CURRENT CONCEPTS IN ACHONDROPLASIA

ALICE FASSIER

A - Diagnosis

What can be said today to parents when announcing the diagnosis of achondroplasia, especially during a prenatal consultation? Some elements are well-known and will be only presented briefly, while others will be developed due to their recency.

Two types of prenatal consultations are frequently encountered: Those where families who are preparing to receive a child with special needs are seeking information, and those presenting for a therapeutic interruption of pregnancy.

When the reason for consultation is a therapeutic interruption of pregnancy, quality of life concerns and psychological suffering are the most concerning aspects for the couple. The surgeon may inform such couples that the life expectancy is almost normal. The availability of a well-advised and well-organized multidisciplinary team, led by a pediatric geneticist, is essential in the hospital setting. The rigorousness of the follow-ups, and the evolving medical, surgical, and psychological risks, especially during the first years of life, should be made clear. Bouts of exposition should also be avoided. Rather, the specific concerns of each parent should be addressed. The final decision to terminate the pregnancy is taken at a later date at specific regional centers. Demands for a therapeutic interruption of pregnancy in France are widely accepted.

If the parents' questions revolve around the accuracy of antenatal diagnostic testing, it should be made clear that, even today, with power ultrasonography machines and experienced sonographers, the diagnosis is not always evident, with the definitive diagnosis being made late in the pregnancy, around the 3rd trimester with an intra-uterine growth restriction (IUGR) associated with a characteristic morphological appearance of the skull and the facies, along with short bony segments of the upper limbs. Differential diagnoses primarily include either less severe (hypochondroplasia) and more severe and lethal forms (thanatophoric dwarfism) of short stature.

If the parents' primary concerns revolve around genetics, they may be informed that achondroplasia is an autosomal dominant disease (50% risk of transmission), but 80% of mutations are de novo (most encountered form of chondrodysplasia with a prevalence of 1/25,000 births).

The FGFR3 gene was discovered by Necker in 1994. This gene codes for a transmembrane fibroblast growth factor receptor, situated on chromosome 16, which is important in the regulation of the growth of long bones (illustration 1). The Necker Institute is planning on carrying

out further research, with actually over 95% of mutations being on the G380R gene. Homozygote patterns are lethal. The classic risk factor is that of a paternal age >35 years old.

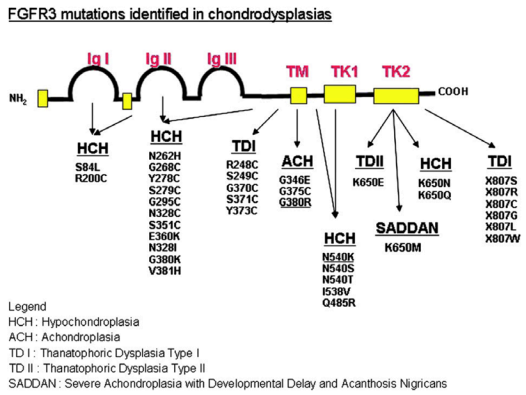


Illustration 1: Baujat et al. 2008

If the parents' primary concerns revolve around the **physical characteristics** of the most common type of dwarfism, the parents should be informed that achondroplasia is characterized by a proportionately more marked shortening of the arms and the thighs compared to the forearms and the legs. The trunk is long and thin. Macrocephaly is associated with frontal prominence and midface hypoplasia (illustration 2).

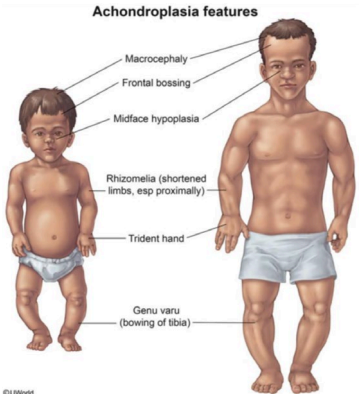


Illustration 2

Generally, the natural history includes psychomotor delay, dental malocclusion, overweight, and psychological distress.

