Advances in understanding etiology of achondroplasia and review of management

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Purpose of review

A summary of management and current research in achondroplasia (OMIM 100800). The most common nonlethal skeletal dysplasia, achondroplasia presents a distinct clinical picture evident at birth. Substantial information is available concerning the natural history of this dwarfing disorder.

Diagnosis is made by clinical findings and radiographic features. Characteristic features include short limbs, a relatively large head with frontal bossing and midface hypoplasia, trident hands, muscular hypotonia, and thoracolumbar kyphosis. Children commonly have recurrent ear infections, delayed motor milestones, and eventually develop bowed legs and lumbar lordosis. People with achondroplasia are generally of normal intelligence.

Recent findings

The genetic cause of achondroplasia was discovered in 1994. Subsequent research efforts are designed to better characterize the underlying possible biochemical mechanisms responsible for the clinical findings of achondroplasia as well as to develop possible new therapies and/or improve intervention.

Summary

Establishing a diagnosis of achondroplasia allows families and clinicians to provide anticipatory care for affected children. Although the primary features of achondroplasia affect the skeleton, a multidisciplinary approach to care for children with achondroplasia helps families and clinicians understand the clinical findings and the natural history of achondroplasia in order to improve the outcome for each patient.

Keywords

achondroplasia, dwarf, fibroblast growth factor receptor-3, skeletal dysplasia

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Abbreviations

FGF fibroblast growth factor
FGFR3 fibroblast growth factor receptor-3

1040-8703

Introduction

There are more than 200 skeletal dysplasias, a heterogeneous group of genetic disorders characterized by differences in the size and shape of the limbs, trunk, and/or skull that frequently result in disproportionate short stature. Diagnosis is made by clinical findings, radiologic criteria, family history and, increasingly, by genetic test results.

Achondroplasia (OMIM 100800) was first described in 1878 [1] and is the most common nonlethal skeletal dysplasia. Inherited in an autosomal dominant fashion, the distinct clinical features of achondroplasia are evident at birth and primarily affect the skeleton, resulting in short-limbed dwarfism. Clinical findings arise secondary to gain-of-function mutations in the fibroblast growth factor receptor-3 (FGFR3) gene, which has been mapped to chromosome 4p16.3.

Etiology

Estimates state that 30–45 of every 100 000 newborns have a skeletal dysplasia [2]. Achondroplasia is the most common form of nonlethal skeletal dysplasia, and the most common type of short-limb dwarfism, with an incidence of 0.5–1.5 per 10 000 births [2]. The causative gene was assigned to chromosome 4p16.3 by linkage analysis in 1994, secondary to the concurrent search for the Huntington disease gene locus [3–5]. Within 6 months achondroplasia-causing mutations were identified in the FGFR3 gene [6,7]. Much work has since been done to increase understanding of the biochemical mechanism underlying the disorder.

More than 99% of people with achondroplasia carry a point mutation at nucleotide 1138 in one copy of the FGFR3 gene: most commonly a G→A transition, although G→C transversion has also been reported [6,7]. Both mutations result in the substitution of arginine for glycine at residue 380 (G380R) in the transmembrane region of the FGFR3 protein [6,7]. Based on the incidence of achondroplasia, the FGFR3 1138 nucleotide, located in a CpG dinucleotide, is one of the most mutable single nucleotides in the human genome [8]. Rare cases of achondroplasia have been attributed to other mutations in FGFR3 (e.g. G375C) [9]. Other disorders linked to mutations in FGFR3 include thanatophoric dysplasia types I and II (OMIM 187600 and 187601), hypochondroplasia (OMIM 146000), severe achondroplasia

with developmental delay and acanthosis nigricans (SADDAN dysplasia), and two craniosynostosis disorders – Muenke coronal craniosynostosis (OMIM 602849) and Crouzon syndrome with acanthosis nigricans [10,11].

Four genes encoding closely related tyrosine kinase fibroblast growth factor (FGF) receptors (FGFR1–FGFR4) are known. Each FGF receptor protein has an N-terminal signal peptide, three immunoglobulin-like domains, an acid-box region containing a run of acidic residues between the IgI and IgII domains, a transmembrane domain and the split tyrosine-kinase domain. The FGF receptors mediate the biological activities of the FGF superfamily, a group of at least 23 structurally related, heparin-binding members, originally recognized for proliferative activities and now thought to play roles in development, angiogenesis, hematopoiesis, and tumorigenesis [12]. Alternative splicing (mRNA) generates multiple forms of FGFR1–FGFR3. FGF receptors have multiple specificities for almost all FGF proteins. After binding with an FGF protein, FGF receptor monomers dimerize and undergo autophosphorylation, activating a downstream signaling cascade to negatively regulate bone growth.

