Editorial

Classification of constitutional disorders of bone: a new perspective

Clasificación de las enfermedades constitucionales del hueso: lo que va de ayer a hoy

Antonio Morales Piga,* Manuel Posada de la Paz

Instituto de Investigación de Enfermedades Raras, Instituto de Salud Carlos III, Madrid, Spain

Since ancient times, "skeletal deformities" have aroused great fascination that goes far beyond the field of medicine, penetrating into areas such as anthropology and art. In addition to the identification-rejection feeling they provoke, such interest could be due to the intrinsic complexity of these disorders. This was already evident clinically and radiologically before new genetic and biochemical techniques making such deformities much more evident were developed. The real impact of intrinsic or constitutional bone diseases (CBD) has not been established. Individually they are of low or very low frequency. However, given the great number of disorders that make up this concept, it is reasonable to assume that jointly they are associated to a non-negligible morbidity and that they bring about a notable decrease in quality of life for the patients who suffer from them.[1]

One of the main difficulties when undertaking a study of these disorders is to define the categories that the concept of CBD itself includes with all their definitions and limits. Bone structure complexity, the different origins of their components and the heterogeneity of underlying pathophysiological mechanisms explain the multiple pathways through which bone and related tissues can become diseased. Initial classification attempts were based on partial criteria, lacked uniformity and were often missing a precise definition. These classifications consequently included entities whose denomination corresponded to a remarkable evolutionary trait (e.g., thanatophoric dysplasia: which can cause death), to an important clinical or radiological characteristic that was not always essential (diastrophic dysplasia: referring to dislocated joints; Cleidocranial dysplasia: affecting the collarbone and head) or to a possible pathogenic mechanism [osteogenesis imperfecta (brittle bone disease); achondrogenesis]. Complex disorders that existed as an uncertain independent entity would normally be called by eponyms (Ellis-Van Creveld's syndrome, Larsen's dysplasia, etc.), as they had frequently been identified by accident or by chance. All of this plagued initial attempts to order these disorders systematically.

With the objective of progressing towards a systematic grouping of bone CBDs, starting from a homogeneous denomination with constant criteria that would be universally accepted, an international committee of experts met in Paris in 1969 and created the first "Nomenclature for constitutional disorders of bone."[2] The committee, led by Pierre Maroteaux, acknowledged that they would not attempt to build a general CBD classification; rather, they would put order into the welter of variegated ideas, confusing terms and abundant eponyms that prevailed at the time. They thus established well-defined nosological categories and standardised terminology. Likewise, they explained that something like this was always subject to review as techniques improved, as they already anticipated would happen; such techniques produce advances in better understanding of these diseases, particularly with regards to clearing up their etiopathogenic mechanisms. This idea was premonitory, given that experts have already carried out up to 6 reviews since then.[3-8] As a result, what in the initial proposal[2] and in the first reviews[3,4] was a mere "nomenclature" based on clinical and morphological criteria, over time has become a "classification,"[5] "nomenclature and classification"[6] or "nosology and classification,"[7,8] as genetic and molecular findings have allowed. In the last review, the term "constitutional" was replaced by "genetic skeletal diseases," directly alluding to the causal factor common to all these processes.[8] In addition, bone dysostosis had been omitted or minimised in previous editions due to the special difficulties it poses, while from the fifth review,[7] and especially in the sixth,[8] it has been widely included again.

However, what is most relevant in this (for now) latest review is that, through a combination of biochemical and radiographic criteria, it reflects the most recent genetic and molecular findings. It thus includes 372 well-documented diseases ordered into 37 groups with precise limits. Of these, 215 are associated to different alterations in one or more of 140 genes, which shows how things have advanced in the last few years. As an example, we mention a few of the relevant lines of investigation to give an idea of the effort that has facilitated this qualitative change in approaching this very complex question.

Fibroblast growth factor receptors (FGFRs) represent a family of 4 transmembrane tyrosine kinase receptors that, with varying affinity, link the fibroblast growth factors and thus regulate the

*Corresponding author.
  E-mail address: amorales@isciii.es (A. Morales Piga).

differentiation of various conjunctive and neuroectodermal cells. Fibroblast growth factors are also implicated in the chemotaxis, angiogenesis and apoptosis of these cells, which is why they are crucial in the normal development and growth of limbs and craniofacial area. The demonstration that the gene that codes FGFR-3 is found in chromosome area 4p16.3[9] led to a flood of findings in this area. In 1994, two groups−Le Merrer at INSERM in París[10] and Velinov in Farmington CT, USA[11]−independently concluded that the gene that caused achondroplasia was found in the telomeric region of band 16.3 in the short arm of chromosome 4. The following year, Bellus showed that replacing glycine with arginine in codon 380 of FGFR-3 would cause achondroplasia.[12] It was later discovered that a mutation in FGFR-1 leads to some forms of Pfeiffer craniosynostosis, while FGFR-2 mutations could cause Apert and Crouzon craniosynostosis, as well as other Pfeiffer variants.[13] Finally, it was shown that different mutations in FGFR-3, which is key for endochondral ossification and for the consequent transformation of normal cartilage into bone, cause disorders in the so-called "achondroplasia family."[14] This important CBD group includes the lethal thanatophoric dysplasia, achondroplasia and SADDAN (severe achondroplasia with acanthosis nigricans), as well as hypochondroplasia, the least severe of these disorders.

Without a doubt, this new way of focusing on CBD, based upon understanding its underlying etiopathogenic mechanisms, opens the doors to the future classification integrating morphology and function. That is, a classification with categories based on the underlying genetic-molecular alterations combined with morphological criteria. It is thus possible to regroup the CBD according to their pathogenic mechanism in 7 groups of clear functional significance: defects in extracellular structural proteins, in metabolic lines, in macromolecule folding or degradation, in hormones and transduction signal mechanisms, in nuclear proteins and transcription factors, in oncogenes and tumour suppressor genes and in RNA/DNA processing and metabolism.[1]

This emergence of findings on a molecular scale has shown the extreme functional complexity of bone and cartilage, with a vast number of cellular processes and metabolic pathways implicated in the genesis and maintenance of the skeleton. As a result, although clinical manifestations and image techniques are still crucial for differential diagnosis of CBD, genetic and biochemical studies are being used more and more frequently to achieve a precise diagnosis. This new focus also favours the development of diagnosis techniques that are increasingly reliable. In turn, these techniques make it possible to clarify the problems of identification and differentiation in certain entities, particularly those in the dysostosis group, which is still pending CBD classification. This focus also facilitates interdisciplinary collaboration, crucial in the approach to disorders presenting multiple facets. Lastly, it makes it possible to identify therapeutic targets for achieving safe and efficient drugs to treat these afflictions that are still considered to be deprived of the attention that they undoubtedly merit.

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