Bone 102 (2017) 1–4

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Editorial

Genetic disorders of bone – An historical perspective

1. Short stature, dwarfs, Lilliputians and superstitious beliefs

Individuals with constitutional diseases of the skeleton attract attention because of their smaller size, because of deformities, and/or because of the disproportion between body parts. Individuals with achondroplasia, a common skeletal short stature condition, have short arms and legs, a head that is usually larger than normal, and a typical facial appearance with a prominent forehead and a sunken nasal bridge. They are usually healthy (at least as children and young adults) and are said to be witty. Although there is no scientific data to confirm the latter claim, their personal perspective on life may lead to particular insights. Perhaps for these reasons, individuals with achondroplasia (along with individuals with other deformities) have often played special social roles in human societies – from being members of royal courts, to participating in circus shows or other public entertainments. Short-statured individuals have also fueled the fantasy of writers, and indirectly of the public, like in Swift's "Gulliver's Travels". The misconception of a separate race (such that of the Lilliputians) was frequent in the past and still lingers even in the present time. Around the turn of the twentieth century, in Paris (France), there existed an institution called "*le jardin d'acclimatation*" where short-statured individuals (with diverse diagnoses ranging from achondroplasia to growth hormone deficiency) were offered a place to live; perhaps an act of charity, but certainly also one of segregation [1]. The halo around individuals with short stature, deformity or disproportion has thus stood in the way of a scientific or medical approach to the definition of their conditions; so much so, that still in 1886, when the French physician Joseph Marie Jules Parrot described a short-limb patient and coined the name "*achondroplasie*", he believed that achondroplasia was a manifestation of rickets, and that rickets itself was a consequence of hereditary syphilis [2]. As late as in 1912, the Dutch orthopaedist Murk Jansen supported the concept that achondroplasia was caused by "amnion-pressure" [3]. Another popular belief was that achondroplasia was caused by "weak semen" (this latter belief may have been prompted by the observation that achondroplasia individuals are often the youngest sibs – in accordance with the paternal age effect on de novo *FGFR3* mutations). The strong aura surrounding little people, or dwarfs, or Lilliputians, is surprising and in contrast with the notion that the genetic difference between an individual with achondroplasia (or pseudoachondroplasia, or spondylo-epiphyseal dysplasia congenita) and a normal-stature individual is a single nucleotide at heterozygosity!

2. From pathology to radiography

In 1892, in his treatise called "On the so-called fetal rickets", the German pathologist Eduard Kaufmann described skeletal deformities affecting newborns. He recognized the heterogeneity of these different conditions [4]. In the illustrations to his work, that still consisted of hand drawings (no radiographs yet), one can recognize today a case of thanatophoric dysplasia, one of metatropic dysplasia as well as one of oro-facio-digital syndrome type IV – quite different conditions indeed. Around the turn of the 19th to the 20th century, the diffusion of x-rays for the investigation of medical conditions, particularly those affecting the skeleton, led to the recognition of several "new" conditions as defined by their peculiar, and sometimes specific, radiographic appearance. Among these conditions (the list is not exhaustive by far) are osteopetrosis [5], the condition called "dysostosis multiplex" (now known to be the skeletal manifestation of lysosomal disorders mucopolysaccharidoses and mucolipidoses) [6–8], diaphyseal dysplasia [9,10], the Morquio syndrome [11], dyschondrosteosis [12], Pyle disease [13,14] and several others. Individuation of new conditions based on specific radiographic signs, often in combination with specific clinical findings, flourished throughout the 20th century and still today constitutes the basis for the identification of the pathogenic gene(s).

3. Chromosomes, lysosomes and enzymes

The years following World War 2 saw a rapid advancement of biochemistry and genetics. Following the implementation of rickets prophylaxis with vitamin, hypophosphatasia was recognized as a "genetic form of rickets" associated with low alkaline phosphatase activity [15]. In the late 1950s, the correct number of chromosomes in man was finally determined; this triggered the recognition of the aneuploidies (trisomies 21, 13 and 18, monosomy X, and more) in rapid sequence. In the Fifties, a new cellular organelle was identified, the lysosome, that contained a number of different hydrolytic enzymes [16,17]. This led to the discovery that some of the previously identified clinical syndromes were caused by genetic deficiency of an enzyme. With chromosomes and enzymes, there were laboratory tests to help the medical geneticists and the pediatricians to confirm a diagnosis and to explore the phenotypic variability of the individual disorders. Thanks to these advancements, the field of medical genetics gained attention and importance.

