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Achondroplasia: Your Guide to Assessment, Management, and Coordination of Care

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Target Audience

This activity is intended for US and global audience of pediatricians, primary care physicians (PCPs), orthopedists & orthopedic surgeons, geneticists, and pediatric endocrinologists.

Goal

The goal of this activity is to improve clinicians' knowledge regarding the burden of disease and complications associated with achondroplasia (Ach), benefits and limitations of current care recommendations, emerging therapies for Ach, and strategies for coordination of care with specialists.

Learning Objectives

Upon completion of this activity, participants will:

Have increased knowledge regarding the

- Burden of disease in individuals with Ach
- Limitations of current care for Ach
- Emerging therapies for Ach

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- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

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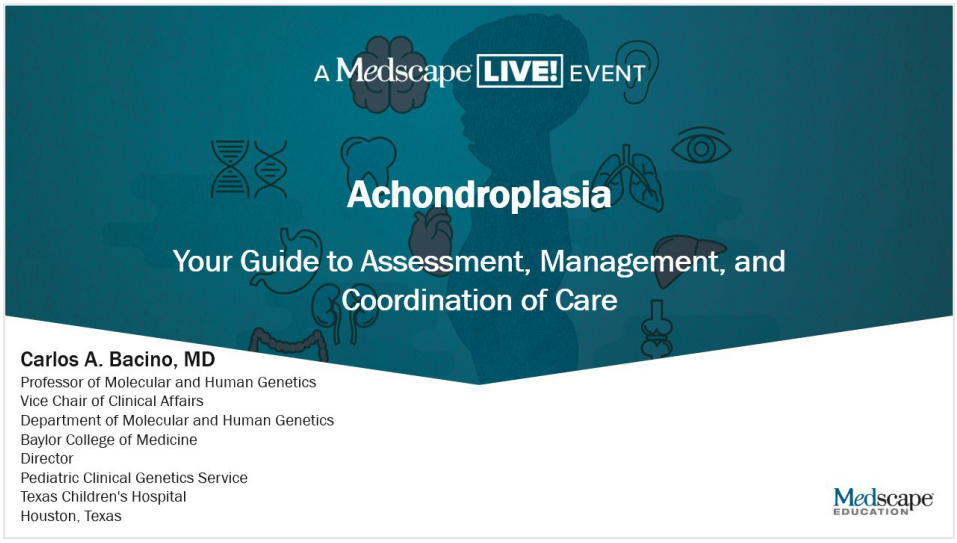
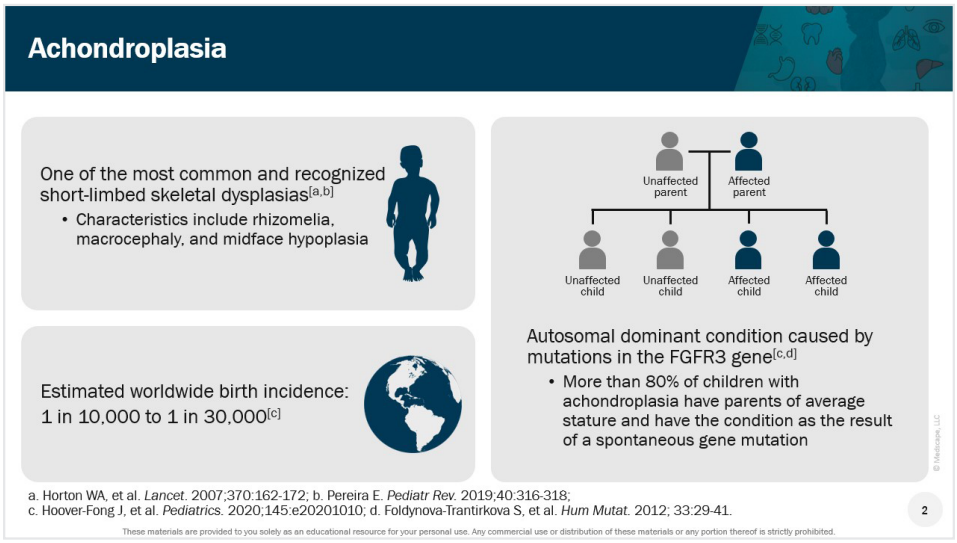
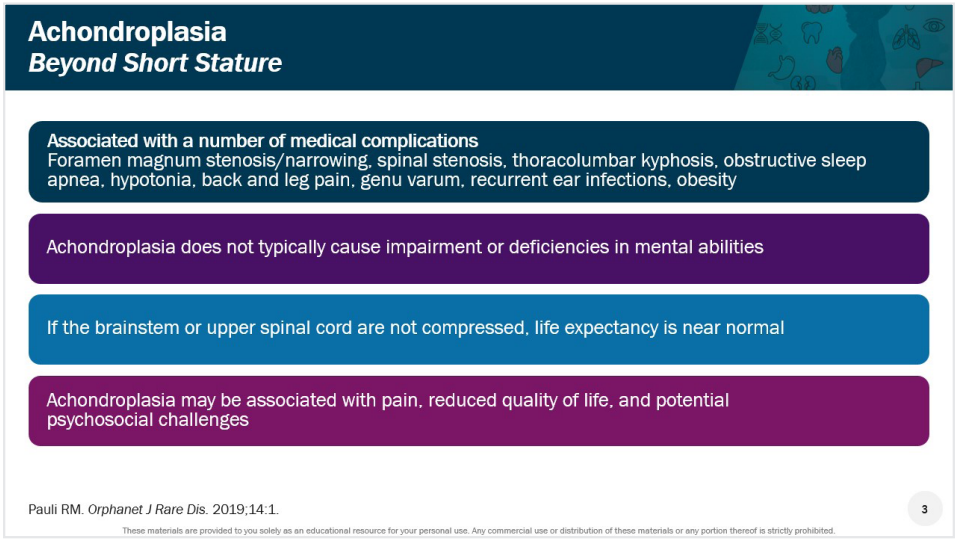


Good evening, I'm Dr Carlos Bacino. I'm a professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas. Welcome to this program titled "Achondroplasia: Your Guide to Assessment, Management, and Coordination of Care." This program will summarize key clinical information that was presented by me and by my colleagues, Dr Julie Hoover-Fong, Dr William Wilcox, and Dr Michael Bober at a live virtual symposium. Essentially, this is about highlighting the burden of disease in individuals with achondroplasia, limitations of current care and recommendations, how to manage patients with achondroplasia, as well as some emerging therapies.

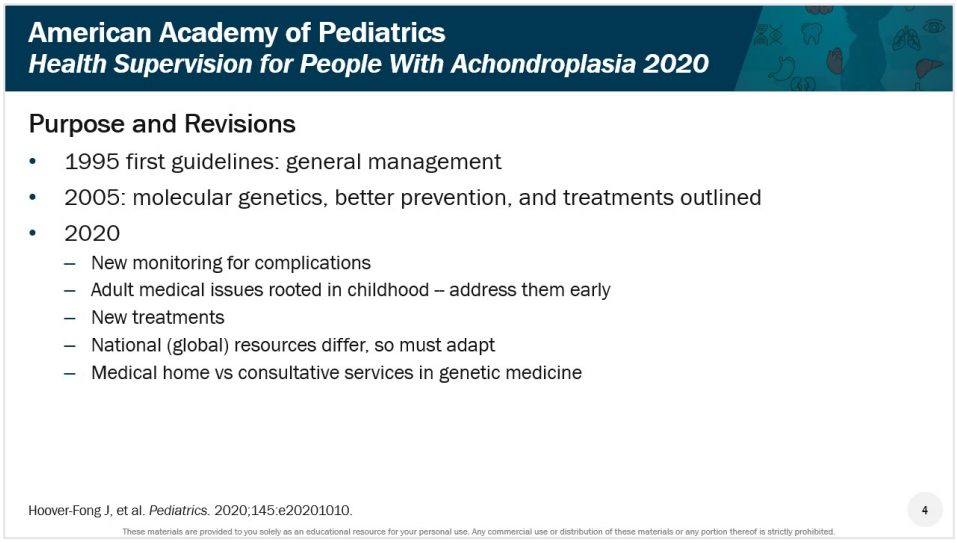


Achondroplasia is the most common and recognized skeletal dysplasia. It is characterized by clinical findings that include shortening of the limbs, more in the proximal part, known as rhizomelia, a large head, and midface hypoplasia. The incidence is approximately one in 15,000 to one in 20,000 individuals. Achondroplasia is an autosomal dominant disorder, meaning that an affected individual will have a 50% chance of having affected children. Having said that, approximately 80% of children with achondroplasia have parents of average stature, meaning that this represents new mutations.

