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Review

Implications of the new etiophatogenic approach in the classification of constitutional and genetic bone diseases

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ABSTRACT

Recent years have seen an unprecedented increase in the knowledge and understanding of biochemical disturbances involved on constitutional bone disorders. Recognition of the genetic background as the common cause of these diseases prompted the substitution of the term "constitutional" by "genetic", in referring to them. Understanding physiopathological bases by finding out the altered metabolic pathways as well as their regulatory and control systems, favours an earlier and more accurate diagnosis based on interdisciplinary collaboration. Although clinical and radiological assessment remains crucial in the study of these disorders, ever more often the diagnosis is achieved by molecular and genetic analysis. Elucidation of the damaged underlying molecular mechanisms offers targets potentially useful for therapeutic research in these complex and often disabling diseases.

Implicaciones del nuevo enfoque etiopatogénico en la clasificación de las enfermedades constitucionales y genéticas del hueso

Palabras clave:
Alteraciones moleculares
Enfermedades óseas genéticas
Osteocondrodisplasias

RESUMEN

El avance en el conocimiento de las alteraciones bioquímicas que causan las enfermedades constitucionales óseas no tiene precedentes. La constatación de que su característica esencial es el trasfondo genético común a todas ellas ha dado lugar a una propuesta de alcance: sustituir el término «constitucionales» por «genéticas» para referirse a estas entidades. La comprensión de los mecanismos fisiopatológicos implicados, identificando el punto exacto de la vía metabólica alterada y sus sistemas de regulación y control, facilita realizar un diagnóstico preciso, basado en la colaboración interdisciplinar, en un tiempo muy inferior del que requería el enfoque tradicional. Además, aunque la correcta valoración de las manifestaciones clínicas y radiológicas sigue siendo crucial, el diagnóstico de certeza se basa cada vez con mayor frecuencia en la aplicación de las nuevas técnicas de análisis genético y molecular. Por último, el esclarecimiento de las complejas alteraciones subyacentes a estos trastornos descubre unas dianas moleculares de gran utilidad potencial en la investigación terapéutica de unas enfermedades que a menudo limitan de manera notable la calidad de vida y que, casi sin excepciones, todavía carecen de un tratamiento eficaz.

What are constitutional bone diseases?

Constitutional bone diseases (CBD) are a large and heterogeneous group of disorders, whose common feature is failure of any of the bone cell systems leading to abnormalities in the transformation of primitive bone into mature bone.[1] Clinical and radiological expression may be manifested by: changes in overall (decrease in size or dwarfism) or partial growth (hypoplasia or aplasia), abnormal modeling (shape) of the bone, and alterations (excess or defect) in bone density.[1,2]

In the classical scheme, the CBD -also called intrinsic bone diseases- were divided into two groups: osteochondrodysplasias (dysplasias and dystrophies) and bone malformations (or dysostosis). Although there is some overlap between these categories, this distinction, with variations over time, has seemed useful at least from the theoretical-

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Table 1
Characteristics and main contributions of the successive attempts to systematize the nomenclature and classification of constitutional bone diseases

Characteristics Proposal (year)[reference]	Purpose/extension	Basic criteria employed	Main contributions
Initial (1971)[6]	Nomenclature/all CBD	Anatomical, radiological and clinical	First internationally accepted nomenclature Definition of terms
1st review (1977)[7]	Nomenclature/all CBD	Clinical, pathological, radiological	–
2nd review (1983)[8]	Nomenclature/all CBD	Clinical, pathological, radiological	New entities included
3rd review(1992)[9]	Classification/osteochondrodysplasias	Radiological	Defined criteria with precise differentiation points, eliminates inconsistencies, incorporates number of MIM (Mendelian Inheritance in Man)
4th review (1998)[10]	Nomenclature and classification/oste	Morphologic, genetic, molecular	Introduces etiopathogenic focus Adds new groups Incorporates OMIM number (on-line Mendelian inheritance in man)
5th review (2002)[11]	Nosologic and classification/All CBD	Morphologic, genetic, molecular	Incorporates dysostosis to known genetic base
6th review (2007)[12]	Nosology and classification/ all genetic skeletal diseases	Morphologic, genetic, molecular	Incorporates new entities from advances in gene and molecular knowledge Erases limits between morphologically separate categories Opens the way for a classification that integrates etiopathogenic mechanisms with morphologic aspects

CBD indicates constitutional bone diseases.

