

Achondroplasia

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Achondroplasia is the most common form of short limb dwarfism in human beings, affecting more than 250 000 individuals worldwide. More than 95% of patients have the same point mutation in the gene for fibroblast growth factor receptor 3 (FGFR3) and more than 80% of these are new mutations. The mutation, which causes gain of FGFR3 function, affects many tissues, most strikingly the cartilaginous growth plate in the growing skeleton, leading to a variety of manifestations and complications. The biology of FGFR3 and the molecular and cellular consequences of the achondroplasia mutation are being elucidated, providing a more complete understanding of the disorder and a basis for future treatments targeted directly at relevant pathogenetic pathways. Furthermore, the natural history of the condition, which has been well delineated in childhood and adolescence, is being defined more fully in adults with achondroplasia; most of the serious complications can be modified favourably or prevented by anticipation and early treatment. Possible future treatments include chemical inhibition of receptor signalling, antibody blockade of receptor activation, and alteration of pathways that modulate the downstream propagation of FGFR3 signals.

Introduction

Achondroplasia (OMIM 100800) is the most common form of human dwarfism and the mutation causing it might be the most common disease-causing mutation to arise de novo in human beings.^{1,2} The condition has been recognised for centuries, with examples seen in art from ancient Egypt, Greece, and Rome.³ Moreover, its name, coined about 100 years ago, implies historical knowledge of disturbed cartilage function during linear bone growth. Today we recognise that cartilage serves a template function during the process of endochondral ossification. Achondroplasia must be distinguished from other forms of disproportionate short stature, which, until recently, were all called achondroplasia.⁴ Indeed, the heterogeneity of disproportionate short stature only began to be appreciated and studied about 40 years ago, leading to the recognition of hundreds of specific clinical entities each with their own clinical and radiographic features, natural history, complications, and genetic basis.^{5,6}

The primary manifestations and medical complications of achondroplasia have received much attention over the past four decades and are now well established for childhood and adolescence.^{5,7–9} By contrast, the natural history is only gradually being delineated for adults, and several new potential complications have been uncovered. Similarly, mutations of the gene for fibroblast growth factor receptor 3 (FGFR3), were discovered in achondroplasia over a decade ago.^{2,10} The nature of these mutations, as well as the biology of the receptor encoded

by FGFR3, and the molecular consequences of the mutations on linear bone growth are becoming better understood.¹¹ Eventually, this knowledge will probably provide the underpinning for future treatments that will be targeted directly at the molecular disturbances caused by the FGFR3 mutations. Even though the most striking feature of achondroplasia involves cartilage growth, the achondroplasia mutation affects many systems.

This Seminar addresses the present state of knowledge about achondroplasia. We discuss the diagnosis and management of typical clinical manifestations, but we give particular attention to recent observations (eg, medical complications in adults with achondroplasia), and focus especially on the molecular pathogenesis of achondroplasia, our understanding of which continues to slowly emerge.

Epidemiology and genetics

The birth incidence of achondroplasia is uncertain because of the frequent inclusion of other disorders in population estimates; however, it is estimated to occur in between one in 10 000 and one in 30 000 livebirths.^{12–14} Achondroplasia is part of a spectrum of disorders caused by different mutations in FGFR3, which includes hypochondroplasia (OMIM 146000), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), and thanatophoric dysplasia, of which two types can be distinguished by radiograph and molecular analysis (thanatophoric dysplasia I [OMIM 187601] and thanatophoric dysplasia II [OMIM 187601]).^{15–17}

Achondroplasia has been known to be an autosomal dominant trait for over 50 years.^{18,19} The achondroplasia locus was mapped to chromosome 4p16.3 in 1994, and heterozygous mutations of FGFR3 were identified shortly afterwards.^{2,4,10} FGFR3 mutations were subsequently discovered for thanatophoric dysplasia and hypochondroplasia (figure 1).^{21–24} Extraordinary degrees of genetic homogeneity and genotype:phenotype correlation soon became apparent since almost all patients with classic achondroplasia were found to have the same Gly380Arg aminoacid substitution in the transmembrane domain of

Search strategy and selection criteria

We searched PubMed and Medline for clinical and basic science articles related to achondroplasia with the key words "achondroplasia", "chondrodysplasia", "skeletal dysplasia", "FGFR3", "FGFR", and "FGF". We also used our own published work accumulated over many years. We paid particular attention to articles published in English since the 1950s, when achondroplasia was delineated as a distinct clinical entity.

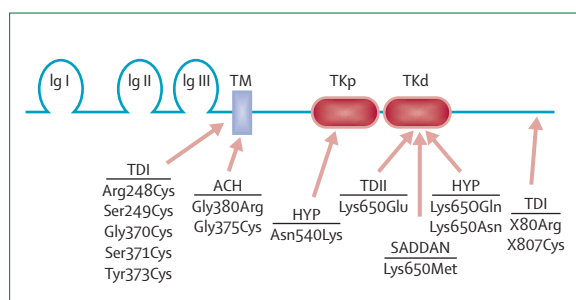


Figure 1: Topology of FGFR3 with major sites of mutation

ACH=achondroplasia. HYP=hypochondroplasia. SADDAN=severe achondroplasia with developmental delay and acanthosis nigricans. TDI=thanatophoric dysplasia type I. TDII=thanatophoric dysplasia type II. TKp/d=proximal and distal tyrosine kinase domains. TM=transmembrane. Modified from reference 20 with permission.

the receptor.^{22,25} A Gly375Cys mutation of FGFR3 also accounts for a few patients with achondroplasia.²⁶

The penetrance of the Gly380Arg mutation is 100%, meaning that all individuals with the mutation have achondroplasia. Most infants with FGFR3 mutations are born to parents without FGFR3 mutations, and there is a strong correlation with advanced paternal age, particularly over 35 years.^{19,27} These findings were initially attributed to increased mutability of FGFR3 during spermatogenesis. However, recent observations have led to the alternative explanation that sperm bearing mutant FGFR3 have a selective advantage over sperm bearing normal FGFR3,^{28–31} which could explain how a pool of premeiotic cells harbouring an FGFR3 mutation could increase in relative size with age and lead to the observed correlation with older paternal age.