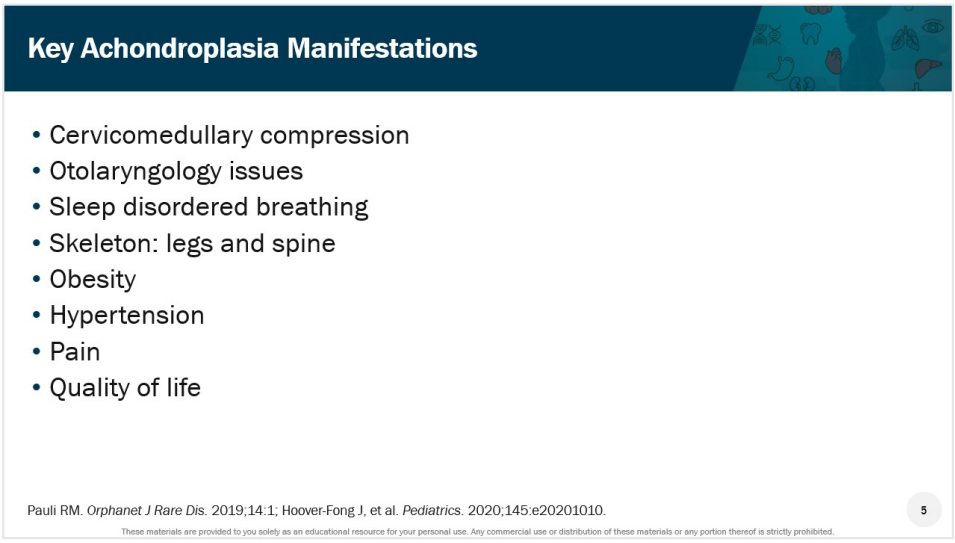


Achondroplasia is not just about short stature, it is more than that. There are a number of medical problems and morbidities associated with this condition including compression of the foramen magnum, spinal stenosis, kyphosis of the thoracolumbar spine, obstructive sleep apnea, back and leg issues, pain, genu varum deformity, recurrent ear infections, as well as obesity.

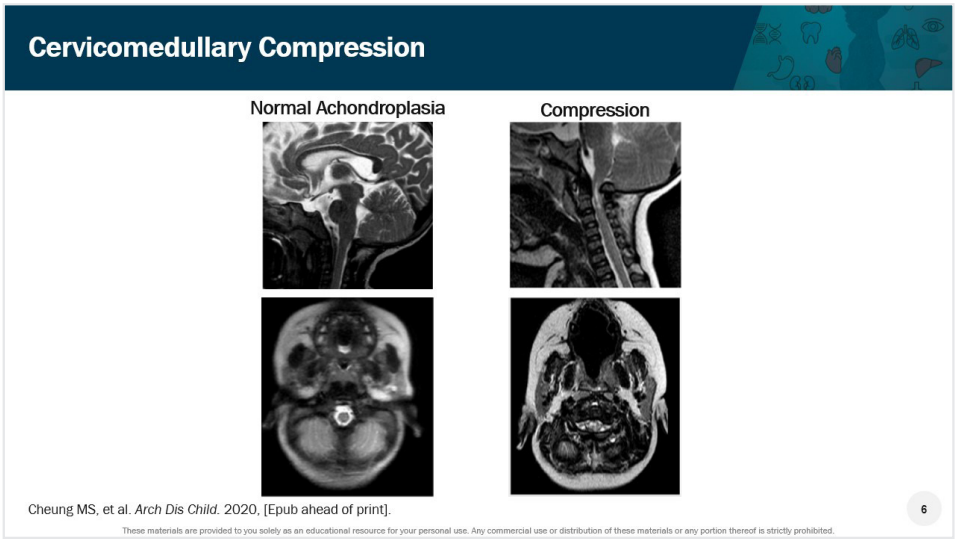
Needless to say, this is a condition that doesn't cause impairment of mental abilities, so these children are cognitively normal. The life expectancy in achondroplasia is near normal; however, if there are issues with brainstem or upper spinal cord compression, there could be issues limiting life expectancy. Achondroplasia can be associated with pain, reduced quality of life, and potential psychological and psychosocial challenges.



For pediatricians, the best document that you could access are the guidelines that have been published by the American Academy of Pediatrics. These were updated in 2005, as well as in 2020, and include information about molecular genetics that was not available early on when it was published. The guidelines also include dealing with complications, dealing with adult medical issues that actually start in childhood, and touch upon some of the new treatments that are available.



So in terms of achondroplasia manifestations, we are going to go over a lot of these medical issues, including cervicomedullary compression, which is the most significant issue, ENT-related problems, sleep disorders, legs and spine, the skeleton in general, obesity, hypertension, pain, and quality of life.



One of the issues that we are the most concerned about is cervicomedullary compression. Patients with achondroplasia have a narrow foramen magnum, which is the part of the skull where the spine comes out. This is something that happens to all patients with achondroplasia, and there are some critical times during development where this particular area narrows the most. And that is approximately around 12 months to 16 months of life.

So as you can see on the left, this is a patient with achondroplasia that has a normal spine at the cervicomedullary junction. And you can see on the right, an individual that has significant stenosis with compression, and you can see some increased signaling, which is actually telling you that this is associated with significant clinical problems.

Natural History and Assessment
Cervicomedullary Compression

- Everyone with achondroplasia has cervicomedullary compression[a]
- Goal: Detect before permanent damage
- Pathologic compression manifests as central apnea and myelopathy[b]
- To assess brainstem/upper cervical cord integrity:[b]
  - Physical exam with neurologic exam
  - Check growth and development
  - Sleep study
  - MRI of craniocervical junction

a. Hecht JT, et al. *Am J Med Genet*. 1989;32:528-535; b. Hoover-Fong J, et al. *Pediatrics*. 2020;145:e20201010.

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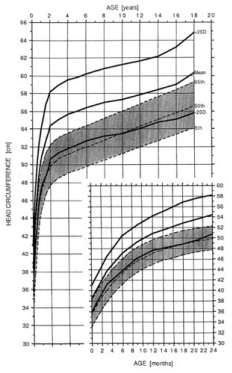
By definition, everyone with achondroplasia has cervicomedullary compression. The goal is to detect it before permanent damage because once you start having increased signaling, you can have permanent damage to the cord. And this manifests clinically in a number of ways. Central apnea or symptoms of compression that can give you an abnormal neurological exam. So things that you can do to assess the brainstem and the upper cervical cord is a good neurological exam to check growth and development, as well as head growth, sleep studies, and eventually MRI, if needed.

Management
Cervicomedullary Compression

- Longitudinal assessment[a]
  - Head circumference on achondroplasia curves
  - Neurologic exam
  - Development
- Consultation with[a]
  - Neurosurgeon with MRI
  - Pulmonologist with sleep study
- Surgical decompression[b,c]
  - Well-tolerated
  - Most are decompressed before 3 years of age
  - Minimal complications in experienced hands



a. Hoover-Fong J, et al. *Pediatrics*. 2020;145:e20201010; b. Bagley CA, et al. *J Neurosurg*. 2006;104(3 Suppl):166-72; c. Shimony N, et al. *Childs Nerv Syst*. 2015;31:743-750; d. Horton WA, et al. *J Pediatr*. 1978;93:435-438.

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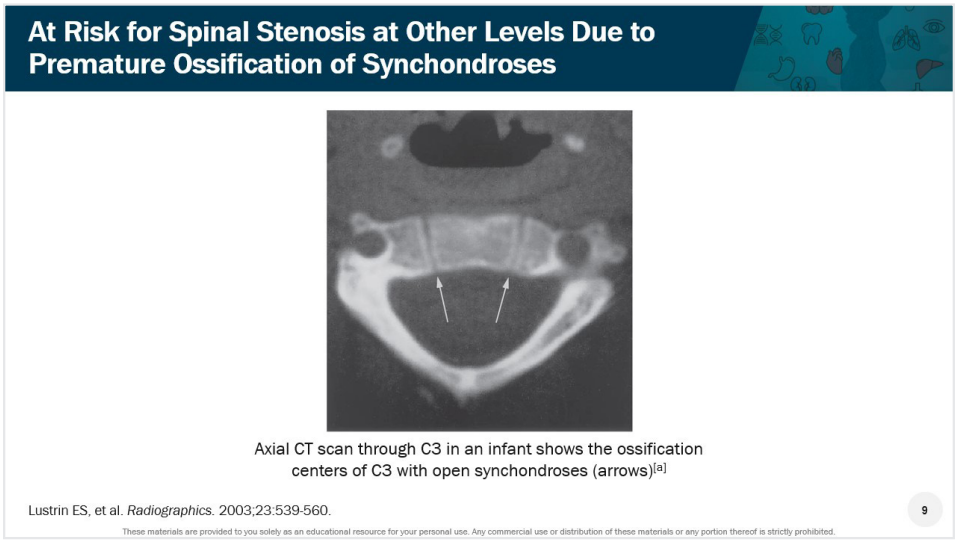
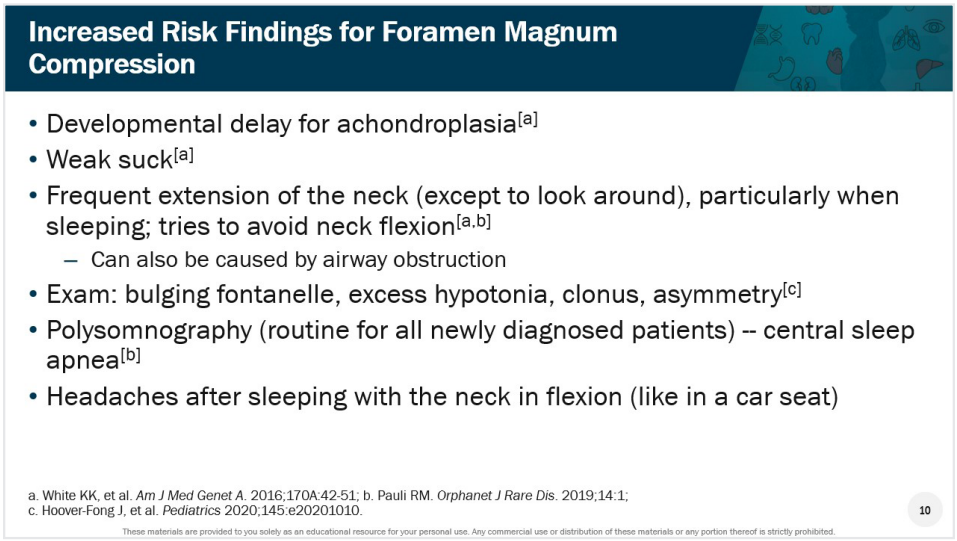
In achondroplasia, you use growth curves that are appropriate for the condition. Why is that? It is because these children grow at a different rate in different areas, and the head actually is a lot bigger than in average stature children. On the right, you see the curves for head circumference that goes from 0 to 24 months, and then also for older individuals. The shaded gray areas represent growth for average stature children. The dark lines represent the achondroplasia growth curve.