From a **skeletal point of view**, a junctional kyphosis is frequently seen during the acquisition of the seated position, along with joint laxity, hip flexion contracture, and large and short hands in the shape of a trident (illustrations 3-5).


Illustration 3

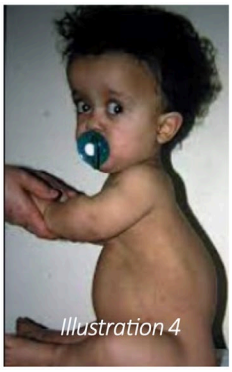


Illustration 4

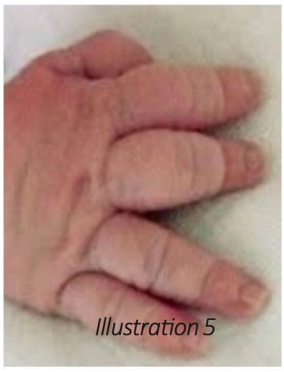


Illustration 5

The most concerning complications are neurosurgical, and ear-nose-throat related, with an increased risk of cervico-occipital stenosis, hydrocephalus, sleep apnea, and hearing difficulties. In adulthood, stenosis of the medullary canal is also seen. Orthopedic complications appear from an early age with sagittal malignment, genu varum, and, eventually, coxa vara (illustrations 6 and 7).

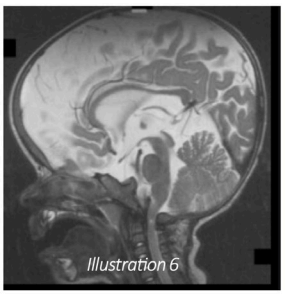


Illustration 6

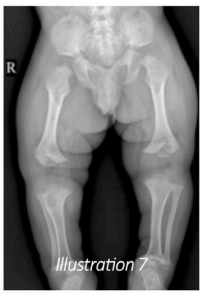


Illustration 7

B – Actualities on potential height

What should parents know about the final expected height in this type of dwarfism? Until recently, potential growth depended solely on the sex of the individual: between 1.2m and 1.3m in females, and 1.25m and 1.35m in males. Today, this prognosis has changed due to the possibility of medical treatment, which will be detailed below.

It should be noted that growth charts on the health record have not been adjusted for children with achondroplasia. Nevertheless, today, height and weight development may be monitored with the dedicated Australian growth charts (illustration 8).

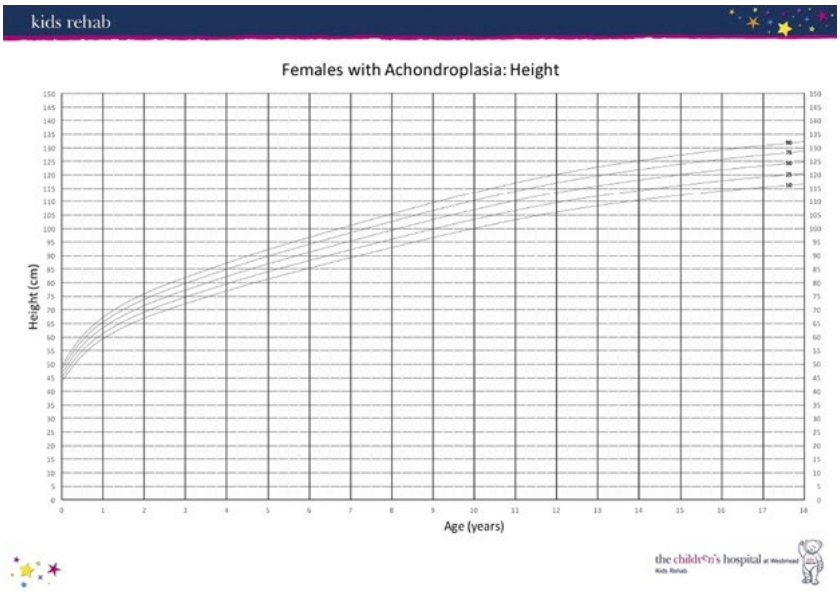
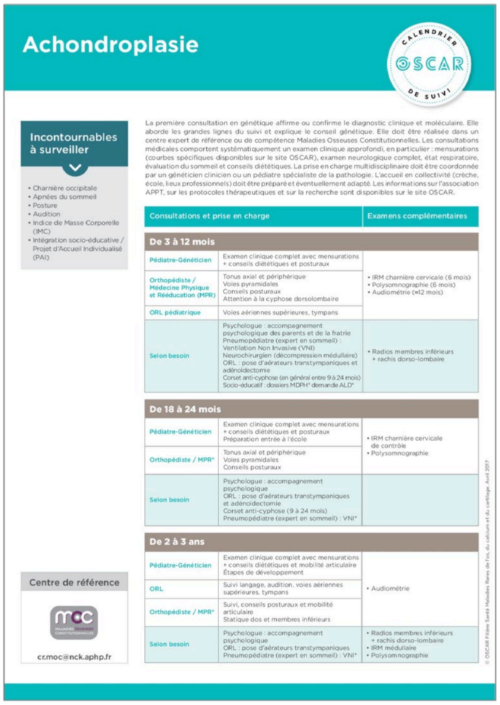


