



## EDITORIAL

### Skeletal dysplasias: New medical treatments<sup>☆</sup>

### Displasias esqueléticas: nuevos tratamientos médicos



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Skeletal dysplasias, a broad and heterogeneous group of genetic diseases that manifest with growth abnormalities associated with alterations in the development and differentiation of bone and cartilage, constitute one of the most important groups of diseases requiring care from specialised paediatric practitioners in the different paediatric age groups.

Two developments in the traditional fields of medicine and radiology have been crucial in improving the diagnosis of these diseases: the spectacular advances in methods for detecting monogenic disease, and the introduction of new therapeutic molecules, which are still undergoing international controlled clinical trials but have shown promising results.

The most recent revision on the nosology and classification of skeletal dysplasias<sup>1</sup> showed that while the number of diseases has decreased from 456 to 436, the number of groups has increased from 40 to 42 and the number of involved genes from 226 to 364 compared to the previous 2011 revision.

Although each skeletal dysplasia is rare, their collective birth incidence is estimated at 1:4000 to 1:5000 live births. Thus, these congenital anomalies are identified in 5% of newborns, even though the actual incidence is probably higher.

When presented with a patient that may have a skeletal dysplasia, the following must be performed: (a) Clinical evaluation: assessment of disproportionate short stature (prenatal, neonatal or postnatal), family history (mean parental height and other possible cases of stature), family tree (comprising at least three generations), weight, length and head circumference at birth, growth rate; (b) Physical examination: length or height, weight, head circumference, upper to lower segment ratio, sitting height and arm span (description of the eventual shortening of the extremities: rhizomelic, mesomelic or acromelic); cranial characteristics, mediofacial hypoplasia, nasal shape, presence of blue sclera, cleft palate, micrognathia, dental abnormalities, pectus excavatum, pectus carinatum, lordosis, scoliosis, genu varum/valgum, brachydactyly. The characteristics of nails, hair and skin should be evaluated, along with potential hearing and/or vision abnormalities and cognitive impairment, and kidney, liver and cardiac function and general laboratory tests should be performed; (c) Radiological assessment: the radiological patterns may include diaphyseal, metaphyseal, epiphyseal, spondylar or mixed abnormalities. The radiological investigation should include radiographs of the skull, upper extremities, lower extremities, thorax, hips

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and spine, and an assessment of bone maturation and mineral density; and (d) Genetic testing: gene sequencing, gene panel analysis, whole-exome sequencing and whole-genome sequencing. Taking cost-effectiveness into account, in cases of skeletal dysplasia the analysis of specific sets of genes using panels may be the most appropriate option if the dysplasia has been thoroughly evaluated and the diagnosis has been narrowed down, while whole-exome sequencing may offer a better yield otherwise. As our knowledge grows in the future, we will be able to provide more specific information.

Given the large number of disease classifications and their considerable genetic heterogeneity, we face great challenges to advance in their diagnosis. The fact that different diseases may share underlying mechanisms has fuelled the interest in finding new therapeutic targets.

### Current situation in the development of therapeutic targets for the treatment of some skeletal dysplasias

Achondroplasia is the most prevalent skeletal dysplasia. In achondroplasia, mutations in the *FGFR3* gene (MIM 134934) lead to abnormalities in chondrocyte proliferation and terminal differentiation and in the synthesis of the extracellular matrix in growth plate cartilage. The *NPR2* gene encodes the natriuretic peptide receptor B (NPR-B), which acts as an endogenous receptor for C-type natriuretic peptide (CNP). C-type natriuretic peptide antagonises *FGFR3* downstream signalling by inhibiting the MAPK pathway. Overexpression of CNP in chondrocytes prevents bone shortening in a mouse model of achondroplasia, suggesting that CNP could be an effective treatment for this disease.

BioMarin Pharmaceutical Incorporated has developed a CNP analogue that is 39 amino acids long for subcutaneous administration (BMN-111). This drug offers an extended half-life due to its resistance to neutral endopeptidase digestion, making it possible to administer it once a day through the subcutaneous route. A multicentre, multinational clinical trial is currently underway and could be completed in 2017 (ClinicalTrials.gov identifier: NCT02055157). A recent review analysed the different therapeutic options for achondroplasia, from surgery to trials involving growth hormone to future treatments, including the CNP analogue.<sup>2</sup> The 39-amino acid long CNP analogue is raising hopes of finding a treatment that could improve bone structure in patients with achondroplasia and possibly hypochondroplasia.