So if you have a rapidly growing head that is beyond what you expect for achondroplasia, you could consider consulting with a neurosurgeon or doing some imaging studies. If you have cervicomedullary compression, the treatment is decompression. What we do is a laminectomy typically in C1 or in C2. Most children are decompressed before three years of age, and there are minimal complications when done in experienced hands.



Why do we have problems with narrowing of the spine? One thing I should mention is that all children with achondroplasia and adults have decreased space inside the spine. And this is due in part to the poor growth of synchondroses. You can see in this slide, the arrows that indicate these synchondroses, which is where the spine essentially grows. Premature ossification makes the space for the spine to grow and to accommodate the medulla a lot smaller and that can cause problems.



So who is at risk for foramen magnum compression? Well, initially you will detect a number of neurological problems, developmental delay, and problems with feeding and weak suck. A child will frequently extend their neck, and that is because when the child flexes the neck, it typically compresses the spine, so there is a tendency to hyper-extend. On exam, you can see an enlarged bulging fontanelle, hypotonia, as well as clonus, asymmetry, and abnormal reflexes. If you do a sleep study in these cases, you may actually diagnose central sleep apnea.

Foramen Magnum Neuroimaging

CT can give foramen magnum size to compare with published achondroplasia norms[a]

- Does not provide information on compression

MRI preferred with CSF flow[a]

- If the neutral is not concerning, imaging with the neck in extension and flexion can be done to exclude dynamic compression

Enlarged ventricles and increased extra-axial fluid are common[b]

- True hydrocephalus is usually caused by occlusion of CSF flow at the foramen magnum or venous hypertension from stenosis at the jugular foramina

a. Hoover-Fong JE, et al. *Pediatrics* 2020;145:e20201010; b. White KK, et al. *Am J Med Genet A*. 2016;170A:42-51.

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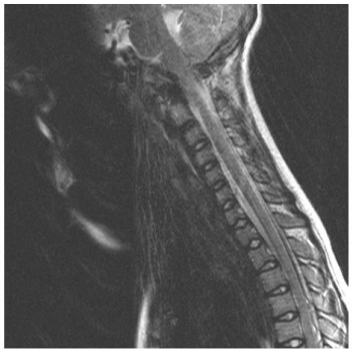
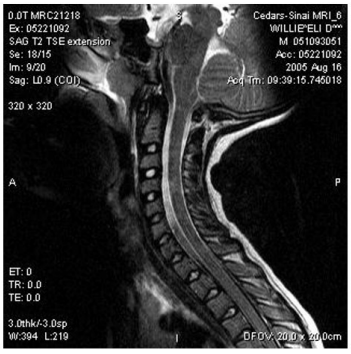
In terms of neuro-imaging, a CT will give you a good measurement of the foramen magnum size. And the foramen magnum size can then be compared with published achondroplasia norms. Another study that is preferred but not always done in all centers is an MRI with CSF flow. This allows imaging with the neck in flexion and extension. Oftentimes, you will see the problem when the neck is in flexion. The imaging that you see normally in achondroplasia of large ventricles is a common finding, but it's not a finding of hydrocephalus. This is just because of the anatomy of the skull.

Dynamic Cord Compression

Flexion



Extension



Danielpour M, et al. *J Neurosurg (6 Suppl Pediatrics)*. 2007;107:504-507.

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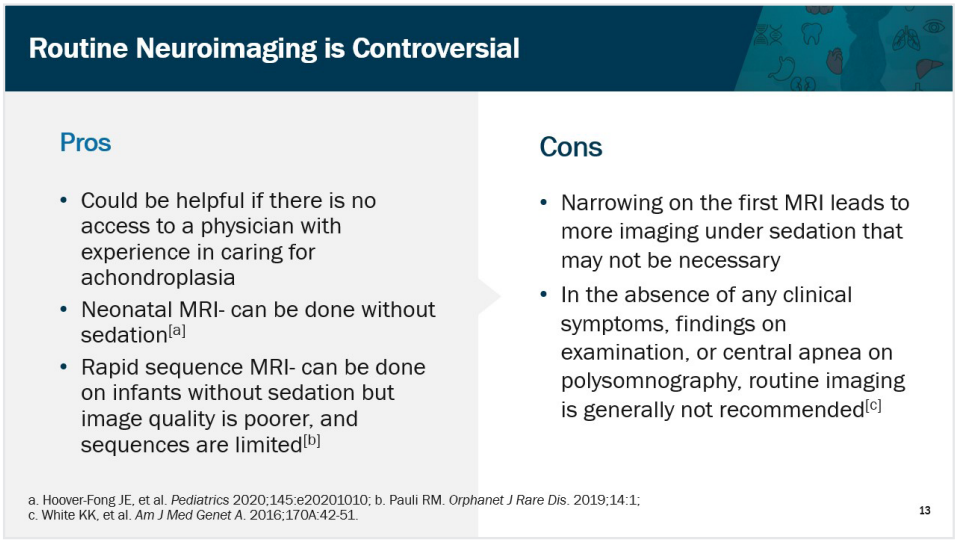
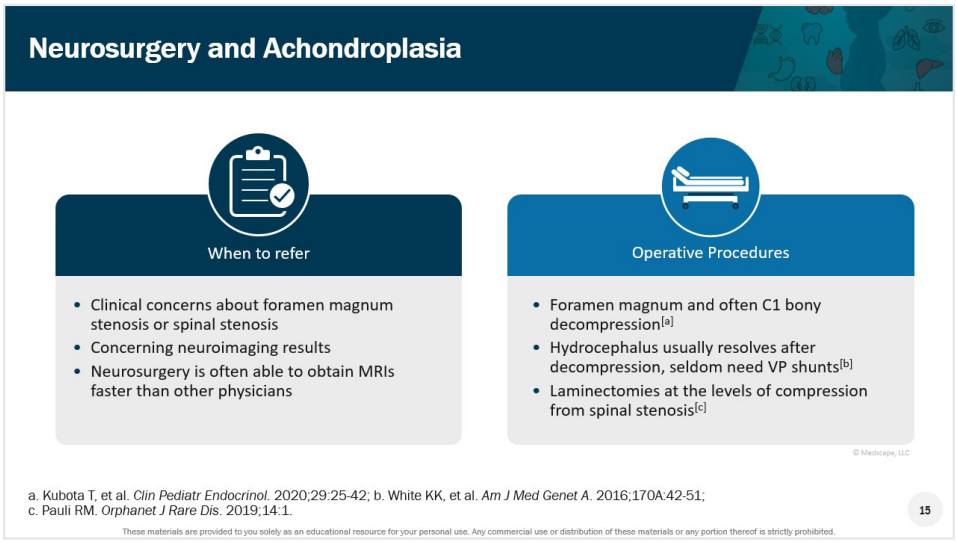
This slide shows the dynamic situation of cord compression when you have flexion and extension. These images show that there is further narrowing of the cervicomedullary junction in flexion, as opposed to extension where you have much more opening of the cervicomedullary junction.