conceptual point of view.[2] The "osteochondrodysplasias" are generalized disease that occur as a result of an abnormality in the gene expression of some of the basic tissues (bone, cartilage or connective tissue) that form the skeleton as a multifunctional structure. This determines that the phenotypes of these entities continue to evolve throughout life so that bones that are initially apparently healthy may show abnormalities later in life. For their part, dysostosis are anomalies in the number, size, shape or position of an individual bone (or a combination thereof) that have their origin in an alteration in the blastogenesis in the first 6 weeks of embryo development. Unlike osteochondrodysplasias, malformations are localized and static in the sense that they do not extend to structures not originally affected, but can evolve in the bones that were compromised initially. With the development and implementation of more reliable and informative complex genetic and biochemical techniques, the concept of CBD and the systematization of the entities it comprises has evolved from a vision based on descriptive-morphological concepts to a more functional one focused on thoroughly clarifying the pathogenic mechanism. Thus, the entities comprising this nosological concept can be differentiated more clearly avoiding the confusion that previously existed. Our goal is to review the key elements that have contributed to this change of undoubted practical impact as it is a very different framework on which to lay the foundation for clinical approach and research into these diseases which, although individually have very low frequencies, together represent a significant proportion of health care due to a variety of orthopedic complications and limitation in the quality of life.[3,4]

Historical perspective of a difficult task: sorting the diverse and simplify the complex

Although it is beyond our purpose to do a thorough review of the successive attempts to systematically organize the CBD, it seems necessary to put into perspective its foundations and its main contributions. At the mid-twentieth century, the development of disciplines such as radiology and pediatrics led a major expansion of the knowledge of intrinsic diseases of the skeleton. However, given the complexity of the bone structures, the diverse origins of its components and the heterogeneity of the underlying pathophysiological mechanisms, the difficulty of identifying the disorders that were true variants eliminating unfounded entity (often eponymous) and superfluous categories was clear from the beginning. After several attempts to systematize the taxonomy of the CBD, which failed because of an inadequate focus,[5] in 1969 an international committee of experts developed the first "Nomenclature for constitutional bone diseases" based on consistent criteri.[6] Aware of the difficulties in this regard, the authors did not attempt to develop a general classification of the CBD. In fact, its purpose was to establish well-defined nosological categories, a consistent terminology that could be universally accepted, and began a path open to further reviews, six so far[7-12] (Table 1).

Without doubt, the greatest achievement of the first classification was to establish a solid base, avoiding misconceptions and eliminating a number of meaningless terms and eponyms. The system subdivided the "constitutional bone diseases"–a total of 128 entities excluding chromosomal abnormalities and secondary extraskeletal diseases (groups that were not broken down)–in 3 main categories: those with a yet unknown pathogenesis, those with known pathogenesis and those secondary to alterations in the extraskeletal systems (endocrine, hematological, etc.).[6] Within the known-pathogenesis diseases were chromosomal abnormalities and primary metabolic disorders (disorders of calcium-phosphorus metabolism, mucopolysaccharidoses, etc.). In terms of their pathogenesis remaining unknown, clearly the larger section, they included 4 groups: osteochondrodysplasias, dysostosis, idiopathic osteolysis and primary impairment of growth (primordial dwarfism, progeria and Marfan syndrome, among others). Within osteochondrodysplasias-undoubtedly the richer sub-group–the following were considered: growth defects of long bones of the spine or both, disorders of disorganized development of cartilage and fibrous components of the skeleton and bone density anomalies. Finally, in the subgroup of dysostosis there were those due to compromise of the head and face, the predominantly axial, and predominant in the extremities.

Except for the inclusion of several new entities, the first[7] and second[8] reviews, issued in 1977 and 1983 respectively (Table 1) did not bring about substantial changes. With some nuances, both maintained the morphological criteria of the original proposal and the term "nomenclature" and the scope covered the whole of the CBD. The third review, published in 1992, introduced a major change, first referring to a "classification" and focusing on the area of interest in osteochondrodysplasias, a group that appeared significantly expanded at the expense of dysostosis, which the committee was incapable of dealing with.[9] Moreover, the classification, with some 200 entities, was based on radiological criteria and eliminated clinical features including age at onset and natural history because of their variability and sometimes inconsistency. Last, but included

