Achondroplasia

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Achondroplasia is one of the most common and recognized short-limbed skeletal dysplasias, with a prevalence of 1 in 26,000 to 28,000 live births. Although achondroplasia is inherited in an autosomal dominant manner, 80% of affected children have a de novo mutation. The *FGFR3* gene is the only gene associated with achondroplasia. Two mutations in this gene account for 99% of cases; both result in an amino acid change (glycine to arginine), which results in continuous activation of the FGFR3 protein. Having a constantly active FGFR3 protein leads to the inhibition of chondrocyte proliferation, which, in turn, inhibits bone growth. The average adult height for patients with achondroplasia is 131 cm for a man and 124 cm for a woman.

Achondroplasia should be considered prenatally if shortened long bones (usually <5th percentile) are noted on third trimester ultrasonography. Some studies have seen a distinctive "collar hoop" sign wherein there is a small bony protuberance at the interface between the femoral metaphysis and the diaphysis. The metaphysis is poorly ossified as well. Prenatal molecular testing of *FGFR3* can confirm the diagnosis.

A neonate with achondroplasia may have physical features that are characteristic of the condition: rhizomelic (proximal) shortening of the upper and lower extremities, with extra skin creases at the knees and elbows; short fingers with a trident configuration of the hand (the second, third, and fourth digits seem similar in length and are splayed); and macrocephaly with frontal bossing and a depressed nasal bridge. Because 20% of neonates with achondroplasia may not have these characteristic features, a skeletal survey should be performed if there is any suspicion for this condition: radiographic abnormalities include metaphyseal changes, rhizomelic shortening, a relatively large cranial vault with a small base of the skull, small squared iliac wings, anteroposterior rib narrowing, and posterior vertebral scalloping.

Early diagnosis is critical because 5% to 10% of infants with achondroplasia experience serious medical problems, such as central apnea and high cervical myelopathy, both of which are secondary to a small foramen magnum. Because the base of the skull is smaller than normal, arterial compression at the level of the foramen magnum can also occur. With a smaller foramen magnum, an affected infant should not be put in a swing or a bouncer.

Infants with achondroplasia require a thorough neurologic examination and neuroimaging with head computed tomography or magnetic resonance imaging. Standard measurements for children with achondroplasia have been established for computed tomography, and the foramen magnum can be seen, but magnetic resonance imaging can better visualize the brain stem and cervical spinal cord. Neurosurgical consultation is advised if any major abnormalities appear on imaging. Polysomnography is likewise indicated because of the risk of obstructive sleep apnea.

AUTHOR DISCLOSURE Dr Pereira has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Frequent monitoring of head circumference is important during the first 2 years after birth because hydrocephalus can develop. If the head circumference rapidly crosses percentiles or if neurologic abnormalities such as lethargy or irritability appear, further imaging may be prudent. Interpretation of such imaging should be guided by the knowledge that extra-axial fluid and ventriculomegaly are common in children with achondroplasia and are usually benign. Also, infants and children with achondroplasia sweat more than the general population, and notable sweating should not be interpreted as a neurologic or cardiac problem if it is the only symptom.

Children with achondroplasia are at risk for orthopedic complications. Thoracolumbar kyphosis is seen in 90% to 95% of these patients. Infants need support to sit until they have the truncal muscle strength to maintain themselves, and soft strollers should be avoided. If the kyphosis is severe, an early orthopedic consultation may be appropriate. Children with achondroplasia typically walk by 2.5 years old. As the child begins to bear weight and walk, the kyphosis (if not severe) usually resolves. External rotation of the hips, a normal feature in infants with achondroplasia, should self-correct within 6 months of weightbearing. Although there can be some bowing of the legs, an orthopedic consult is warranted for chronic pain or a positional deformity that leads to difficulty walking. A general orthopedic evaluation should be considered when the child is 5 years old.

Obstructive sleep apnea has a prevalence of 10% to 87% in patients with achondroplasia. More commonly seen in older children and adults, it is secondary to adenoidal and tonsillar hypertrophy and midfacial retrusion that decreases the size of the airway. Obesity increases the risk, so avoiding excessive weight gain is an important preventive measure.