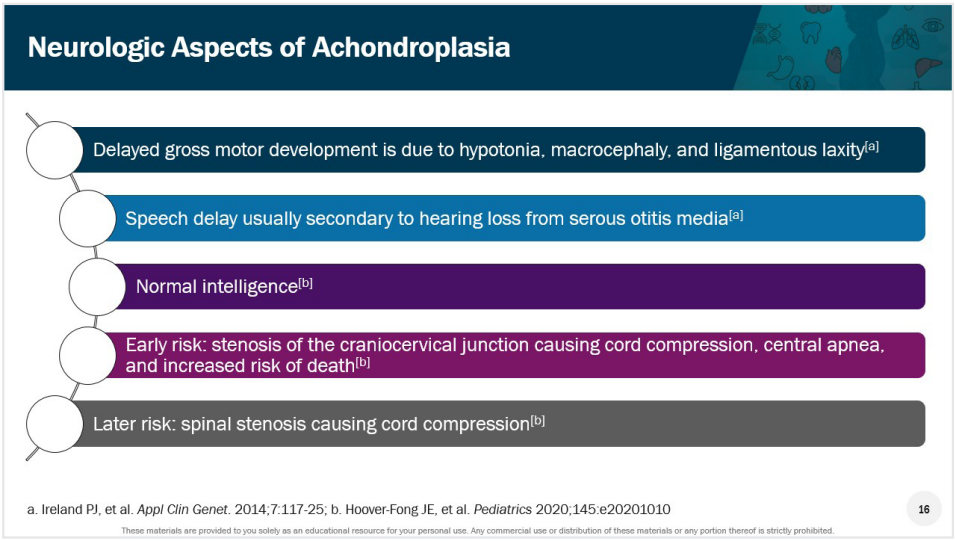


Is routine imaging something that you will do in all cases? Well, that's controversial. It is helpful if you don't have access to a physician that has experience in achondroplasia. You can always do a neonatal MRI without sedation with some swaddling. Rapid MRIs nowadays can be done. The problem with rapid MRIs, you can get a measurement of the cervicomedullary junction, but the image quality is relatively poor and has limited sequencing.

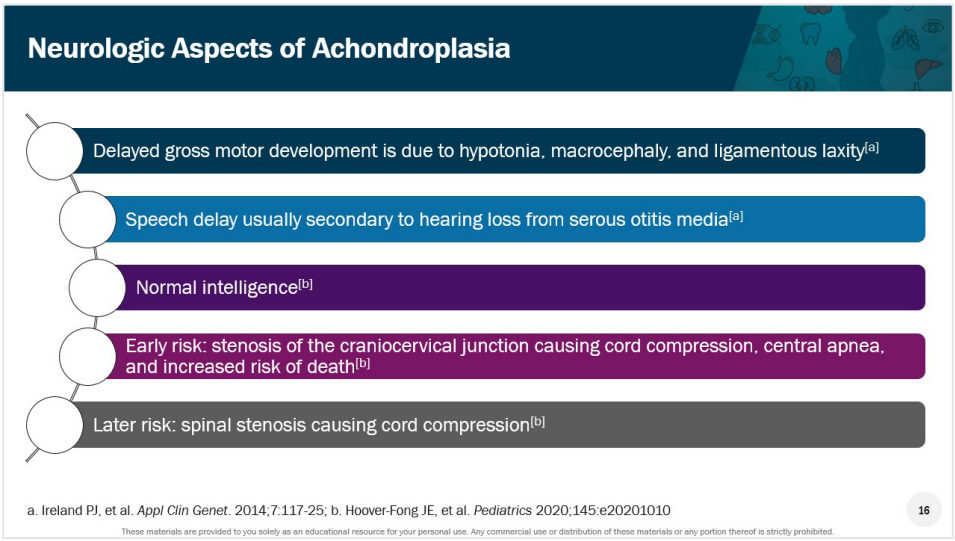
The cons of routine imaging are that if you see some narrowing, and most of the time you will see some degree of narrowing, you will end up doing more imaging and then you may require sedation. Some people say that in the absence of any clinical findings, like central sleep apnea or abnormal neurological exam, routine imaging is not generally recommended.



There is another thing to remember, which is spinal stenosis. This is common in older adults, and can even happen before age 18. It presents with neurological signs including fatigue, numbness, tingling of the legs and difficulties, essentially, ambulating with some degree of anesthesia. There could be radicular pain. If it's more severe, you can have loss of bowel and bladder function, and you may have problems with ability to walk. Clonus is common with asymmetric reflexes. If a patient presents with these findings, do a spinal MRI and contact a neurosurgeon.

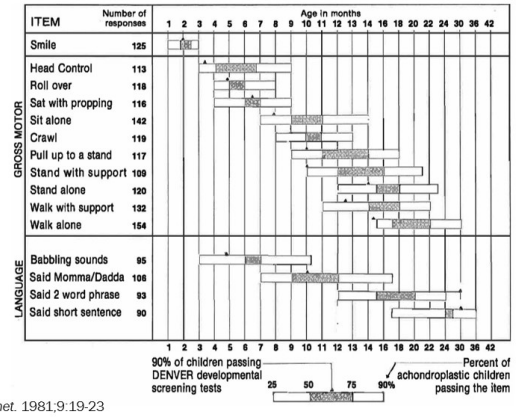


When do you refer a patient to neurosurgery? That is something that you do when you have clinical concerns about foramen magnum stenosis or spinal stenosis, or you have problems in your imaging. The neurosurgeon will typically do, when needed, a foramen magnum C1 decompression. Hydrocephalus may need to be treated, but frequently. Typically, if you have any increased pressure, you will resolve it with decompression and it will rarely need a VP shunt. Depending on where you have the spinal stenosis, you may end up having laminectomies.



What are the neurologic aspects of achondroplasia? You can have issues related to delayed gross motor development. That is typically due to hypotonia, macrocephaly, and ligamentous laxity. These children have a lower muscle tone, a very large head to carry, and then their lax joints cause them to have delays in sitting, standing up, and ambulating. Speech delays can be seen secondary to middle ear disease from otitis media. These patients have normal intelligence, as we said. They have a risk for stenosis of the craniocervical junction, which can cause cord compression, central apnea, and increased risk for death. And a later risk, as we mentioned, is spinal stenosis causing cord compression.

Developmental Screening Tests in Achondroplasia



Todorov AB, et al. *Am J Med Genet.* 1981;9:19-23

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This is a study done by Todorov that shows the developmental milestones in achondroplasia. It shows when children of average stature acquire a milestone, and in comparison, what happens with achondroplasia. As you will see, all of the gross motor milestones are slightly behind compared to the average stature children. That's because of their inability to control the head or problems controlling and maintaining the spine erect, pulling to stand, and abnormalities in the spine, including kyphosis and lordosis. Also you can have some degree of delays, essentially in the speech area, but that is if you have abnormalities of hearing secondary to otitis media.

Feature
Otolaryngology Issues

- Chronic middle ear fluid
- Recurrent or refractory otitis media[a]
- Secondary hearing deficit, speech delay[b]
- Hypertrophy of tonsils, adenoids[c,d]
- Upper airway obstruction

a. Hunter AG, et al. *J Med Genet.* 1998;35:705-12; b. Tunkel D, et al. *Am J Med Genet A.* 2012;158A:1551-1555;
c. Collins WO, et al. *Arch Otolaryngol Head Neck Surg.* 2007;133:237-44; d. Lyford-Pike S, et al. *Otolaryngol Clin North Am.* 2012 ;45:579-98.