4. The golden Sixties

The discovery of chromosomal and biochemical bases for their clinical observations must have reassured pediatricians and geneticists that what they were observing was real and this freed their minds. It was no longer necessary to be conservative by forcing different observations into one category; if the Fifties were still hesitant and had seen new entities named as "recessive achondroplasia" and "pseudoachondroplasia",

http://dx.doi.org/10.1016/j.bone.2017.07.025

the Sixties flourished with newly recognized entities that were given new names, such as diastrophic dysplasia (Maroteaux and Lamy, 1960) [18], familial metaphyseal dysostosis (Spahr and Spahr-Hartmann, 1961) [19], cartilage-hair hypoplasia (McKusick, 1965) [20], spondylo-epiphyseal dysplasia congenita (Spranger and Wiedemann, 1966) [21], tricho-rhino-phalangeal syndrome (Giedion, 1966) [22], metatropic dysplasia (*der metatropische Zwergwuchs;* Maroteaux, Spranger and Wiedemann, 1966) [23] (the list is arbitrary and not exhaustive). This "freedom to recognize genetic disorders" in the Sixties culminated in the Birth Defects Conferences, a first series of which was organized between 1969 and 1971 at the Johns Hopkins Hospital; their proceedings are still a pleasure to read because of the richness in new observations as well as the freshness of the presentations and discussions.

5. Atlases and classifications

In 1951, the British orthopaedic surgeon Thomas Fairbank published an "Atlas of generalized affections of the skeleton" [24]. Sir Fairbank was strongly interested in genetic bone disorders; among other disorders, in 1947, he had described a form of "dysplasia epiphysealis multipla", multiple epiphyseal dysplasia [25]. Although rudimentary by today's standards, this work was a milestone in the development of the field of constitutional disorders of bone. In 1961, Pierre Maroteaux and his mentor, Maurice Lamy published a monography on "genotypic chondrodystrophies" [26]. Unlike the Fairbank atlas, this work did not discuss all genetic skeletal conditions but was focused on the "chondrodysplasias". In 1964, the radiologist Philip Rubin from Rochester University published his "Dynamic classification of bone dysplasias" [27]. Although some of the diagnoses were still naïve (i.e., rhizomelic chondrodysplasia punctata called "congenital multiple epiphyseal dysplasia"), the book was remarkable because it classified disorders based on the "dynamic pathogenesis" (i.e., trying to speculate on what dynamic process on bone growth and remodelling was affected) and Rubin made extensive correlations to what was known at the time about bone modelling. Rubin modestly wrote that the success of his book would be measured "paradoxically" by the rapidity in which its content would become outdated. In 1974, Jurgen Spranger, Len Langer and Hans-Rudolph Wiedemann published their "Bone Dysplasias: Atlas of Constitutional Disorders of Skeletal Development", an extensive atlas that was based on the correlation of radiographic, clinical, and genetic data to delineate conditions [28]. In 1975, the radiologists Hooshang Taybi and Ralph Lachman published their "Radiology of Syndromes and Skeletal dysplasias", a collection that did not have the Spranger-Langer-Wiedemann's depth but did have a wider coverage of genetic syndromes [29]. Both the Spranger and the Taybi-Lachman books have been revised periodically and are in their 4th and 5th editions, respectively.