Identified as a member of the FGF receptor family in 1991 [13], FGFR3 is prominently expressed in rudimentary cartilage while diffusely expressed in the developing central nervous system, the developing lens, and in the differentiating hair cells of the cochlear duct [14]. FGFR3 functions as a negative regulator of bone growth [15]. FGFR3 mutations that result in the clinical features of achondroplasia occur in the transmembrane domain and are gain-of-function mutations causing constitutive FGFR3 tyrosine kinase activity and signaling in the absence of ligand binding [16,17]. Chondrocyte proliferation and differentiation are inhibited, decreasing bone growth rates. The precise biochemical mechanism by which achondroplasia-causing FGFR3 mutations act to constitutively activate FGFR3 is not fully understood. When FGFR3 proteins with achondroplasia mutations dimerize, it is believed that tyrosine kinase activity of the receptor is enhanced [17]. In addition, studies have shown that the increased kinase activity leads to higher numbers of activated FGFR3, which in turn leads to amplified signaling [18].

Inheritance

Achondroplasia is an autosomal dominant genetic disorder. Individuals with clinical symptoms of achondroplasia have a mutation in one of their FGFR3 genes (heterozygous for the mutation). Homozygous achondroplasia, where individuals have mutations in both of their FGFR3 genes, is neonatally lethal and the skeletal manifestations are those of exaggerated achondroplasia: pronounced rhizomelic dwarfism, marked midface hypoplasia, a large head, a very small foramen magnum, and short ribs resulting in a small thorax and restricted respiration. Death usually results secondary to respiratory compromise or from cervical cord compression.

Individuals with achondroplasia have a 50% chance to pass on the FGFR3 gene mutation and a 50% chance to pass on the working copy of the FGFR3 gene to their offspring. A child who inherits the achondroplasia-causing mutation will have the clinical findings of achondroplasia and will also have a 50% chance to pass or not to pass the mutation on to his/her children. A child who does not inherit the achondroplasia-causing mutation will not have the clinical findings of achondroplasia. He/she will have no increased chance to have children of his/her own with achondroplasia. In families where both parents have achondroplasia, each has a 50% chance to pass on his/her FGFR3 gene with the mutation each and every time they conceive a child. Such couples have a 25% chance that both parents would pass on the achondroplasia mutation to offspring, resulting in homozygous achondroplasia.

More than 75% of individuals with achondroplasia are born to two average-statured parents. In these cases, the dominant achondroplasia mutation in the FGFR3 gene occurred as a sporadic (de-novo) mutation. Advancing paternal age is associated with sporadic achondroplasia-causing FGFR3 mutations [19,20]. Studies of families with sporadic cases of achondroplasia suggest that the majority of, if not all, de-novo achondroplasia-causing mutations in the FGFR3 gene occur in the paternally derived FGFR3 allele [21].

Usually in sporadic cases the mutation is confined to the one individual within a family who has the clinical findings seen in achondroplasia. The exception to this rule is germline or gonadal mosaicism, which refers to an individual with two genetically different populations of germ cells. A Canadian study surveyed 11 genetic centers and determined that the chance for unaffected couples to have more than one child with achondroplasia is one out of 443 (0.02%) [22].

Molecular genetic testing

Molecular genetic analysis of the FGFR3 gene is not necessary to diagnose achondroplasia postnatally. Clinical testing for FGFR3 mutations is available, however, and may be helpful to establish a diagnosis in atypical cases. If a diagnosis of achondroplasia is suspected during the prenatal period, confirmatory FGFR3 mutation analysis of prenatal specimens through prenatal genetic diagnosis by means of chorionic villus sampling or amniocentesis is available. Short limbs are observed prenatally in a varied group of conditions and it can be difficult to make a specific diagnosis of achondroplasia in the pregnancy based on ultrasound findings alone. Misdiagnosis and inaccurate prenatal counseling of families is

common. FGFR3 mutational analysis can therefore be offered where a short-limb disorder is detected by ultrasound in the latter stages of pregnancy [23].