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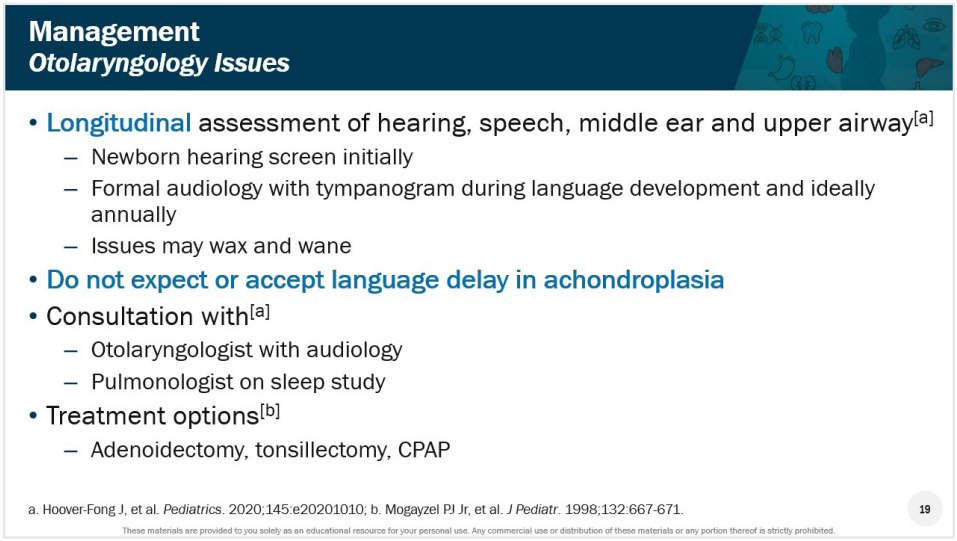
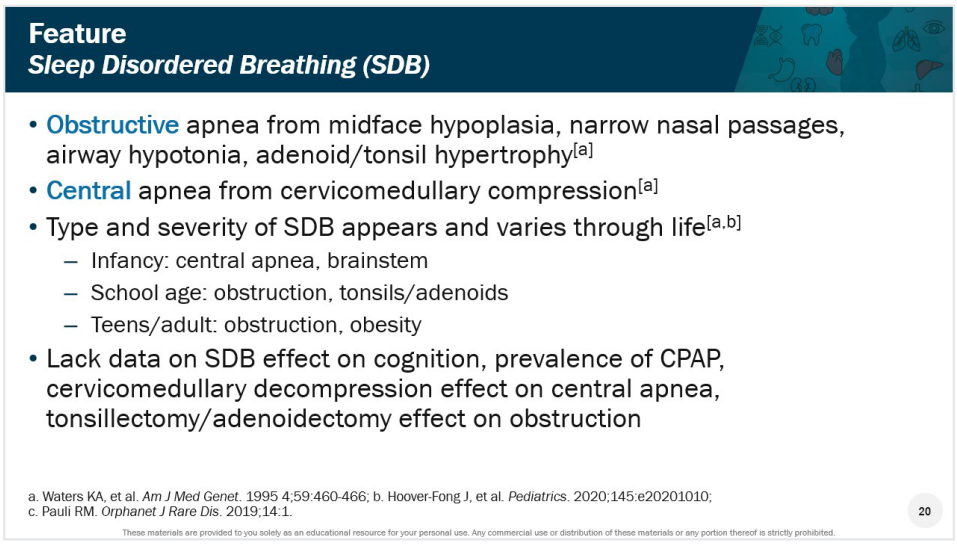
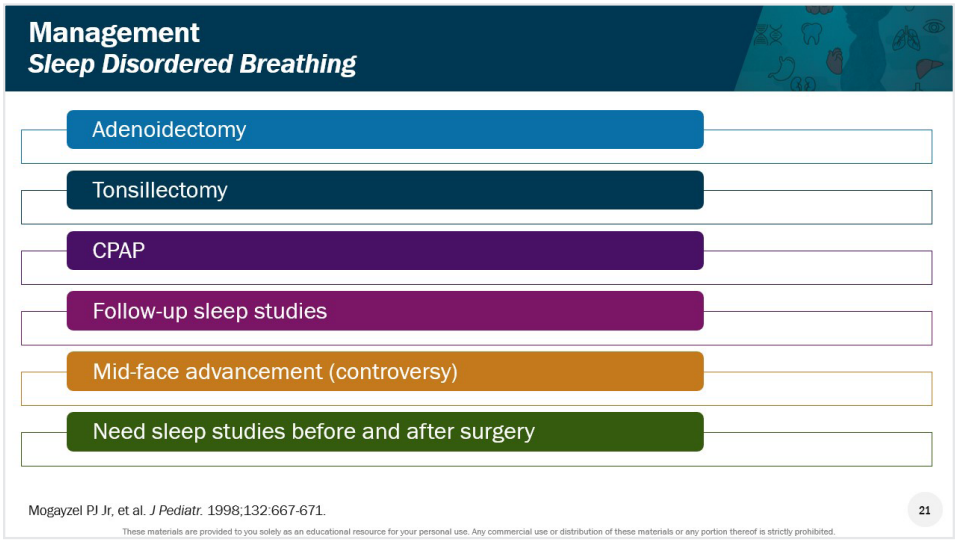
These are the otolaryngology issues patients with achondroplasia have. One is chronic middle ear fluid and this is because the anatomy is slightly different to average statured children. They do have refractory or recurrent otitis media, and because of that, may have hearing deficits. These need to be taken care of right away and treated with pressure equalization tubes. In addition, you have other ENT-related issues with hypertrophy of tonsils and adenoids and upper airway obstruction.



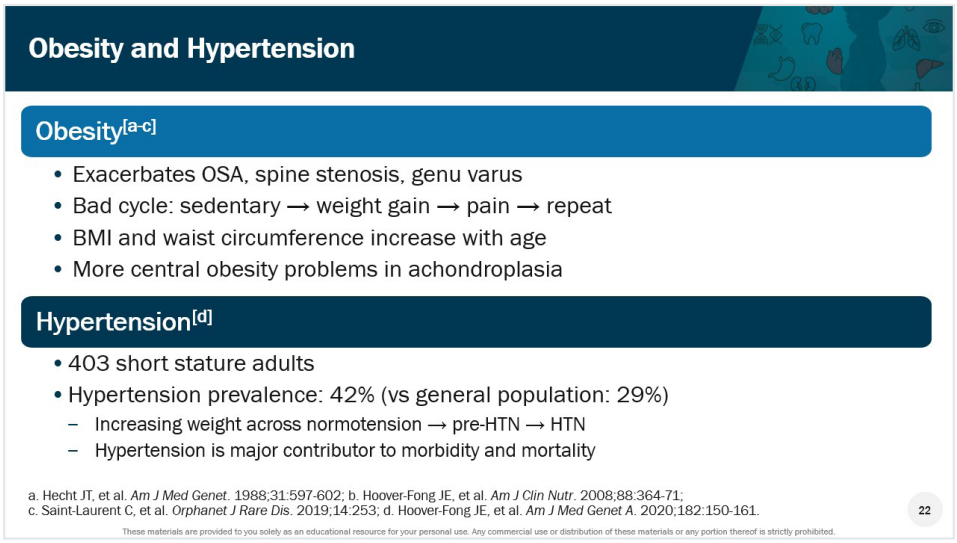
So what do you do for these issues? Well, you need to be very attentive about the hearing and you have to check the hearing early on. That's done in the newborn screen. Then around one year of age, you do a formal audiological exam with tympanogram. You should not accept any language delay in achondroplasia, because it is likely due to a medical issue that can be treated and taken care of. Airway –related issues are also found in achondroplasia. These can be treated with adenoidectomy or tonsillectomy, and if needed, a CPAP.



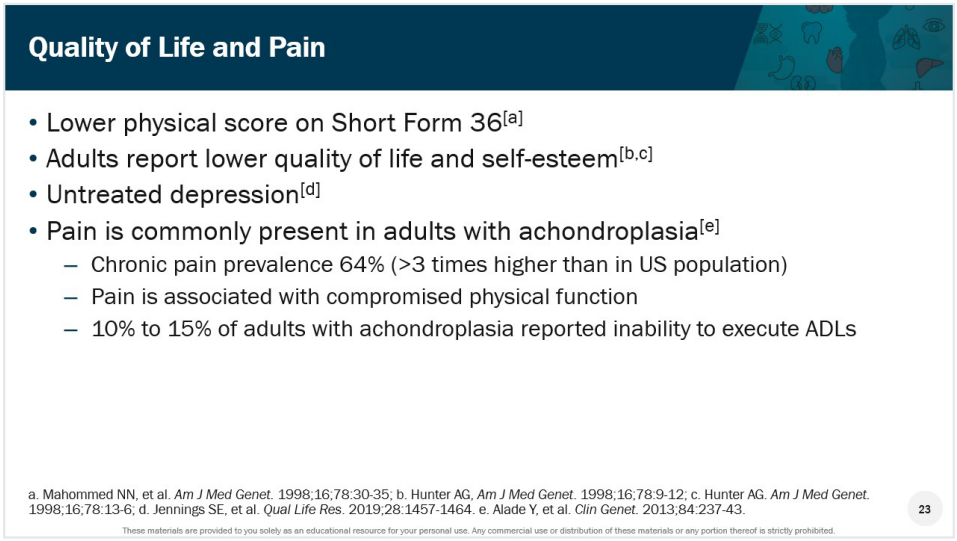
Children with achondroplasia also have sleep disordered breathing (SDB). Those are essentially obstructive sleep apnea, and more rarely, central apnea due to cervicomedullary compression. Obstructive apnea results from mid-face hypoplasia, narrow nasal passages, and also hypertrophy of the adenoids and tonsils. You will see that patients with achondroplasia have a flatter mid-face, and that also leaves less space overall for the passage of air. The types of SDB vary through life. And at this time, there are no data about SDB on cognition, and that's something that still needs to be looked at.



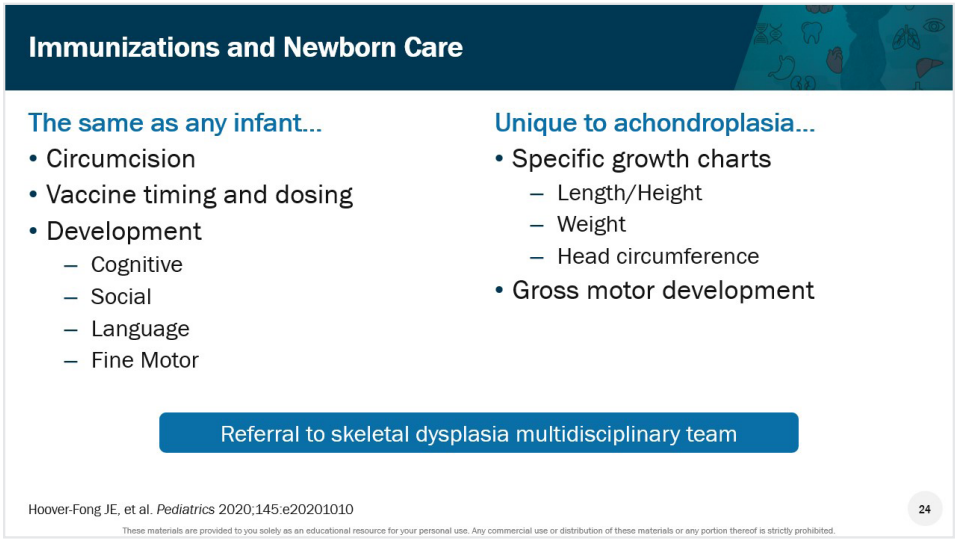
How do you manage these disorders? You do a sleep study and if the sleep study is abnormal, then you send the patient to an ENT specialist. So, oftentimes doing an adenoidectomy or tonsillectomy is probably enough. But in some cases, you'll need to go to CPAP if you repeat the sleep study and the patient is still showing signs of sleep apnea. So, you have to do sleep studies before and after, and you have to continue doing studies. There are some people who have proposed to do advancement of the midface, but these are very complex surgeries that have very high morbidities. This is not something that we'd normally recommend.