6. From a nomenclature to the nosology

Coping with the growing number of different conditions, it was noted in the late Sixties that in some instances, different names had been given to the same condition; thus, in the wake of the Birth Defects conference on skeletal dysplasias, a group of experts (mainly radiologists) convened in Paris in 1970 to prepare an "International nomenclature of constitutional diseases of bones". This list of conditions, grouped by their main radiographic or clinical features, was much needed and was so welcome that it was published, as the "Paris nomenclature", with minor variations and comments, in at least 5 different journals [30–34]. The 1970 nomenclature underwent revisions in 1977, 1983, 1992, 1997, 2001, 2005, 2010 and 2015 [35–42]. Following the foundation of the International Society for Skeletal Dysplasias in 1999, the revisions are prepared by an ad hoc group within the ISDS; the term nomenclature has been replaced with that of "nosology". The last revision has been prepared between 2013 and 2014 (published in 2015 [42]) and the next revision is scheduled for the 2017 meeting of the ISDS in Bruges, Belgium. The Nosology should help in the delineation of new conditions by providing a list of those conditions that have been recognized as distinct entities on clinical, radiographic and genetic grounds. Notwithstanding the many ties of friendship between the Nosology experts and the late Victor A. McKusick and the subsequent curators of the MIM catalogue, there are several inconsistencies between the Nosology and OMIM owing to the fact that while OMIM grows rather appositionally, the Nosology committee does more pruning of obsolete entities.

7. Molecular data and the clinical-radiographic classifications

There have been times when skeletal dysplasia experts suffered from a dubious reputation. For many colleagues, it seemed hard to believe that there was a rationale for preparing long lists of very rare conditions with Greek-derived names. Yet, cell biology, biochemistry and molecular genetics have confirmed the work of the clinical and radiographic "stamp collectors": there is an extraordinary variety of molecular mechanisms at the basis of skeletal conditions. Morphogenesis, development, growth and homeostasis of the skeleton and its over 200 distinct elements is a complex mechanism with many levels of integration and control; and because of our ability to recognize morphologic changes in children and adults, as well as in bones on radiographs, the skeleton is a sensitive reporter. Thus, if biochemical bases of genetic bone disease (such as the many forms of genetic rickets, or the lysosomal storage disorders) have been identified in the Sixties; the Seventies and early Eighties saw the first evidence of "molecular pathology" with the collagens (collagen 1 and osteogenesis imperfecta, collagen 3 and the Ehlers-Danlos syndrome type IV, and collagen 2 and chondrodysplasias), and the late Eighties (thanks to the possibility of molecular cloning and then, particularly, the polymerase chain reaction technique) saw the underlying gene mutations unravel. In 1983, a multi-exon deletion in COL1A1 was identified in lethal osteogenesis imperfecta [43], in 1988, a multi-exon deletion in COL3A1 was identified in EDS type IV [44] (not a skeletal condition, but the "collagen field" was united at that time); and in 1989, a single-exon deletion was identified in a family segregating congenital spondylo-epiphyseal dysplasia [45]. At the time, exon deletions were easier to identify by Southern blotting, while single nucleotide variations necessitated extensive cloning and sequencing; in 1986, a heterozygous single nucleotide substitution in COL1A1 was identified as the cause of lethal osteogenesis imperfecta [46]; rapidly, glycine substitutions in the triple helical domain of collagen type 1 were established as the main cause of severe osteogenesis imperfecta. In 1988, a homozygous point mutation in the *TNSALP* gene was identified as the cause of lethal hypophosphatasia [47]. The Nineties surprised with the notion that the genes at the basis of skeletal diseases were not only structural proteins or enzymes, but frequently genes involved in signalling pathways and in transcription regulation, such as *FGFR3* or *CBFA1*/*RUNX2* [48]. A first molecular-pathogenetic classification was drafted [49]. Ever since, there has been a constant flow of new gene-phenotype identification; while a small number of genes may account for a large proportion of individuals with genetic skeletal conditions, rarer associations are still being found on a monthly basis. As an example, the majority of cases of osteogenesis imperfecta are determined by mutations in COL1A1 and COL1A2 but no less than twenty other genes can produce a brittle bone phenotype, although the number of cases is much smaller. In general, molecular data have determined some degree of "lumping", i.e., the regrouping of conditions sharing a similar pathogenesis; but on the other side, the data continue to reveal extensive heterogeneity and to identify novel conditions, leading to "splitting" and thus to a steady increase in the number of conditions listed in the nosology.