Clinical features

Achondroplasia primarily affects the skeletal system. Although the word achondroplasia literally means 'without cartilage formation', in this disorder the problem is not in cartilage formation but in converting cartilage to bone, particularly in the long bones of the arms and legs, the spine, and the skull. FGFR3 mutations alter the cartilage growth plate architecture; endochondral bone formation is therefore affected.

The average height of an adult male with achondroplasia is 131 cm (52 inches, or 4 foot 4 inches) and the average height for adult females is 124 cm (49 inches, or 4 foot 1 inch). The use of growth charts and standards based on the growth and development of average-statured children is not appropriate for children with achondroplasia. Growth charts have been developed for children with achondroplasia [24,25] and should be used in the assessment of all children.

Evaluation and management

Diagnosis is made based on clinical examination and radiographic features. Infants with achondroplasia typically present with mild to moderate shortening of limbs, macrocephaly with midfacial hypoplasia, hypotonia, and thoracolumbar kyphosis [26]. Radiological features in children include narrowing of the interpediculate distance, a notchlike sacroiliac groove, and chevron-shaped epiphyseal ossification centers on the metaphysis [26]. Adults with achondroplasia usually develop a pronounced and permanent curve of the lower back (lordosis), and symptomatic spinal stenosis is common in the third and fourth decades of life, often requiring surgery [26]. Bony changes of the vertebral spine house an average-sized spinal cord and neural elements, predisposing individuals with achondroplasia to neurologic complications including cranio-cervical junction problems in infancy, spinal stenosis and neurogenic claudication in adulthood [27].

Although the relationship between craniofacial morphology in children with achondroplasia and sleep apnea is not clear, midface hypoplasia and stenosis of the upper airway can induce sleep-disordered breathing, including snoring and apnea [28].

The skull base is small, with associated foramen magnum stenosis. Ventriculomegaly is common and often mild, without progression or cause for treatment with shunting. Young children should have a baseline computed tomography scan of the brain and cervical spine and/or musculoskeletal resonance imaging of the entire spine [29]. In addition, cerebral spinal fluid flow studies can be performed across the foramen magnum during magnetic resonance imaging, and performing the magnetic resonance imagingin a flexed position may contribute important information [29]. One study [29] prospectively assessed indications for suboccipital decompression and found several risk factors, including lower limb hyperreflexia or clonus, central hypopnea at polysomnography, and stenosis of the foramen magnum. Another study [30] reviewed computed tomography scan and clinical data, and found no correlation between infantile hypotonia and foramen magnum size.

Angular deformities (i.e. genu varum) are common in children with achondroplasia. Surgical realignment of these deformities is available [31,32]. Bilateral leg lengthening is available to increase adult height and may be combined with angular deformity correction. The decision to undergo surgical realignment should be based on radiographic measurement and clinical judgment [31,32]. Limb lengthening requires multiple operations, large amounts of hospital time, and a strong commitment on the part of patients and families [33].

Thoracolumbar kyphosis is a common finding in children with achondroplasia and usually improves without treatment as children begin to walk. Persistent thoracolumbar kyphosis is typically prevented with supportive sitting modifications to avoid abnormal spine flexion and, in some cases, back bracing [34] (Fig. 1). Uncorrected kyphosis may result in a permanent vertebrae deformity. In a proportion of patients, thoracolumbar kyphosis becomes fixed and surgical correction (e.g. spinal fusion) is necessary to prevent neurological and musculoskeletal sequelae such as spinal stenosis and compensating lumbar lordosis [35–38].

