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Annales d'Endocrinologie xxx (2017) xxx–xxx

Annales d'Endocrinologie
Annals of Endocrinology

Klotz Communications 2017: From the shortest to the tallest

Bone dysplasia

Dysplasies osseuses

Agnès Linglart [a,*], Valérie Merzoug [b], Anne-Sophie Lambert [a], Catherine Adamsbaum [b]

[a] *Service d'endocrinologie et diabétologie pour enfants, centre de référence des maladies rares du métabolisme du calcium et du phosphate, plateforme d'expertise Paris Sud des maladies rares, filière OSCAR, hôpital Bicêtre Paris Sud, AP–HP, 94270 Le Kremlin-Bicêtre, France*

[b] *Service de radiologie pédiatrique, plateforme d'expertise Paris Sud des maladies rares, filière OSCAR, Medical School, hôpital Bicêtre Paris Sud, Paris-Sud University, AP–HP, 94270 Le Kremlin-Bicêtre, France*

Abstract

Bone dysplasia is a large group that encompasses 436 rare diseases. Many of them are characterized by short stature or decreased growth velocity during puberty. The diagnosis of short stature due to skeletal dysplasia relies on (i) physical features such as disproportionate trunk/limbs, short limbs or extremities and/or stocky build, (ii) radiographic features to analyze mineralization, maturation and bone morphology, and (iii) whenever possible, the genetic characterization. Bone dysplasia mostly affect many organs, and therefore require multidisciplinary follow-up and care. The role of the pediatric endocrinologist is to assess the growth potential of these patients in coordination with the other caregivers, offer the best management of the growth to limit the psychosocial consequences of the extreme short stature and bone deformities.

Keywords: Bone dysplasia; Growth plates; Short stature; Growth hormone

Résumé

Les dysplasies osseuses sont des maladies rares qui ont été regroupées dans une nouvelle classification comportant 436 pathologies. La plupart d'entre elles sont caractérisées par une petite taille et un ralentissement de la croissance au moment de la puberté. Le diagnostic de petite taille due à une pathologie du squelette repose sur l'association de (i) signes cliniques tels qu'une disproportion tronc/membres, un aspect trapu, des membres courts, des mains et des pieds petits, (ii) des anomalies radiologiques variées à type de défaut de minéralisation de morphologie ou de maturation osseuse, et (iii) quand c'est possible, de la caractérisation génétique. De nombreuses pathologies osseuses ont des atteintes multi-organes, ce qui implique un suivi et une prise en charge multidisciplinaire des patients. Le rôle du pédiatre endocrinologue est d'évaluer le potentiel de croissance de ces patients, en coordination avec l'équipe multidisciplinaire et d'offrir aux patients et à leur famille la meilleure prise en charge de la petite taille disponible, afin de limiter les conséquences psychosociales graves de l'extrême petite taille et des déformations osseuses.

Mots clés : Dysplasie osseuse ; Cartilage de croissance ; Petite taille ; Hormone de croissance

The classification of skeletal dysplasia gathers 436 disorders with significant bone involvement, metabolic bone diseases, dysostoses, skeletal malformation and or/or reduction. Diseases are grouped by molecular (FGFR3), biochemical (hypophosphatemic) or radiographic (metaphyseal) characteristics. Short stature may be a feature of each category of skeletal dysplasia (Table 1). In some diseases, it often reveals the diagnosis. This review is focused on skeletal dysplasia, mineralization disorders and storage diseases associated with short stature.

1. Some skeletal dysplasia associated with short stature

1.1. FGFR3 chondrodysplasia group: achondroplasia and hypochondroplasia

Achondroplasia is the most common form of short-limb dwarfism. It is due to de novo activating mutations of *FGFR3*

* Corresponding author.
E-mail address: agnes.linglart@aphp.fr (A. Linglart).

http://dx.doi.org/10.1016/j.ando.2017.04.011
0003-4266/

Table 1
Height and response to growth hormone in different skeletal dysplasia.