The initial results of the use of KRN23 in patients with X-linked dominant hypophosphataemic rickets (XLH) have been published recently.<sup>3</sup> KRN23 is a monoclonal antibody that inhibits the activity of fibroblast growth factor 23 (FGF23), which mediates the deficient phosphate reabsorption from the kidney and the abnormal vitamin D metabolism. The results of the trial show a beneficial effect, with increased thresholds of phosphate reabsorption and increased serum levels of phosphate and calcitriol in adults. A clinical trial in children with XLH aged 5–12 years is underway (ClinicalTrials.gov identifier: NCT02163577) and will be expanded to include patients aged 1–5 years in Phase III.

When it comes to hypophosphatasia due to congenital deficiency of tissue-nonspecific alkaline phosphatase (AP), an ongoing international clinical trial is evaluating the

efficacy and safety of the use of asfotase alfa (recombinant alkaline phosphatase) in children aged less than 5 years with the most severe forms of the disease (perinatal/infancy) (ClinicalTrials.gov identifier: NCT01176266). This experimental treatment is relevant due to the systemic scope of this disease, with severe involvement of other organs and systems in addition to the skeleton, and an exceedingly high mortality in the most severe early-onset forms. Favourable outcomes of this treatment have already been reported,<sup>4</sup> with improvements in radiological findings, lung function and physical ability in infants and young children with potentially fatal forms of hypophosphatasia, and long-lasting effects in the recovery of growth, strength, agility and motor functioning resulting from the skeletal improvement experienced after sustained treatment over three years with this drug, which has been recently approved by the European Medicines Agency (EMA).

A single gene (*TNSALP* or *ALPL*, 1p36.12) encodes the liver/bone/kidney AP. The more than 300 mutations on the *ALPL* gene known to date determine the development of the different clinical phenotypes of hypophosphatasia ([http://www.sesep.uvsq.fr/03\\_hypo\\_mutations.php](http://www.sesep.uvsq.fr/03_hypo_mutations.php)).

Denosumab, a monoclonal antibody that inhibits RANKL, is a potent and effective treatment for pathological processes involving bone resorption, such as osteoporosis and different types of bone tumours and metastases (for which its use is already indicated in adults). In children, it has been used off label to treat malignant hypercalcaemia and fibrous dysplasia.<sup>4</sup> An ongoing international multicentre clinical trial is evaluating its use in children aged 5–10 years with moderate to severe osteogenesis imperfecta (ClinicalTrials.gov identifier: NCT01799798). At present, the use of bisphosphonates to prevent fractures in these patients is questioned to some degree.

Another group of skeletal dysplasias in which there has been considerable progress in the development of specific therapies is the mucopolysaccharidose (group 27 in the 2015 nosology classification).<sup>1</sup>

At present, the FDA and the EMA authorise enzyme-replacement therapy for mucopolysaccharidosis type I (aronidase), type II (idursulfase), type IV (elosulfase alfa) and type VI (galsulfase); while intrathecal therapy for types I, II, and IIIA is currently undergoing clinical trials (due to the inability of these molecules to cross the blood-brain barrier).<sup>5</sup>

In addition to enzyme-replacement therapy, haematopoietic stem cell transplantation is the gold standard for treatment of severe forms of mucopolysaccharidosis type I, and may be useful in severe forms of type II and in types VI and VII. Gene therapy approaches involving direct delivery to the brain or autologous transplants of previously modified cells for children with mucopolysaccharidosis subtype IIIA are currently in the clinical trial phase.

In conclusion, the paediatrician must take on new diagnostic challenges for the routine evaluation of the multiple skeletal dysplasias through an organised approach and incorporating emerging genetic testing methods in everyday practice. An accurate diagnosis will allow the application of new treatments that are starting to show highly promising results in specific diseases. We welcome these diagnostic and therapeutic advancements that, thanks to research, can improve the symptoms and quality of life of our children.

## References

1. Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, et al. Nosology and classification of genetic skeletal disorders: 2015 revision. *Am J Med Genet A*. 2015;167:2869–92.
2. Bouali H, Latrech H. Achondroplasia: current options and future perspective. *Pediatr Endocrinol Rev*. 2015;12:388–95.
3. Martos-Moreno GÁ. «El hueso» en movimiento. *Rev Esp Endocrinol Pediatr*. 2014;5:5–8.
4. Whyte MP, Rockman-Greenberg C, Ozono K, Riese R, Moseley S, Melian A, et al. Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia. *J Clin Endocrinol Metab*. 2016;101:334–42.
5. Del Toro Riera M. Introducción a las mucopolisacaridosis. In: *Guía para el manejo de las MPS*. Madrid: Ergón; 2015. p. 7–18. ISBN: 978-84-16270-04-0.