for the first time, the MIM number (Mendelian Inheritance in Man, Mc Kusick catalog) and some genetic information, recognizing that knowledge of the CBD was too fragmentary to attempt a causal classification. However, in the next review,[10] published in 1998, it identified a number of underlying cellular and enzyme disorders allowed for the first time the development of a "nomenclature and classification" with a causal approach. Despite progress, the fourth review was limited almost exclusively to the osteochondrodysplasias group excluding most dysostosis or bone malformations that the panel was still considered incapable of addressing. In this proposal, the categories in which osteochondrodysplasias were initially subdivided were replaced by 32 groups formed by reasonably homogeneous entities, with clear differentiation between them. It was not until the 5th review,[11] issued in 2001 and published a year later, that the expansion of knowledge in this area allowed to return to the original concept, renamed "Nosology and classification" and embracing all the CBD again including the dysostosis, many of which had managed to identify the chromosomal region involved, and even, especially in the craniosynostosis group, the causal genetic alteration.

Finally, the 6th review published in 2007[12] introduces an innovation of great importance by proposing that the term "genetic" should replace 'constitutional' to refer to these processes. Without a doubt, this change, while encouraged and required by the latest molecular genetic findings is powerful because not only can it lead to the addition of new entities as they are being recognized, but enables a more dynamic and functional grouping of the same in keeping with new etiopathogenic information to be incorporated. In the following lines we will discuss the implications of this latest attempt of systematic ordering of the CBD as it opens the door to a classification that integrates structured morphological categories on criteria consistent with categories related to the alteration of basic molecular pathogenesis.

Towards a comprehensive classification

The latest review proposed by the international committee of experts (see extract in Table 2) represents a substantial change to the previous[12] classification. The criteria to be met by an entity to be included are: 1) relevant skeletal condition, according to the definition of skeletal dysplasia, metabolic bone disease, dysostosis syndrome or malformation and / or reduction, 2) the publication or listing in the MIM catalog; 3) proven or very probable genetic basis, 4) nosologic personality confirmed by molecular analysis of linkage or based on the presence of unequivocal diagnostic features or observation of multiple individual cases or families. Using this combination of molecular criteria, including biochemical and clinical and radiographic, 372 entities in 37 groups are described, with clear boundaries and of these, 215 different diseases are associated with alterations in one or more than 140 genes.

Groups 1 to 6 have been newly created or reformed in depth to accommodate the related entities and molecular genetic alterations that caused it. In groups 7 to 16 grouping criteria based on anatomical or radiological pattern prevails. The groups 17 to 19 are defined by macroscopic criteria and clinical features (curved or tapered bones , the presence of multiple dislocations.) Groups 20 to 25 and 27 reflecte the changes in mineralization and bone density and, therefore, morphological and radiological appearance remain predominant. Group 26 represents the large group of lysosomal disorders with skeletal disease. Group 28 includes entities associated with the so-called "abnormal development of skeletal components" such as exostosis, enchondroma and the various forms of ectopic calcification. Finally, groups 29 to 37 (group 29 includes the cleidocranial dysplasia, a classic example of transition between dysplasia and dysostosis) is dedicated to the always difficult dysostosis sector following anatomical criteria (skull, face, axial skeleton, limbs) with additional criteria reflecting aspects of embryonic development.

Table 2
Extract from the latest classification by the international committee: main groups and entities included