Group of diseases in the classification [29]	Name of disease	Final height	rGH efficacy
1. FGFR3 chondrodysplasia group	Achondroplasia [30,31]	131 ± 5.6 cm in males 124 ± 5.9 cm in females	No
	Hypochondroplasia [32,33]	145–160 cm in males 133–151 in females	Yes, mild
10. Multiple epiphyseal dysplasia and pseudoachondroplasia group	Multiple epiphyseal dysplasia [34]	150–180 cm	?
11. Metaphyseal dysplasia	Metaphyseal dysplasia [4,26]	< −3.5 SD	Yes, mild
13. Spondylo-epi-(meta)-physeal dysplasia	Spondylo-ephyso-metaphyseal dysplasia [8,9]	Metatropic dysplasia: 130 cm Opsismodysplasia: < −3 SD	No
15. Acromelic dysplasia	Acromelic dysplasia [23,35,36]	Acromicric dysplasia: 133 cm in males, 129 cm in females PHP (iPPSD): −3 SD	Acromicric dysplasia: no PHP (iPPSD): yes
17. Mesomelic and rhizo-mesomelic dysplasia	Leri–Weill dyschondrosteosis [8,37]	LWD: < −2 SD	Yes
	Langer mesomelic dysplasia	LMD: −6 to −9 SD	?
	Idiopathic short stature [38]	ISS: < −2 SD	Yes
23. Osteopetrosis and related disorders	Pycnodysostosis	135–155 cm (−4 SD to −5 SD)	Yes
25. Osteogenesis imperfecta and decreased bone density	Osteogenesis imperfecta [11]	−2 to −6 SD	Yes
26. Abnormal mineralization group	Hypophosphatasia [14]	0 to −3 SD	?
	Hypophosphatemic rickets [12]	−2 SD	Yes
27. Lysosomal storage diseases with skeletal involvement	Mucopolysaccharidosis [15]		?

(G380R) leading to an abnormal endochondral bone development and premature fusion of growth plates of long bones. As consequences, patients present with sleep apnea, pulmonary infections, narrow foramen magnum and possible brain compression, kyphosis, hyperlordosis, obesity, lumbar spine stenosis and extreme short stature. On radiographs, patients present with a narrowed lumbar spine with shortening in the AP diameter and scalloping of the posterior endplates, shortening of the vertebral pedicles, shortening of the femoral head (in infants they look like ice cream), reduced size of the foramen magnum; bone age is delayed in infants, but rapidly catches up then exceeds chronological age and growth plates fuse prematurely (Fig. 1).

As recombinant growth hormone is poorly/not efficient, novel therapies are under development such as CNP analogs (phase 2 clinical trial), tyrosine kinase inhibitors, or blockade of the ligand binding to the FGFR3, hence limiting its activation [1].

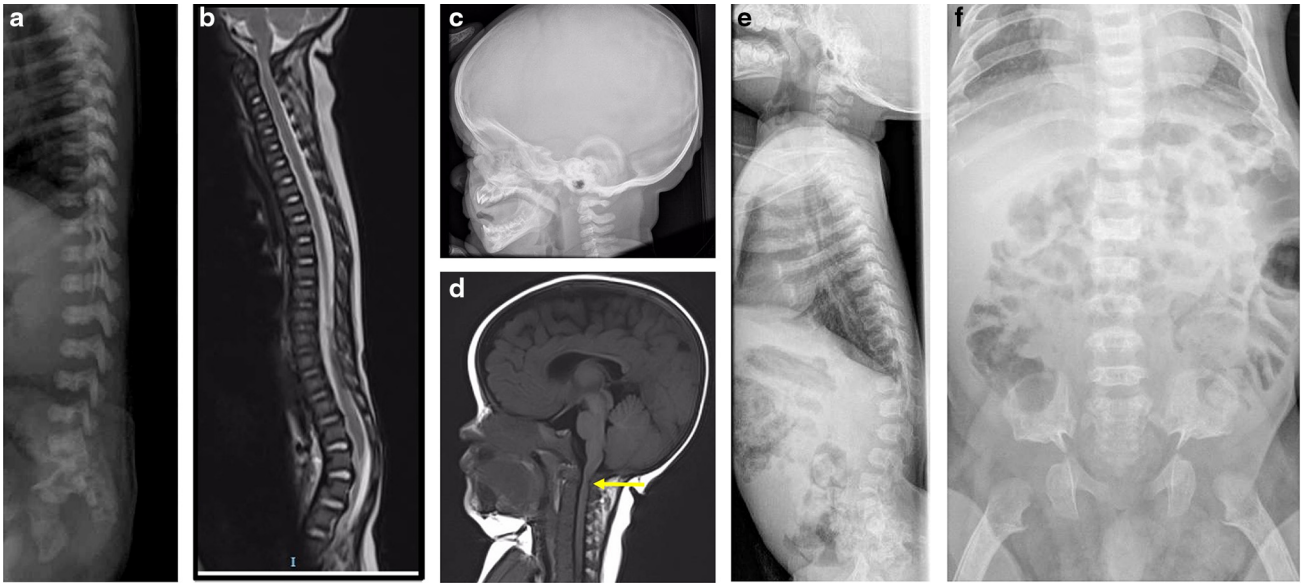

Fig. 1. Achondroplasia. Features of achondroplasia at birth (a), at the age of 2 months (b and c) showing the lordosis, at the age of 4 months (d) showing the basilar impression (arrow), and at the age of 1 year (e and f). Radiographs show narrowed vertebrae, kyphosis, typical trident image of the iliac bone and femoral heads looking like an ice-cream cone.

Please cite this article in press as: Linglart A, et al. Bone dysplasia. Ann Endocrinol (Paris) (2017), http://dx.doi.org/10.1016/j.ando.2017.04.011