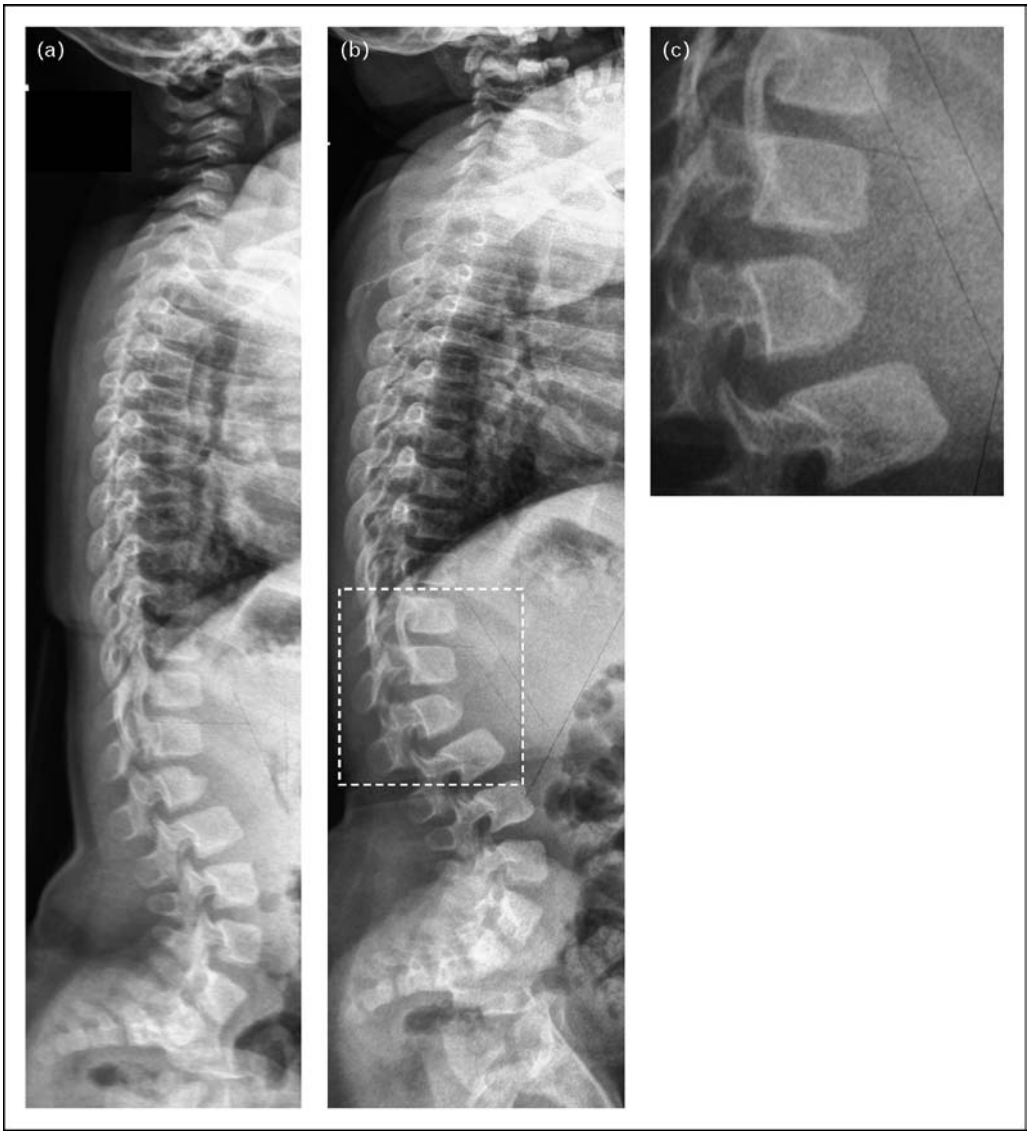
A referral for genetic counseling can help families and individuals with achondroplasia to better understand the cause of achondroplasia as well as the chances of having another child with achondroplasia. Genetic counseling can assist with family planning, and resources for support. Genetic counseling regarding prenatal testing options is important so that families can understand their reproductive options.

Weight gain and obesity are major problems in achondroplasia and contribute to morbidity associated with spinal stenosis and nonspecific joint problems. Early nutritional counseling is recommended to help children with achondroplasia stay within 1 SD on height-for-weight curves developed for children with achondroplasia [24].

Multidisciplinary follow-up and management are important for children with achondroplasia. Recommendations

Figure 1 Lateral spine X-ray image of a 1.5-year-old girl with achondroplasia and thoracolumbar kyphosis

(a) In brace. (b) Out of brace. (c) Cut out view of hashed section from (b). Note vertebrae deformity.



for follow-up and management have been presented [39,40]. In 2005, the American Academy of Pediatrics [41,42••] updated their 1995 policy statement concerning health supervision for children with achondroplasia. This policy statement provides an indispensable resource for primary care physicians working with families and children affected with achondroplasia. It presents a comprehensive review of the clinical, developmental, and social features of achondroplasia, including growth charts for height, head circumference, and height-for-weight, developmental screening guidelines, examination, social/support resources, and anticipatory guidance for health practitioners from infancy through adulthood, including obstetric care [28]. See Figure 2 for recommendations.