1. FGFR3 group (fibroblast growth factor receptor 3): includes achondroplasia and related problems
2. Collagen type II group: Type 2 achondrogenesis, congenital spondylo-epyphiseal dysplasia…
3. Collagen type XI group: includes Stickler type 2 syndrome
4. Sulphatation alteration group: includes type 1B achondrogenesis
5. Perlecan group: includes bisegmented dysplasia
6. Filamin group: includes Larsen's syndrome (multiple congenital luxations)
7. Short rib group: chondro ectodermic dysplasia…
8. Multiple epyphiseal displasias and pseudoachondroplasia
9. Metaphyseal dysplasias (Schmid, McKusick and Jansen types, among others)
10. Spondylometaphyseal dysplasias (Kozlowski)
11. Spondyloepimetaphyseal dysplasias: with joint laxity, progressive immune and pseudorheumatoid bone
12. Severe spondylodysplasic dysplasia: achondrogenesis…
13. Moderate spondylodysplasic dysplasias
14. Acromelic dysplasias: tricho-rhino-falangeal dysplasia, familial arthropathy with brachydactylia…
15. Acromesomelic dysplasias
16. Meso and ryzomelic dysplasias: dischondrosteosis…
17. Curved bone dysplasia: campomelic dysplasia
18. Thin bone dysplasia
19. Multiple joint dyslocation dysplasia: Desbuquois (type 1) dysplasia
20. Chondrodysplasia punctata dysplasia
21. Osteosclerotic neonatal dysplasia: Caffey's disease…
22. ↑ in bone density: osteopetrosis (6 types), picnodysostosis, osteopoichilia, meloreostosis…
23. ↑ in density and meta or diaphiseal alterations: Camurati-Engelmann, endostal hyperostosis (Van Buchem), osteoectasia with hyperphosphatasia (juvenile Paget), Pyle's disease, pachidermoperiostosis…
24. ↓ in bone density: osteogenesis imperfecta (7 types), idiopathic juvenile osteoporosis…
25. Defect in mineralization: hypophosphatasia, hypophosphatemic rickets, hypocalciuric hypercalcemia …
26. Alterations in lysosomal storage: mucopolysacharidosis (10 types)
27. Osteolysis: expansive familial osteolysis, progeria…
28. Due to abnormal development of bone components: fibrous dysplasia, multiple cartilaginous exostosis (3 types), enchondromatosis (Ollier), progressive ossifying fibrodysplasia, progressive bone heteroplasia …
29. Cleido-craneal dysplasia group
30. Craneosynostosis and other abnormalities of cranial ossification: Pfeiffer, Apert, Crouzon syndromes..
31. Dysostosis with predominant craneo-facial affection: oral-facial-digital syndrome…
32. Dysostosis with predominant vertebral and rib affection
33. Patellar dysplasia: Patella-nail syndrome…
34. Crachydactilia: Albright's hereditary osteodystrophy …
35. Limb hypoplasia: Fanconi's anemia, Holt-Oram syndrome..
36. Polydactilia-syndactilia-triphalangism
37. Defects in joint formation: multiple synostosis (2 types), proximal synphalangism (2 types)…

Drawing on this classification (which is still in the process of improvement), the current expansion of genetic and biochemical knowledge can regroup the CBD on the basis of pathogenic-molecular alterations in 7 categories of clear functional significance.[3,13] Outlining in detail, according to these categories, the large number of diseases with genetic alterations that have been identified would exceed the limits of this review. However, it seems useful, from the most recent data, to point out some representative examples within each group defined by the pathogenic mechanism involved (Table 3).

Defects in extracellular structural proteins

This group includes some of the best characterized "families" of CBD and which affect the most abundant collagen in the bone–collagen type 1–(it is also important in skin and tendons),

and which predominates in cartilage–collagen type 2.[14] Therefore, perhaps it is the largest group and includes several of the most frequent diseases that cause greater clinical impact. These include osteogenesis imperfecta, which is considered the paradigm of the CBD characterized by decreased bone density. In 1979 Sillence proposed distinguishing 4 types of osteogenesis imperfecta type I, the common form with blue sclerae, type II, lethal in the perinatal period, type III, a progressive form with normal sclerae, and type IV, similar to type I but with normal sclerae.[15] From this schematic way of classifying OI we have come to include 7 main types and 16 subtypes with distinct genetic alterations, resulting in different transmission patterns and marked clinical differences.[12] This complexity corresponds to the combination of possible mutations that can occur in one or other of the two chains of type 1 collagen (α-1 and α-2 with coding genes located on different chromosomes) of the 'cartilage-associated protein" and prolyl 3-1hidroxilase activity (leprecan).[16,17]