Obesity, as I'd mentioned, exacerbates obstructive sleep apnea, and it also can create more problems with spinal stenosis and difficulties with gait because of the genu varum deformity. So, these patients are short and they carry about the same weight, and that puts them in a difficult situation. They don't move as well, and they don't move as much. They tend to be sedentary and they tend to gain more weight. So, this is something that you need to address very early on and hopefully engage the patient in more activities and healthy diets. There is a whole issue about hypertension and there was a recent study done on patients with achondroplasia that showed that there is a prevalence of over 40% in achondroplasia versus 29% in the general population.



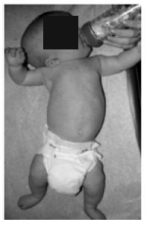
This is from a study that shows that quality of life and self-esteem is lower in patients with achondroplasia. Depression is frequently seen because of the medical complications and because of self-esteem. And pain is also an issue, especially chronic pain associated with difficult physical function.

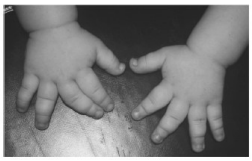


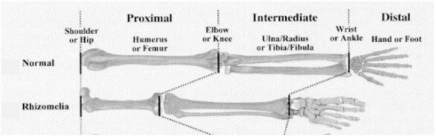
With regard to regular pediatric care, essentially, you have to do the same thing that you will do for any other regular child, from vaccines, to eye checks, hearing checks, and developmental check. When it comes to achondroplasia, you need to be aware that there are some specific charts unique to achondroplasia, such as for head circumference, length and height, and development.

Achondroplasia – Clinical Features

- Average birth parameters
- Rhizomelia
- Relative macrocephaly
- Large fontanelle
- Frontal bossing
- Midface hypoplasia
- Trident hand







Rust OA, et al. *Obstet Gynecol Clin North Am.* 1998;25:553-571; Pauli RM. *Orphanet J Rare Dis.* 2019;14:1.

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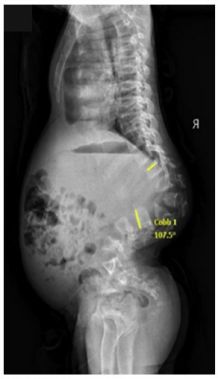
What are the clinical features for achondroplasia? These patients typically have average birth parameters, but they already show some shortening of the limbs. They do have a large head, with a generous fontanelle. You can see frontal bossing, midface hypoplasia, and you can see in some cases, the shortened fingers, called trident deformity. And when you look at the limbs and the legs and the arms, you can see that there is some proximal shortening overall.

Thoracolumbar Kyphosis

- > 90% resolve when walking
- Bracing indications
  - > 2 years
  - Kyphosis > 50°, stiff
  - Anterior vertebral wedging
- Symptomatic progression can lead to surgery



Pauli RM, et al. *J Pediatr Orthop.* 1997;17:726–733; Xu L, et al. *Spine (Phila Pa 1976).* 2018;43:1133-1138; Siebens AA, et al. *Arch Phys Med Rehabil.* 1987;68:384-388; Ireland PJ, et al. *Appl Clin Genet.* 2014;24;7:117-25; Yilar S, et al. *World Neurosurg.* 2019:S1878-8750(19)30077-4.

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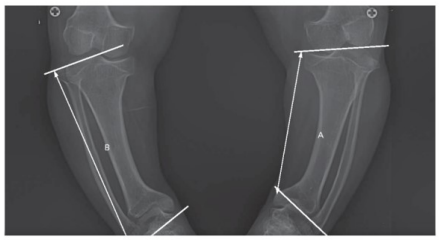
One thing that you need to assess and that you see in patients with achondroplasia is kyphosis of the thoracolumbar spine. Typically, this is something that goes away as soon as they start bearing weight, and this is often not a clinical problem. However, in some patients, the thoracolumbar kyphosis can be significant, and may require bracing

Genu Varum

- Most have some degree
  - Not always progressive
  - Not always symptomatic
- Etiologies unclear but include:[a-c]
  - Fibular overgrowth
  - Ligamentous laxity
  - Obesity
  - Asymmetrical growth of proximal tibial physis
- Indications for treatment[a]
  - Increasing varus deformity in the skeletally immature child
  - Lateral thrust during gait
  - Knee pain



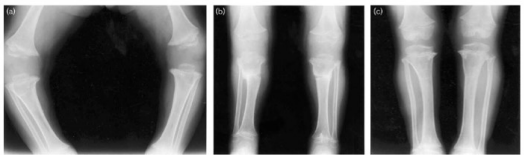
a. Wright MJ, et al. *Arch Dis Child*. 2012;97:129-134; b. Ain MC, et al. *J Pediatr Orthop*. 2006;26:375-379; c. Lee ST, et al. *J Bone Joint Surg Br*. 2007;89:57-61.

27

One other condition that you see is genu varum deformities, where the knees are pretty much going out. This occurs due to a number of different problems. One is that the joints are very laxed, so the knees kind of give out. In addition, there is a progressive bowing of the extremities, often related to an increased size of the fibula, or fibular overgrowth. That can be worsened by obesity and bearing of weight.

Limb Realignment

- Procedures depend upon:
  - Age
  - Level of deformity + fibula
    - Proximal tibia
    - Distal tibia
    - Distal femur
  - Number of levels
  - Severity of deformity
  - +/- Internal tibial torsion

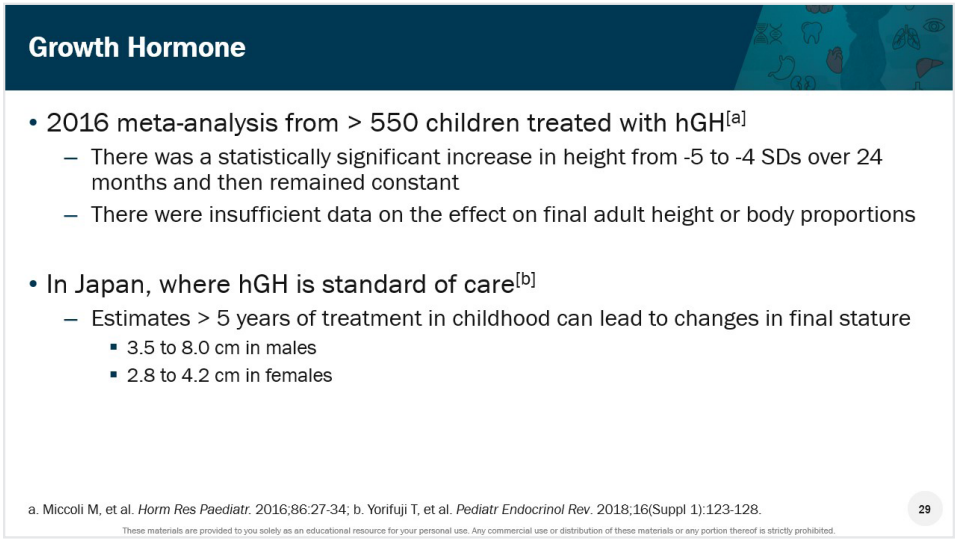


a. Anterposterior standing radiograph at age 5 years demonstrates significant varus at the knee joint, a long proximal fibula, and mild varus within the tibia. (b) Following proximal tibial osteotomy and excision of the proximal fibular physis demonstrates improvement in alignment. (c) At age 9 years demonstrates remodeling and maintenance of good alignment.

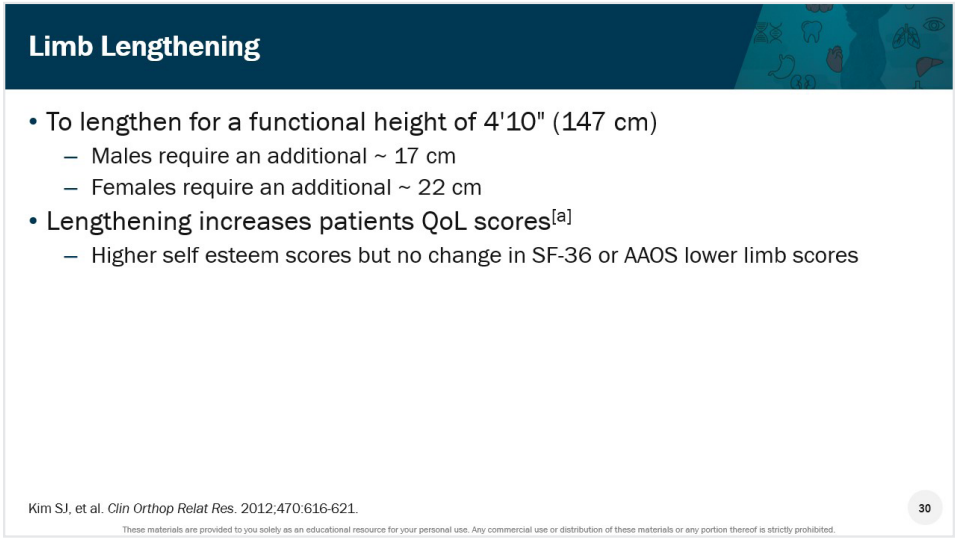
Beals RK, et al. *J Pediatr Orthop B*. 2005;14:245-249.