Treatment

Identification of the FGFR3 gene and enhanced tyrosine kinase activity granted by gain-of-function mutations that cause achondroplasia has revisited the development of possible new therapies and interventions. Some tactics involve targeting the receptor and dampening its overactive tyrosine kinase activity; others involve blocking, with antibodies, the FGF ligand from binding to the receptor [43]. Another strategy uses molecules to target and block FGFR3-induced intracellular signaling cascades in chondrocytes, thereby blocking the negative tyrosine kinase effect on proliferation and differentiation [44]. Horton provides a recent review of these developing therapeutic approaches [45••].

Figure 2 Recommendations for anticipatory guidance and management of individuals with achondroplasia

(1) monitor height, weight and head circumference using growth curves standardized for achondroplasia [25,42••];
(2) careful neurologic examinations (including computed tomography, magnetic resonance imaging (MRI), somato-sensory evoked potentials and polysomnography);
(3) surgical enlargement of the foramen magnum in cases of severe stenosis;
(4) management of frequent middle ear infections and dental crowding. Repeated audiometry should be routinely performed during the first 3 years of life;
(5) measures to control obesity starting in early childhood;
(6) growth hormone therapy (still experimental);
(7) limb lengthening of the long bones;
(8) tibial osteotomy or epiphysiodesis of the fibular growth plate to correct bowing of the legs;
(9) lumbar laminectomy for symptomatic spinal stenosis (typically in early adulthood);
(10) genetic counseling for individuals and families to understand the cause of achondroplasia, the chance to have another child with achondroplasia, and to understand their reproductive options;
(11) pregnant women with achondroplasia can deliver by cesarean section;
(12) prenatal detection of fetuses with achondroplasia through ultrasound (e.g. short femora < 24weeks gestation).

Although achondroplasia is not associated with growth hormone deficiency, trials investigating the efficacy of growth hormone therapy in increasing height in achondroplasia have long been reported. Growth hormone plays an important role in regulating linear skeletal growth by promoting chondrocyte proliferation directly or indirectly through insulin-like growth factor-1. The majority of growth hormone trials in children with achondroplasia have been short-term [46–52]. These studies report an increase in growth velocity (65–75%) during the first year or a gain of 0.2–0.5 SD of height during the first year of treatment. One longer-term study [53] examining growth hormone treatment of children with achondroplasia over 5 years (a cycle of 2 years of growth hormone treatment followed by 1 year of observation without treatment, and then 2 years of further growth hormone treatment) showed an increase (1.5 SD) in relative height without any adverse effect on trunk–leg disproportion. Another longer-term study (uncontrolled) [54] examined growth hormone treatment of children with achondroplasia over 6 years. The height SD increased significantly during the first 4 years of treatment and the growth velocity was significantly increased in the first year of therapy (related to age of the patient; median age at start of treatment, 2.3 years); increased growth velocity was maintained throughout treatment. While these studies show an increase in growth velocity, it remains to be seen whether the final height is increased for individuals with achondroplasia who have undergone growth hormone therapy. Families and children must work with their practitioner to determine whether the benefit of potential height gain outweighs the inconvenience of daily injections of growth hormone. In addition, the potential long-term side effects of growth hormone therapy (e.g. increased serum insulin-like growth factor-1 levels) are currently unknown.

Conclusion

Achondroplasia is the most common form of nonlethal skeletal dysplasia and the most common type of short-limb dwarfism. Diagnosis is based on clinical findings, radiographic features, and genetic test results. The natural history is well understood; professional guidelines are available to assist families and healthcare providers in multidisciplinary anticipatory care and support for children, adolescents, and adults.

Achondroplasia is inherited in an autosomal dominant pattern. Clinical findings occur secondary to gain-of-function mutations in the FGFR3 gene located at chromosome 4p16.3. FGFR3 is a negative regulator of bone growth; constitutive activation through achondroplasia mutations disrupts chondrocyte proliferation and differentiation, disrupting the growth plate architecture. Discovery of the genetic basis of achondroplasia opened the door for exploration of the biochemical mechanisms that cause the underlying clinical features of the disorder. Studies exploring these biochemical mechanisms as well as targeting the effects of the gene mutation at the cellular level are still in the developmental stage.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 117).

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