In the absence of neurologic compromise, people with achondroplasia have normal intelligence, but developmental milestones are delayed. Standardized developmental milestones and condition-specific growth curves are available for children with achondroplasia. Yearly hearing tests are recommended to check for conductive hearing loss. Occupational therapy from an early age can help affected children use adaptive aids for both the home and school settings. Foot support is important to keep the feet from dangling when the child is seated on a chair or toilet. Because of cervical spinal stenosis, collision sports and gymnastics are usually discouraged; noncontact activities such as swimming and biking are less likely to cause neurologic complications.

Females with achondroplasia are at increased risk for uterine fibroids, so oral contraception, which can worsen fibroids, should be avoided for long-term use. Consultation with a gynecologist or an adolescent medicine provider well versed in contraceptive methods can be helpful. Any pregnancy should be considered high risk. Baseline respiratory function studies should be performed early in pregnancy because respiratory compromise can develop over time. Cesarean delivery is usually advised because a small pelvic outlet and spinal stenosis make vaginal delivery dangerous for most women with achondroplasia.

A child born to a parent with achondroplasia has a 50% chance of inheriting the *FGFR3* gene mutation and having achondroplasia. If both partners have achondroplasia, each fetus has a 25% chance of having a homozygous mutation that is not compatible with life, a 50% of having achondroplasia; and a 25% chance of having normal stature. If one partner has achondroplasia and the other has a different skeletal dysplasia, each child has a 25% chance of having normal stature, a 25% chance of having achondroplasia, a 25% chance of having the other skeletal dysplasia, and a 25% chance of inheriting both pathogenic variants, which can lead to a different phenotype and different clinical features. Prenatal genetic counseling is recommended to clarify reproductive options and outcomes.

Currently, no medications or supplementations are recommended as treatment for achondroplasia. Several clinical trials are underway to determine whether growth hormone can be effective at increasing final height, but as yet no compelling evidence establishes real benefit. Whether the benefits of limb-lengthening techniques outweigh their limitations is questionable.

Pediatricians caring for children with achondroplasia should be prepared at each visit to provide both practical advice and emotional support. If possible, the child's home should be fitted with helpful adaptations such as lowered door handles and light switches. Although some physical accommodations will be necessary in school for classroom seating, toileting, and moving from class to class, other special privileges are not routinely needed. Importantly, as the child reaches school age, discussions should address how to talk to other children about short stature. Most patients with achondroplasia can live independent and fulfilled lives, so children with achondroplasia and their families should be encouraged to facilitate the strengths needed for independent living. The Little People of America

(http://www.lpaonline.org/) is a wonderful resource for patients and families for emotional support.

COMMENT: In an age when social media has helped make bullying rampant, children perceived as "different" become tempting targets for abuse. Children with achondroplasia are no different from their peers in their intelligence and their sensitivities, in all the inner qualities that make each of us who we most essentially are. But to the eye of the beholder who looks for the opportunity to taunt, markedly short stature is an open invitation to exploit. The children, their families, and their teachers all need to be aware of this sad reality. Strategies aimed at prevention, especially at school, and at support in the face of physical and cyber bullying are essential to the care we give. Children who are victims of bullying are likewise at risk for depression, anxiety, drug use, and suicide, all of which warrant appropriate screening.

– Henry M. Adam, MD
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Clarification

In the print version of the April 2019 review "Tuberculosis in Children" (Holmberg PJ, Temesgen Z, Banerjee R. *Pediatr Rev.* 2019 Apr;40(4):168-178; doi: 10.1542/pir.2018-0093), the second sentence under the section "Treatment of LTBI in Children," on page 174 describes a recommendation that has changed. This sentence should read, Any of these regimens is considered adequate, but most experts prefer the shorter regimens. (28)" The online version of the article has been updated, and a clarification notice has been posted with the online version of the article.

ANSWER KEY FOR JUNE 2019 PEDIATRICS IN REVIEW

Health Literacy: Implications for Child Health: 1. A; 2. E; 3. E; 4. D; 5. A.
Sports Injuries: 1. B; 2. E; 3. D; 4. E; 5. D.
Common Conditions Requiring Emergency Life Support: 1. A; 2. C; 3. B; 4. E; 5. C.