On the other hand, mutations in type 2 collagen (group 2[12]) cause a wide variety of CBD.[18] The most common is spondylo-epiphyseal dysplasia, congenital Strudwick-type, which presents with short stature (with a disproportionately short trunk) and multiple joint epiphyseal dysplasias as well as platyspondylia. Other type 2 collagen mutations result in milder forms of spondylo-epiphyseal dysplasia and Kniest dysplasia (similar to the congenital form of spondylo-epiphyseal dysplasia).[19] Finally, in this group we find achondrogenesis and type 2hypochondrogenesis, two relatively common lethal entities before birth4. This group is also noteworthy in that mutations in α-1 chain of collagen type 10 cause Schmid[20] type metaphyseal dysplasia, more frequent and less intense than metaphyseal dysplasia (Group 9 of the last clasificación[12]). Among the entities that respond to this mechanism it is also interesting to consider the changes in two related proteins that serve as a bridge between proteins of the extracellular matrix of cartilage: the cartilage oligomeric matrix protein (COMP) and 'matrillin 3' (group 812). The phenotypic manifestations caused by mutations in these proteins depend on the tissue expression of corresponding genes. Thus, mutations in COMP can lead to a pseudoachondroplasia or type 1 multiple epiphyseal dysplasia,[21,22] while mutations in matrillin 3 cause multiple epiphyseal dysplasia type 3.[23] This section ends with alterations in proteoglycans, whose importance in the collagen matrix made them clear candidates to join the list of defective proteins in relation to the CBD. Several years ago it was shown that mutations in one of its components, perlecan, led to dissegmented dysplasia and Schwartz-Jampel type 1.[24] More recently, mutations have been reported in several genes related to aggrecan (the most abundant proteoglycan of cartilage extracellular matrix and a key factor in endochondral ossification, decisive in the final stature) as a cause of chondrodysplasia with attending dwarfism and intense vertebral compromise. Specifically, a mutation in the variable region gene AGC 1 causes a variant of spondyloepiphyseal dysplasia associated with intense primary osteoarthritis.[25] Finally, a recessive form of dysplasia characterized by very intense spondylo-epimetaphyseal dwarfism was due to a mutation in the domain "C-type lectin".[26]

Table 3
Classification of bone constitutional diseases with a known genetic basis according to their molecular-pathogenic mechanism: examples most representative

1. Defects in extracellular structural proteins
Collagen 1: osteogenesis imperfecta
Collagen 2: achondrogenesis type 2, hipochondrogenesis, congenital spondyloepiphiseal dysplasia, spondyloepimetaphiseal dysplasia, Kniest dysplasia, type 1 Stickler syndrome
Collagen 10: metaphyseal dysplasia (Schmid)
Cartilage olygomeric matrix protein (COMP): pseudoachondroplasia, type 1 multiple epiphyseal dysplasia
Matrillin 3: type 3 multiple epiphyseal dysplasia
Perlecan: bisegmented dysplasia and type 1 Schwartz-Jampel
Agreccan: spondyloepyphiseal dysplasia with intense primary osteoarthritis (AGC 1 mutation) and recessive spondyloepymetaphyseal dysplasia (lectin type C mutation)

2. Defects in metabolic pathways
Alkaline phosphatase (without tissue specificity): hypophosphatasia
Vacuolar ATPase (TCIRG-1 subunit): severe childhood osteopetrosis grave
Chloride channel 7: severe adult osteopetrosis
Carbonic anhydrase 2: osteopetrosis with intracranial calcifications and renal tubular acidosis
Sulphate transporter: achondrogenesis 1B, Dyastrophic dysplasia, recessive multiple epyphiseal dysplasia
Arylsulphatase E: chondrodysplasia punctata linked to chromosome X
Transitory Receptor Potential Vanilloid 4 (TRPV 4): Kozlowski's spondylometaphiseal dysplasia, brachiolmia and metatropic dysplasia

3. Defects in folding or degradation of macromolecules
Lysosomal enzymes. Storage diseases: mucopolysacharidosis
Catepsin K: picnodysostosis
Sedlin: X linked late spondyloepyphiseal dysplasia

4. Defects in hormones and signal transduction
Vitamin D 25-α hydroxylase: Type 1 Vitamin D dependent rickets/osteomalasia
Vitamin D 25-α hydroxylase: Type 1 Vitamin D resistant rickets/osteomalasia
Stimulating adenyl cyclase Protein G (subunit α) [GNAS1]: pseudohypoparathyroidism
PTH receptor/PTHrp: Jansen metaphyseal dysplasia
Proteinase for the peroxisomal import receptor: x linked hypophosphatemic rickets
Fibroblast growth factor receptor 23: autosomal dominant hypophosphatemic rickets
Fibroblast growth factor receptor 1: craniosynostosis (some forms of Pfeiffer)
Fibroblast growth factor receptor 2: craniosynostosis (Apert, Crouzon and variants of Pfeiffer)
Fibroblast growth factor receptor 3: "achondroplasia family": tanatophoric dysplasia, achondroplasia and "SADDAN" (severe achondroplasia with acantosis nigricans) and hypochondroplasia
Activator of the nuclear factor Kβ receptor (TNFRSF11A): familiar expansive osteolysis