28

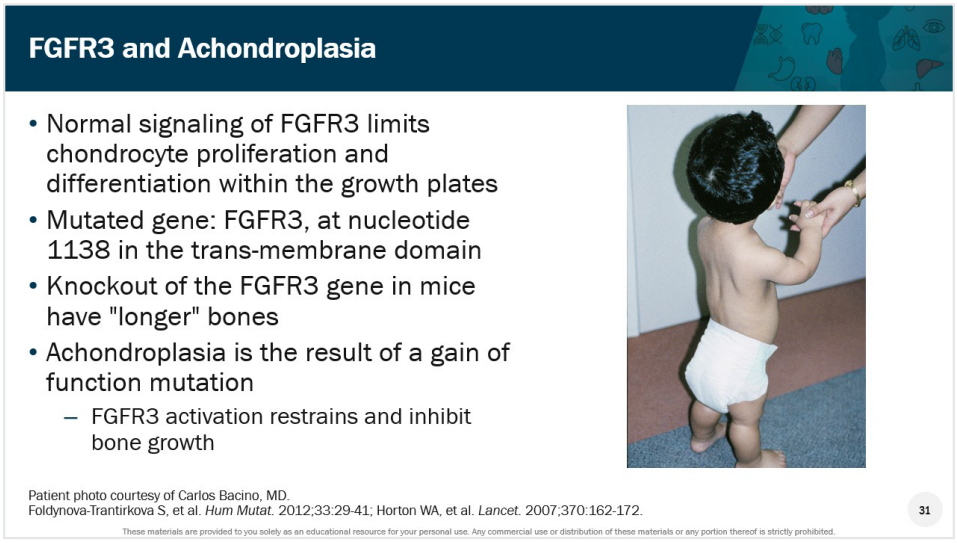
Some situations may require surgical correction, and that is typically of the proximal tibia. Although, sometimes you may require distal tibia correction as well.



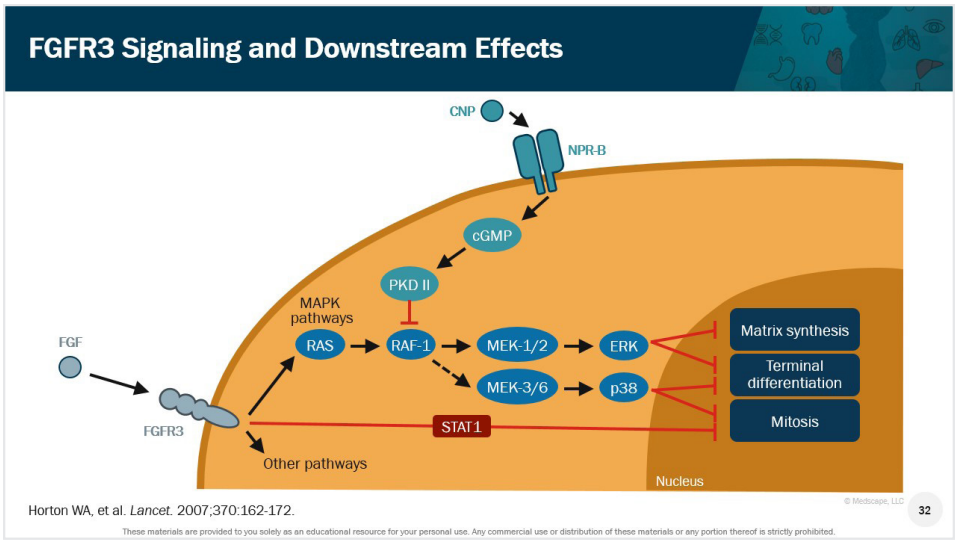
Growth hormone has been used in the past, but is not used in the US. It certainly doesn't cause a significant increase, and typically like growth hormone does, it will increase some height over the first 12 to 24 months, and then will stop. One other concern is that growth hormone may exacerbate disproportion.



There is also a procedure called limb lengthening that is now popular in some patients, where intramedullary rods are placed in the long bones. This procedure may lengthen patients' height from 15 cm to 20 cm approximately. This surgery is not covered by insurance, and is extremely costly.



What is achondroplasia from the biological standpoint? This is a condition caused by a mutation in FGFR3, which is a molecule that controls growth by inhibiting growth. You can imagine the bone growing and there's some signal for the growth, but then there are some other signals for the growth to stop. Well, FGFR3 takes care of that. When FGFR3 is activated, it limits chondrocyte proliferation and differentiation within the growth plates, stopping long bone from growing. There is a classical mutation that is present in most patients with achondroplasia, and this is fairly unique for a genetic disorder. And we know that this is a gain of function mutation, meaning that this is actively restraining growth. This is an overgrowth of growth inhibition. If you take mice and you knock out the FGFR3 gene, actually they are taller. They have longer bones, which actually shows that if you don't have this particular signaling, you will have further growth.



FGFR3 constitutively activates the MAP kinase and ERK pathways, and this is what ultimately activates kinases that will downregulate growth of the chondrocyte. There is an alternative pathway that may actually interfere with that particular action, and that is the natriuretic peptide receptor pathway. It was found that if you stimulate this particular receptor ,and what stimulates these receptors is the cartilage natriuretic peptide (CNP), you can actually stop this pathway from inhibiting growth or restraint of growth. In essence, it's an inhibition of the inhibition.

What Is Vosoritide?

- A recombinant CNP analog that has longer half-life than its endogenous form
- Once-daily subcutaneous administration of vosoritide
  - Promotes long-bone growth in juvenile, skeletally normal mice and monkeys
  - Corrects the dwarfism phenotype in mice with achondroplasia

Savarirayan R, et al. *N Engl J Med.* 2019;381:25-35.

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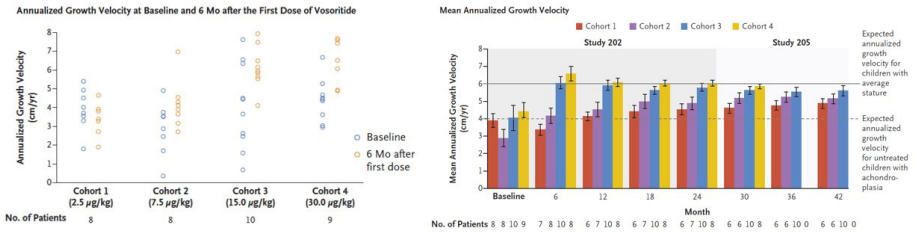
And that actually led to the use of a drug that is called vosoritide. This is a recombinant C-type natriuretic peptide that has a longer half-life than its endogenous form. This is a drug that if you give once daily, subcutaneous administration, it promotes long bone growth. And this has been tried in juvenile skeletally normal mice and monkeys, and actually corrected dwarfism phenotype in mice that are specifically designed with achondroplasia. Essentially, it can stop and reverse growth problems that these animals have.

Vosoritide Phase II Trial
Annualized Growth Velocity

- Doses of 15 µg/kg/day and up were associated with sustained increase in height velocity



Savarirayan R, et al. *N Engl J Med.* 2019;381:25-35.

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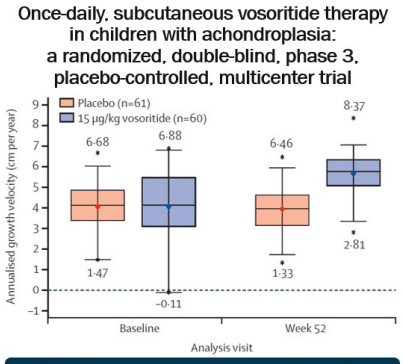
This is a Phase 2 trial that was done with vosoritide looking at annualized growth velocity (AGV). You can see on the left there are 4 different cohorts treated with different doses of vosoritide, 2.5 µg/kg all the way to 30 µg/kg. On the right, you see that Study 202 was the initial study, and then an extension (study 205), totaling to 42 months. If you pay attention to the higher doses, which are 15 and 30 µg/kg (blue and yellow bars), you will see that over time there was a significant growth of AGV over the expected for achondroplasia. There are two horizontal bars, one is a dotted line, and that is the expected AGV for patients with achondroplasia. And then you have a solid line on top, and that is the expected AGV for children that have average stature. The patients who received higher doses of vosoritide achieved a much higher height in general than expected for achondroplasia, and in some cases, getting close to the AGV of normal stature individuals.

Vosoritide Therapy in Children With Achondroplasia
Phase III Trial

- N = 121 participants with achondroplasia
- 52 weeks clinical trial
- Vosoritide 15 µg per kg SC had increased in AGV
- No clinically significant side effects
- No adverse effects on upper to lower body segment proportionality or bone maturation



AGV averaged 1.57 cm/year (0.90-1.84 cm)

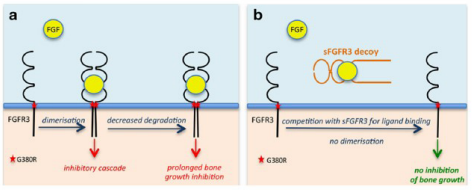
Savarirayan R, et al. *Lancet*. 2020;396:684-692.