Illustration 8

C – Actualities on patient follow-up

The most frequently asked questions by future parents are related to the medical and surgical follow-up. Recommendations were published in 2017 by the Reference center for constitutional bone diseases, based in the Necker Imagine Institute. The post-natal multidisciplinary follow-up is well defined. It concerns the pediatrician, geneticist, orthopedist, rehab physicians, physiotherapists, ENTs, neurosurgeons, pulmonologists, dieticians, psychologists, and psychiatrists.

Summary sheets are available on the website of the French rare diseases Healthcare Network: bone, cartilage, and calcium diseases (OSCAR) (https://filiere-oscar.fr/fileadmin/ user_upload/calendrier-de-suivi-achondroplasie- oscar-avril-2017.pdf). The latter have detailed information on optimal management based on the child's age group from birth until adulthood (illustrations 9 and 10).



Achondroplasie

CALENDRIER OSCAR DE SUIVI

Incontournables à surveiller

- Charnière occipitale
- Apnées du sommeil
- Posture
- Audition
- Indice de Masse Corporelle (IMC)
- Intégration socio-éducative / Projet d'Accueil Individualisé (PAI)

La première consultation en génétique affirme ou confirme le diagnostic clinique et moléculaire. Elle aborde les grandes lignes du suivi et explique le conseil génétique. Elle doit être réalisée dans un centre expert de référence ou de compétence Maladies Osseuses Constitutionnelles. Les consultations médicales comportent systématiquement un examen clinique approfondi, en particulier : mensurations (courbes spécifiques disponibles sur le site OSCAR), examen neurologique complet, état respiratoire, évaluation du sommeil et conseils diététiques. La prise en charge multidisciplinaire doit être coordonnée par un généticien clinicien ou un pédiatre spécialiste de la pathologie. L'accueil en collectivité (crèche, école, lieux professionnels) doit être préparé et éventuellement adapté. Les informations sur l'association APPT, sur les protocoles thérapeutiques et sur la recherche sont disponibles sur le site OSCAR.