5. Defects in nuclear proteins and transcription factors
Gen SOX 9: campomelic dysplasia
Calcium activated Nucleotidase 1: Desbuquois dysplasia

6. Defects in oncogenes and tumor suppressing genes
Exostosin 1 and 2: multiple types 1 and 2 exostosis

7. Defects in DNA and RNA processing and metabolism
RMRP gene (codifies RNA part of MRP-RNAase): cartilage-hair hypoplasia

Defects in the process of bone metabolism

Entities that respond to this mechanism highlight the importance of some metabolic pathways in bone modeling and remodeling. Thus, different mutations in the gene for alkaline phosphatase, a key enzyme in the metabolism of phosphate and pyrophosphate (essential elements in the process of mineralization), cause various forms of hypophosphatasia: neonatal (lethal), infantile and adult.[27] On the other hand, mutations in the genes encoding the synthesis of certain proteins involved in the transport process of H + in the area of resorption (between the 'brush' edge of osteoclasts and the bone surface), where acidification is a prerequisite for the dissolution of hydroxyapatite crystals, are responsible for different forms of osteopetrosis. A mutation of the subunit TCIRG 1 of the vacuolar ATPase causes the severe juvenile form,[28,29] related to chloride channel 7 and giving rise to the severe adult form,[30] and that associated with alterations in carbonic anhydrase 2 causes osteopetrosis with renal tubular acidosis and intracranial calcifications.[31] As for sulfate metabolism enzymes, which have been involved as an important factor in endochondral ossification, mutations have been described in the sulfate transporter gene giving rise to different recessive osteochondrodysplasias as type 1B achondrogenesis , diastrophic dysplasia and recessive multiple

epiphyseal dysplasia.[32] In addition, a mutation in the arylsulphatase E, a steroid sulphatase has been observed in osteoblastic cell lines and could play an important role in cartilage formation, leads to chromosome-linked chondrodysplasia punctata X.[33] But the newer and more important finding in this section occurred in relation to Spondylo-metaphyseal dysplasias (including entities of the groups 10 and 11[12]), conditions that, although with different intensity and some individual variability and group sharing features such as short stature, scolyosis (with platyspondylia and a peculiar aspect of the vertebral pedicles) and abnormalities in the metaphyses of long bones. The group includes Kozlowski type Spondylometaphyseal dysplasia (the best defined entity), brachiolmia (milder) and metatropic dysplasia. The discovery of different allelic mutations in the gene encoding vanilloid receptor 4 of the transient potential channels (TRPV-4) as a cause of these processes[34] is a good example of how this new approach based on causal knowledge is changing the clinical concept and thus, the grouping based on morphological traits. TRPV-4 is a member of the superfamily of ion channel receptors. In particular, it is a calcium channel protein found in cell membranes that regulates the flow cell of this ion. This finding involving three entities that share similar phenotypic changes paving the way for grouping in a new family of dysplasia, which most likely will happen in the next review of the classification of the CBD.

Defects in folding or degradation of macromolecules

Most of the entities included in this section are lysosomal storage diseases such as mucopolysaccharidosis, caused by deficiencies in enzymes involved in the degradation of glycosaminoglycans. This is a large group of tesaurismosis with dysostosis phenotype whose detailed description (including relevant genetic alteration) was added to the classification of the International Committee of experts from the 5th review onward (group 22)[11] and expanded in the last review (Group 26).[12] Also, picnodisostosis is a part of this mechanism, caused by alterations of cathepsin K, an endoprotease that acts on the degradation of extracellular[35] matrix components. Finally, it should be noted that mutations in the Sedlin endoplasmic reticulum protein involved in the folding and transport of proteins leads to X-linked spondyloepiphyseal dysplasia, the most common spondyloepiphyseal[36] dysplasias.

