in osteoporosis. Expert Opin Drug Metab Toxicol. 2016;12(4):389-98.
7. Roca-Ayats N, Falcó-Mascaró M, García-Giralt N, Cozar M, Abril JF, Quesada M, et al. Estudio genético de la fractura femoral atípica mediante la secuenciación del exoma en tres hermanas afectas y tres pacientes no relacionadas. Rev Osteoporos Metab Miner. 2018;10(4):108-18.
8. Roca-Ayats N, Ng PY, Garcia-Giralt N, Falcó-Mascaró M, Cozar M, Abril JF, et al. Functional characterization of a GGPPS variant identified in atypical femoral fracture patients and delineation of the role of GGPPS in bone-relevant cell types. J Bone Miner Res. 2018; 33(12):2091-8.

9. Perez-Nuñez I, Perez-Castrillon JL, Zarrabeitia MT, Garca-Ibarbia C, Martinez-Calvo L, Olmos JM, et al. Exon array analysis reveals genetic heterogeneity in atypical femoral fractures. A pilot study. Mol Cell Biochem. 2015;409(1-2):45-50.
10. Marcano A, Taormina D, Egol KA, Peck V, Tejwani NC. Are race and sex associated with the occurrence of atypical femoral fractures? Clin Orthop Relat Res. 2014;472(3):1020-7.
11. Hagen JE, Miller AN, Ott SM, Gardner M, Morshed S, Jeray K, et al. Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry. J Bone Joint Surg Am. 2014;96(22):1905-9.
12. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical Femur Fractures – Review of epidemiology, relationship to bisphosphonates, prevention and clinical management. Endocr Rev. 2018 Aug 29; [Epub ahead of print].