Consultations et prise en charge		Examens complémentaires
De 3 à 12 mois		
Pédiatre-Généticien	Examen clinique complet avec mensurations + conseils diététiques et posturaux	• IRM charnière cervicale (6 mois) • Polysomnographie (6 mois) • Audiométrie (≈12 mois)
Orthopédiste / Médecine Physique et Rééducation (MPR)	Tonus axial et périphérique Voies pyramidales Conseils posturaux Attention à la cyphose dorsolombaire	
ORL pédiatrique	Voies aériennes supérieures, tympans	
Selon besoin	Psychologue : accompagnement psychologique des parents et de la fratrie Pneumopédiatre (expert en sommeil) : Ventilation Non Invasive (VNI) Neurochirurgien (décompression médullaire) ORL : pose d'aérateurs transtympaniques et adénoidectomie Corset anti-cyphose (en général entre 9 à 24 mois) Socio-éducatif : dossiers MDPH* demande ALD*	• Radios membres inférieurs + rachis dorso-lombaire
De 18 à 24 mois		
Pédiatre-Généticien	Examen clinique complet avec mensurations + conseils diététiques et posturaux Préparation entrée à l'école	• IRM charnière cervicale de contrôle • Polysomnographie
Orthopédiste / MPR*	Tonus axial et périphérique Voies pyramidales Conseils posturaux	
Selon besoin	Psychologue : accompagnement psychologique ORL : pose d'aérateurs transtympaniques et adénoidectomie Corset anti-cyphose (9 à 24 mois) Pneumopédiatre (expert en sommeil) : VNI*	
De 2 à 3 ans		
Pédiatre-Généticien	Examen clinique complet avec mensurations + conseils diététiques et mobilité articulaire Étapes de développement	• Audiométrie
ORL	Suivi langage, audition, voies aériennes supérieures, tympans	
Orthopédiste / MPR*	Suivi, conseils posturaux et mobilité articulaire Statique dos et membres inférieurs	
Selon besoin	Psychologue : accompagnement psychologique ORL : pose d'aérateurs transtympaniques Pneumopédiatre (expert en sommeil) : VNI*	• Radios membres inférieurs + rachis dorso-lombaire • IRM médullaire • Polysomnographie

Centre de référence

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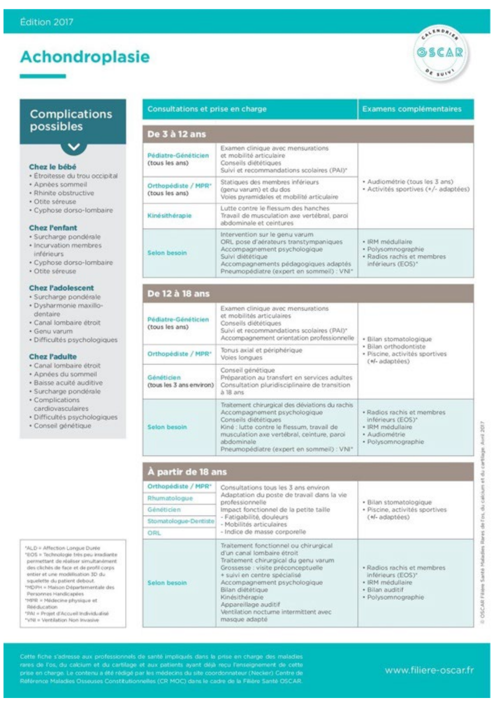
Illustration 9



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Achondroplasie

CALENDRIER OSCAR DE SUIVI

Complications possibles

Chez le bébé
- Étroitesse du trou occipital
- Apnées sommeil
- Rhinite obstructive
- Otite séreuse
- Cyphose dorso-lombaire

Chez l'enfant
- Surcharge pondérale
- Incurvation membres inférieurs
- Cyphose dorso-lombaire
- Otite séreuse

Chez l'adolescent
- Surcharge pondérale
- Dysharmonie maxillo-dentaire
- Canal lombaire étroit
- Genu varum
- Difficultés psychologiques

Chez l'adulte
- Canal lombaire étroit
- Apnées du sommeil
- Baisse acuité auditive
- Surcharge pondérale
- Complications cardiovasculaires
- Difficultés psychologiques
- Conseil génétique