Defects in hormones and signal transduction mechanisms

This broad, heterogeneous and complex group includes entities caused by disturbances in the signaling and cellular communication mechanisms operating either over long distances (endocrine systems), next to where the measurable components are produced (paracrine) and even the cell itself where they originate (autocrine). Among the endocrine disorders there are alterations in the synthesis of vitamin D and parathyroid hormone calcium axis (PTH). Thus, mutations in the gene that regulates the synthesis of 25-α hydroxylase lead to rickets / osteomalasia vitamin D-dependent type I[37] and 1.25-α hydroxylase leads to rickets / osteomalasia resistant to vitamin D.[38] It has also been shown that pseudohypoparathyroidism is caused by mutations in the α subunit of stimulatory G protein of adenylyl cyclase, involved in the signal transduction of PTH.[39] Alterations in the PTH receptor, with a significant effect on the differentiation of chondrocytes in the growth plate, cause Jansen[40] type metaphyseal dysplasia. Finally, defects in the peroxisomal proteinase import receptor cause, in a relatively common manner rickets / X-linked hypophosphatemic osteomalacia.[41,42] Among the disorders associated with alterations in the of autocrine-paracrine signal mechanisms, a less common form of hypophosphatemic rickets / osteomalacia, , the autosomal dominant, is caused by a mutation in the receptor for fibroblast growth factor 23, a protein with phosphaturic[43] action . In this same subgroup, disorders of fibroblast growth factors were included, essential in cell proliferation as well as in normal development and growth of the limbs and craneofacial[44] area. Thus, a receptor mutation in fibroblast growth factor 1 results in some forms of craniosynostosis, Pfeiffer, while receptor fibroblast growth factor 2 cause the Apert and Crouzon craniosynostosis, and other variants of Pfeiffer.[45] For its part, different mutations in the receptor fibroblast growth factor 3, key in endochondral ossification and, therefore, in normal cartilage transformation into bone, lead to disruption of the so-called "achondroplasia family". This important group of entities includes, in descending order of severity, thanatophoric dysplasia, achondroplasia and "SADDAN" (severe achondroplasia with acanthosis nigricans) and hypochondroplasia.[44,46-48] Finally, the RANK receptor, a member of the TNF receptor superfamily, has a decisive influence on the differentiation of osteoclasts and their response to PTH. It is therefore logical that activating mutations in the gene encoding the receptor of nuclear factor Kβ activator (TNFRSF11A) led to expansive familial osteolysis.[49]

Defects in nuclear proteins and transcription factors

The basic characteristic of this group mainly consisting in dysostosis is a structural change in a nuclear protein or transcription factor.[50] For example, mutations in the SOX 9 gene encoding the DNA binding protein transcription factor HMG, of great importance in chondrogenesis, are associated with campomelica[51] dysplasia. Another interesting example of this group is Desbuquois dysplasia type 1, an autosomal recessive chondrodysplasia from the group of multiple dislocations (Group 19[12]), which is characterized by a significant reduction in height (with shortening of the limbs), joint laxity and progressive scoliosis. In this condition 7 different mutations in the gene encoding the calcium-activated nucleotidase 1, an enzyme whose exact function is unknown, though one of its substrates is involved in important signaling functions, including the release of calcium intracelular[52] have been described.

Defects in oncogenes and tumor suppressor genes

A representative example of this group which currently includes a few entities are cartilaginous exostosis type 1 and 2, caused by mutations in the genes encoding the exostosins 1 and 2, involved in cell differentiation and the tumoral[53] genesis.

Defects in processing and metabolism of RNA and DNA

This group is justified mainly by the peculiarities of RMRP gene (encoding the RNA-RNase MRP) whose mutation results in cartilage-hair[54] hypoplasia.

Epilogue: summary and implications

Initial attempts to classify CBD were based on partial, inconsistent criteria and lacking a precise definition. Disorders whose existence as independent entities was uncertain were usually referred to by eponyms, which frequently responded to accidental or irrelevant features. In order to move towards a homogeneous group based on consistent criteria, an international committee of experts developed in 1969 the first "Nomenclature for constitutional bone diseases", which was universally accepted. Since then there have been 6 reviews that also establish well-defined nosological categories, and terminology have been standardized by solving problems such as the place occupied by dysostosis, particularly difficult to frame. But more important

has been the incorporation of new knowledge in genetics and molecular nature. Thus, the last review published in 2007 was based on basic pathogenic alteration in combination with objective morphological criteria, opening the door to a future classification with clearly defined groups of functional significance. The new findings have revealed the extreme complexity of bone and cartilage, with a large number of cellular processes and metabolic pathways involved in their structure and physiological functions. Consequently, although radiographic abnormalities remain essential for the differential diagnosis of CBD, the genetic and biochemical studies already occupy a prominent place as tools to achieve an accurate diagnosis. In addition, this new approach allows the development of new diagnostic techniques and facilitates interdisciplinary collaboration that is so critical in addressing a very complex disorder. Finally, the discovery of some therapeutic targets is allowing safe and effective drug development to treat these diseases that sooner or later have to lose their status as "orphans."

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