35

In the phase 3 clinical trial, they used the 15 µg/kg dose. In this trial, half of the patients were treated with placebo and half with vosoritide. This was a one-year study for children five years of age and older. In the group who received vosoritide, AGV averaged approximately 1.6 cm over the expected AGV. In the placebo group, there were no improvements in height. In addition, there were no significant side effects and there were no issues with disproportion or worsening of this proportion.

Soluble FGFR3 Decoy Therapy

- sFGFR3 binds FGF2, FGF9, and FGF18, decreasing FGFR3 signaling in chondrocytes
- sFGFR3 treatment decreases spinal and skull deformities associated with achondroplasia
- sFGFR3 restores skeletal bone growth in Fgfr3ach/+ mice
- sFGFR3 increases survival of Fgfr3ach/+ mice



Schematic representation of FGFR3-mediated inhibition of bone growth in achondroplasia (a) and of the sFGFR3 decoy strategy (b)[b]

a. Garcia S, et al. *E.Sci Transl Med.* 2013;18;5:203ra124.
b. Creative Commons Attribution License 4.0 (Unger S, et al. *Curr Osteoporos Rep.* 2017;15:53-60.) https://creativecommons.org/licenses/by/4.0/

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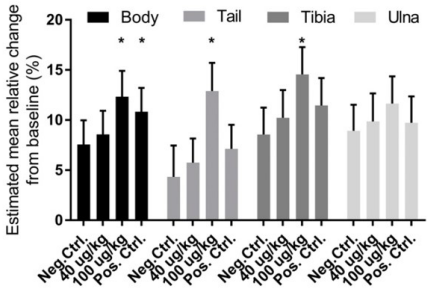
Briefly, I want to mention other drugs that are being investigated. One is called a decoy therapy. Essentially a soluble FGFR3 goes circulation and traps FGF2, FGF9, and FGF18. I mentioned to you that these fibroblast growth factors will actually get together with the FGFR3 receptor and then dimerize and activate the receptor signaling. If you have something that is trapping these fibroblast growth factors, what's happening is that this is now being occupied by this molecule, the decoy molecule, and then there are no fibroblast growth factors that are acting on the receptor. That is actually a mechanism that acts directly on the FGFR3, different to the CNP model, and animal models have shown that this is useful to restore skeletal growth in mice that have achondroplasia.

Other Trials
Long Acting CNP

- Long acting prodrug of CNP
- Once weekly injections
- Phase 2 trials underway
- Promising results in animal models vs daily formulations



Growth from baseline of body, tail, tibia, and ulna following weekly administration of long-acting CNP to juvenile male Macaques

Breinholt VM, et al. *J Pharmacol Exp Ther.* 2019;370:459-471.

37

There is another long-acting cartilage natriuretic peptide now in clinical trials. This is administered once weekly, instead of daily single injections. The modified chemistry allows the CNP to last and to be released slowly.

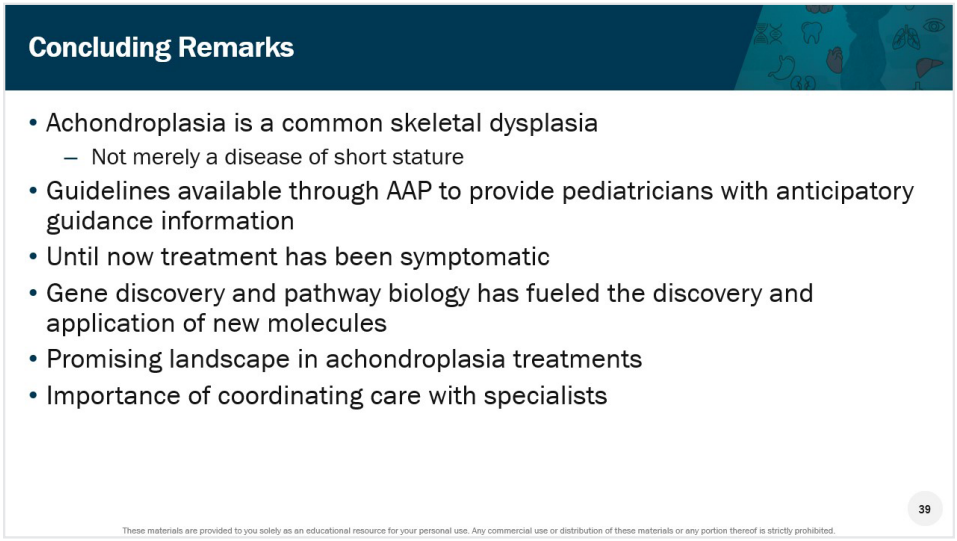
Tyrosine Kinase Inhibitors

- Pan-FGFR TKI (NVP-BGJ398) reduces FGFR3 phosphorylation and corrects the femoral growth plate and calvaria in organ cultures from embryos of the Fgfr3 Y367C/+ mouse model of Ach[a]
- TKIs can cause significant inhibition of FGF23 and hyperphosphatemia[b]
- Infigratinib: FGFR1-3 TK inhibitor in phase 2 trials[c]

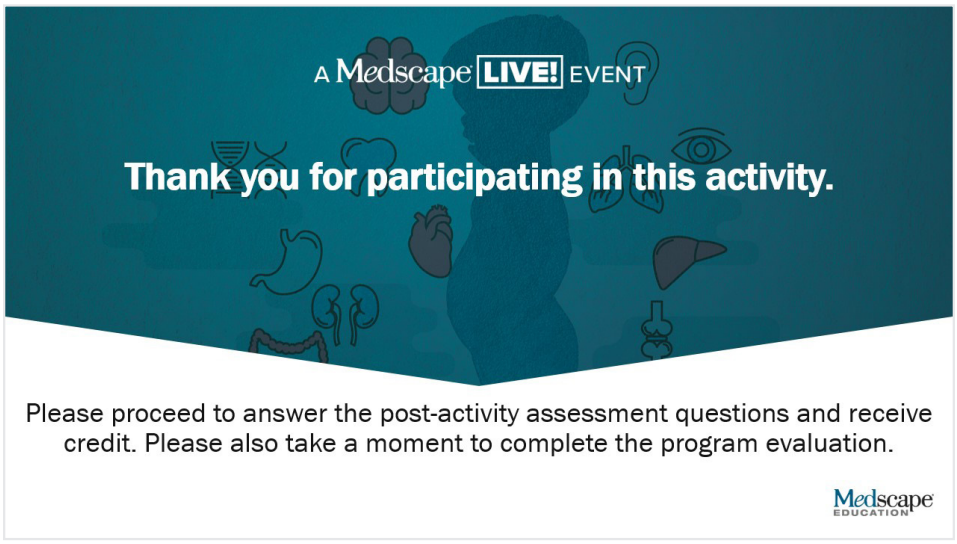
a. Komla-Ebri D, et al. *J Clin Invest.* 2016;2;126:1871-1884.
b. Wohrle S, et al. *J Bone Miner Res.* 2013;28:899-911.
c. ClinicalTrials.gov. NCT04265651.

38

Tyrosine kinase inhibitors are another group of drugs being studied. FGFR1-3 tyrosine kinase inhibitor is one example. This particular drug, theoretically, is going to counteract with MAP kinase and ERK pathway by inhibiting downstream signaling. There are some concerns that this may cause inhibition of FGF23 and cause hyperphosphatemia, but that also could be clinically taken care of.



In summary, achondroplasia is a common skeletal disorder. It's not just a condition that is associated with short stature, because as we have shown, there are a lot of morbidities associated with it. There are clear guidelines that are available through the American Academy of Pediatrics that provide pediatricians with a very good anticipatory guidance. We have only treated these patients in a symptomatic fashion, but now with the gene discovery of the FGFR3 pathway and understanding what happens, a number of drugs have been discovered that are being used in clinical trials and very soon will be available for the use of patients. This condition has a very promising landscape. And lastly, you need to understand the problems and the medical issues that these patients have in order to allow proper coordination and care with the different specialties, such as neurosurgery, ENT, et cetera.



I want to thank you for participating in this activity, and hopefully this will have helped you understand this disorder and what's coming in the future. Thank you very much.

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Abbreviations

AAOS = American Academy of Orthopedic Surgeons
AAP = American Academy of Pediatrics
Ach = achondroplasia
AGV = annualized growth velocity
BMI = body mass index
C/S = Caesarean section
cGMP = cyclic guanosine monophosphate
CMD = coronary microvascular dysfunction
CNP = C-type natriuretic peptide
CPAP = continuous positive airway pressure
CSF = cerebrospinal fluid
CT = computed tomography
FGFR3 = fibroblast growth factor receptor 3
hGH = human growth hormone
HTN = hypertension
LPA = Little People of America
MRI = magnetic resonance imaging
NPR-B = natriuretic peptide receptor B
OSA = obstructive sleep apnea
QoL = quality of life
SC = subcutaneous
SDB = sleep disordered breathing
SDs = standard deviation score
SF-36 = 36-Item Short Form Survey