Consultations et prise en charge		Examens complémentaires
De 3 à 12 ans		
Pédiatre-Généticien (tous les ans)	Examen clinique avec mensurations et mobilité articulaire Conseils diététiques Suivi et recommandations scolaires (PAI)*	• Audiométrie (tous les 3 ans) • Activités sportives (+/- adaptées)
Orthopédiste / MPR* (tous les ans)	Statiques des membres inférieurs (genu varum) et du dos Voies pyramidales et mobilité articulaire	
Kinésithérapie	Lutte contre le flessum des hanches Travail de musculation axe vertébral, paroi abdominale et ceintures	
Selon besoin	Intervention sur le genu varum ORL pose d'aérateurs transtympaniques Accompagnement psychologique Suivi diététique Accompagnements pédagogiques adaptés Pneumopédiatre (expert en sommeil) : VNI*	• IRM médullaire • Polysomnographie • Radios rachis et membres inférieurs (EOS)*
De 12 à 18 ans		
Pédiatre-Généticien (tous les ans)	Examen clinique avec mensurations et mobilités articulaires Conseils diététiques Suivi et recommandations scolaires (PAI)* Accompagnement orientation professionnelle	• Bilan stomatologique • Bilan orthodontiste • Piscine, activités sportives (+/- adaptées)
Orthopédiste / MPR*	Tonus axial et périphérique Voies longues	
Généticien (tous les 3 ans environ)	Conseil génétique Préparation au transfert en services adultes Consultation pluridisciplinaire de transition à 18 ans	
Selon besoin	Traitement chirurgical des déviations du rachis Accompagnement psychologique Conseils diététiques Kiné : lutte contre le flessum, travail de musculation axe vertébral, ceinture, paroi abdominale Pneumopédiatre (expert en sommeil) : VNI*	• Radios rachis et membres inférieurs (EOS)* • IRM médullaire • Audiométrie • Polysomnographie
À partir de 18 ans		
Orthopédiste / MPR* Rhumatologue Généticien Stomatologue-Dentiste ORL	Consultations tous les 3 ans environ Adaptation du poste de travail dans la vie professionnelle Impact fonctionnel de la petite taille - Fatigabilité, douleurs - Mobilités articulaires - Indice de masse corporelle	• Bilan stomatologique • Piscine, activités sportives (+/- adaptées)
Selon besoin	Traitement fonctionnel ou chirurgical d'un canal lombaire étroit Traitement chirurgical du genu varum Grossesse : visite préconceptuelle + suivi en centre spécialisé Accompagnement psychologique Bilan diététique Kinésithérapie Appareillage auditif Ventilation nocturne intermittent avec masque adapté	• Radios rachis et membres inférieurs (EOS)* • IRM médullaire • Bilan auditif • Polysomnographie

*ALD = Affection Longue Durée
*EOS = Technologie très peu irradiante permettant de réaliser simultanément des clichés de face et de profil corps entier et une modélisation 3D du squelette du patient debout.
*MDPH = Maison Départementale des Personnes Handicapées
*MPR = Médecine physique et Rééducation
*PAI = Projet d'Accueil Individualisé
*VNI = Ventilation Non Invasive

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Cette fiche s'adresse aux professionnels de santé impliqués dans la prise en charge des maladies rares de l'os, du calcium et du cartilage et aux patients ayant déjà reçu l'enseignement de cette prise en charge. Le contenu a été rédigé par les médecins du site coordonnateur (Necker) Centre de Référence Maladies Osseuses Constitutionnelles (CR MOC) dans le cadre de la Filière Santé OSCAR.

www.filiere-oscar.fr

Illustration 10

D – Actualities on medical management

Medical treatment options in achondroplasia are a hot topic. In fact, biotherapy has been part of the therapeutic arsenal of achondroplasia ever since multiple treatment avenues have advanced to the therapeutic trials phase.

Actually, Vosoritide is the only available expanded access drug available, and that as part of a cohort study in France. This molecule is an analogue of the natriuretic peptide. FGFR3 activation sets in motion a cascade of signal transmission, a complex mechanism that will not be detailed in this chapter. Nevertheless, it should be noted that no side effects have been reported to this day. This medication, which should be conserved in the refrigerator, similarly to the growth hormone, is administered as a daily subcutaneous injection. Its cost should, however, be put to question: 260,000 EUR annually for an annual gain of 1.5cm, leading to a maximum gain of 10cm during a 6-year treatment period. As such, such a gain would not allow the patient to reach the height of the general population, but only to decrease the gap. As of today, injections can be received at the Necker, Lyon, Marseille, Toulouse, Nantes, and Strasbourg centers.