8. Genetic disorders of bone and their contributions to genetics and medicine

In many ways, the skeletal field has had a pioneering role in medical genetics and by contributing fundamental concepts. Among these are: the observation that a single nucleotide substitution at the heterozygous state may result in a lethal phenotype (lethal OI, lethal collagen 2 dysplasias) [46]; the concept of "protein suicide", precursor of the concept of "dominant negative" [50]; the concept of functional topology of a molecule (different mutations in *COL1A1* giving different phenotypes because they affect different functional domains); the formulation of the concept of disease families with mild to severe manifestation arising from a same gene (collagen 1, collagen 2, *COMP* and *FGFR3*) [51]; the observation of gonadal mosaicism as the explanation of affected sibs born form clinically unaffected parents (again *COL1A1* mutations) [52]; the discovery of highly recurrent mutations such as the "achondroplasia mutation" G380R in *FGFR3* that occurs at the nucleotide with the highest mutation rate known in the human genome [53,54], and the demonstration that they occur almost exclusively of paternally derived alleles, highlighting the paternal age effect [55]. These concepts that are firmly accepted today were pioneered by the "bone dysplasia" field.

9. The changing diagnostic scenario

As ontogeny reflects phylogeny, the approach to diagnosis does in part reflect the history. Thus, the diagnosis of constitutional skeletal disorders relies mainly on the meticulous analysis of skeletal radiographs. Correlation with the clinical data (growth curve, clinical findings, history of fractures or pain, other specific features) is essential. Biochemical evidence may be diagnostic (e.g., calcium or phosphate imbalance, or reduced activity of a specific enzyme). Molecular genetic confirmation has long been the last step in the process. The power of massive parallel sequencing and its increasing affordability has changed this scenario drastically. The analysis of gene panels (e.g. a "dysplasia panel", a "bone fragility panel", or a "chondrodysplasia punctata panel") has already replaced single-gene analysis in most instances. Even broader approaches, such as that of exome sequencing, are already being used as first-line tests. With further reduction in sequencing costs, a "genotype first – phenotype later" approach may be implemented soon. Is the time of careful analysis of clinical features and radiographs lost forever? Probably not, but the approach will be changed. The so-called "reverse phenotyping", i.e. to verify whether the patient's features (clinical, radiographic, or biochemical) do fit with a genotype identified by unbiased sequencing, needs as strong an expertise as the a priori generation of a diagnostic hypothesis. The findings from massive sequencing will confront the genetic physician with "common" genetic disorders, but also with rare, ultra-rare or even private conditions; no literature will be available (at least not for some time) to guide him. Sensitive and accurate sequencing, large databases and precise bioinformatics prediction tools will be needed as much as clinical observation skills and acumen.

10. Old and novel therapeutic approaches

If the exploration of the pathogenetic bases of skeletal dysplasias has been fascinating, the therapeutic fallout has followed at a much slower pace. Well-structured observational studies, providing much needed information on the natural history of each disorder and its complications, are available only for the more common conditions. Because surgery is so difficult to standardize, there is no high-level evidence on the risk and benefit of most surgical interventions in individuals with skeletal dysplasias. For some conditions, knowledge of the molecular pathogenesis has resulted in the development of specific medical interventions. Several of the lysosomal storage diseases are now amenable to enzyme replacement, substrate reduction, or both (although the skeletal system is less likely to benefit from these treatments than other organs). Enzyme replacement therapy in hypophosphatasia is highly effective and beneficial [56]. Several distinct approaches are being studied to counteract increased FGFR3 signalling in achondroplasia and related conditions (guanyl cyclase activation by a long-lived C-Naturetic Peptide analog [57], modulation of FGF signalling with a soluble "decoy" FGFR3 receptor [58], and specific inhibitors to inhibit the tyrosine kinase activity of FGFR3 [59]). In osteogenesis imperfecta and other conditions with fragile bones, the use of bisphosphonates, that is moderately effective, should soon be accompanied, or replaced, by approaches that target the overall bone architecture (such as sclerostin antibodies [60,61]).

Our evolution in understanding of the pathogenesis of the skeletal dysplasias has undergone rapid changes in the last decades. These studies have unearthed key concepts in genetics. They have also demonstrated the importance of properly naming a condition in order for it to be recognized by others; scientists, doctors, patient advocacy groups. We are all cautiously optimistic that these steps along a long and winding road will lead to therapeutic advances for our patients.

Acknowledgements

We are thankful to our friend and teacher, Jürgen W. Spranger, for making the diagnosis of OFD type IV in one of the cases in the 1892 Kaufmann book (see references).

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