E – Actualities on orthopedic treatment

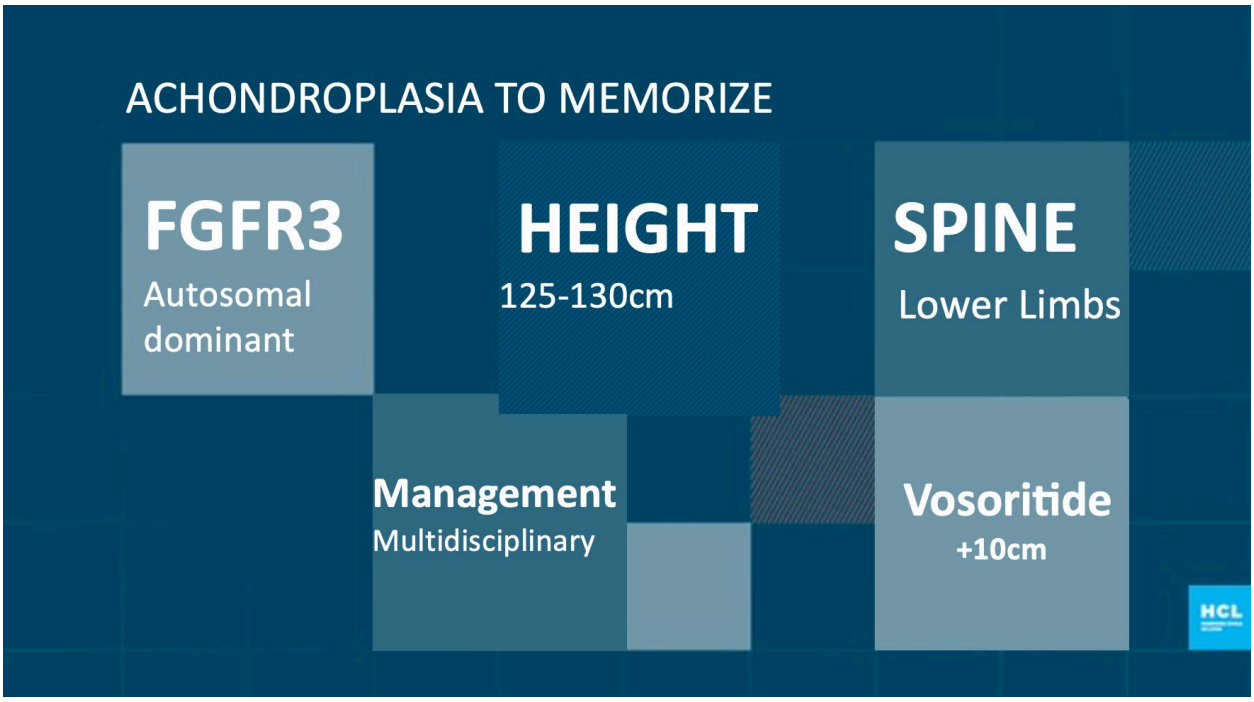
The actualities on surgical treatment will be discussed in a later chapter.

F – Actualities on adapted physical activities

The most recent developments which will be discussed in this chapter include adapted physical activity (APA). APA instructors are trained at a Department of Science and Techniques of Sports and Physical Activities (STAPS), with a specialization in adapted physical activities early on in their training.

Their interaction with these children takes place either in dedicated halls or gyms in the hospital or a reeducation center, or through video tutorials. Suggested sporting activities are adapted to the specific patient's requirements, contraindications, preferences, and motor skills. These trainers have become an integral part of our constitutional skeletal diseases multidisciplinary teams, where they play a pivotal role as motivators.

To memorize:


ACHONDROPLASIA TO MEMORIZE
FGFR3
Autosomal dominant
HEIGHT
125-130cm
SPINE
Lower Limbs
Management
Multidisciplinary
Vosoritide
+10cm
HCL