Pathophysiology

The distinction between genetics and pathogenesis is important. During the past decade there has been tremendous progress in mapping gene loci, identifying disease loci, and finding specific mutations. However, emphasis is now shifting from genetics as such to pathogenesis with special attention to molecular mechanisms. This section addresses what is known about the molecular biology of FGFR3 and the specific interactions and pathways that are disturbed by mutation—ie, the functional consequences of FGFR3 mutation.

Receptors

FGFR3 encodes one of four closely related receptors for fibroblast growth factor (FGFR1–4) in mammals.³² All have an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain that contains a split tyrosine kinase subdomain. The receptors differ in their temporal and spatial distribution of expression. Additional diversity is generated by alternative splicing that affects ligand specificity. Mutations similar to those in FGFR3 have been observed in FGFR1 and FGFR2 in human craniosynostosis syndromes.³³ Pro250Arg mutations of FGFR3 are

associated with craniosynostosis involving the coronal suture (Muenke syndrome, OMIM 602849).³⁴

Mutations associated with achondroplasia have been shown to cause a gain of FGFR3 function, the extent of which correlates with the severity of the clinical phenotype.^{35–42} Referred to as activating mutations, their consequences differ depending on the cell type involved. For instance, FGFR3 activation promotes mitosis in many non-chondrocytic cell types. In fact, FGFR3 mutations associated with thanatophoric dysplasia, as well as those not associated with thanatophoric dysplasia, have been found in colon and bladder carcinoma and multiple myeloma as well as in benign adenoid sebaceous keratoses.^{43–46} The association of FGFR3 mutations and tumours is exclusively somatic. In growth plate chondrocytes, however, activation of FGFR3 has the opposite effect, as discussed later.

The binding of fibroblast growth factor (FGF) ligands to FGFR3 monomers leads to receptor dimerisation.⁴⁷ Which of the 22 known FGFs are the physiological ligand(s) for FGFR3 is not known, although FGFs 2, 4, 9, and 18 are probably the best candidates based on the distribution of expression, ability to bind and activate FGFR3, and the phenotype of mice lacking these particular ligands.^{48–51} Heparin sulphate-bearing proteoglycans on the cell surface also affect binding specificity.^{52–54}

Dimerisation activates the intrinsic tyrosine kinase activity of the receptor and promotes transphosphorylation of key tyrosine residues in the cytoplasmic domain.^{47,53} These residues serve as docking sites for adaptor proteins and signal effectors that are recruited to the activated receptors and which propagate FGFR3 signals.^{47,55–57}

Signalling pathways

FGFR3 is one of many physiological regulators of linear bone growth. It normally functions as an inhibitor,

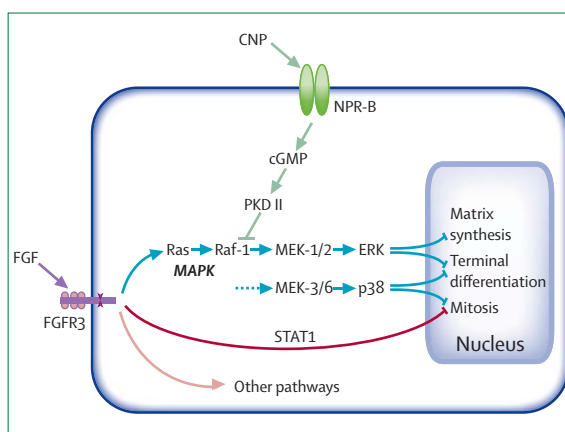


Figure 2: Signalling pathways of FGFR3 most relevant to growth plate chondrocytes

FGFR3 signals propagated through STAT1, MAPK-ERK, MAPK-p38, and other pathways inhibit chondrocyte proliferation, post-mitotic matrix synthesis, and terminal (hypertrophic) differentiation. The CNP-NPR-B pathway inhibits the MAPK pathways. Modified from reference 20 with permission.

acting negatively on both proliferation and terminal differentiation of growth plate chondrocytes.^{36,37} Achondroplasia mutations are thought to exaggerate this normal physiological function.

FGFR3 signals affect many cellular events and processes largely through inducing or repressing expression of target genes in a cell-specific context. Four main signalling pathways have been implicated to date: STAT1 (signal transducer and activator of transcription 1), MAPK (mitogen activated protein kinase), PLC γ (phospholipase C γ), and PI3K-AKT (phosphatidylinositol phosphate-3-kinase-serine/threonine kinase; protein kinase B) with the first two receiving the most attention (figure 2).^{53,58–63} STAT signals seem to inhibit chondrocyte proliferation, whereas MAPK signals negatively affect proliferation, terminal differentiation, and post-mitotic matrix synthesis via both the p38 and ERK (extracellular signal-regulated kinase) pathways.^{61,64–66} Studies of target gene expression suggest that FGFs initiate signals in many pathways that result in the induction of antiproliferative functions and down-regulation of growth promoting molecules.⁶⁷

There are also signalling pathways that modulate the strength of FGFR3 signals. The best defined at present involves C-type natriuretic peptide (CNP).⁶⁸ Through interaction with its receptor, natriuretic peptide receptor B (NPR-B), CNP induces accumulation of intracellular cyclic guanosine monophosphate (cGMP; figure 2). Of note, mutations of NPR-B are responsible for acromesomelic dysplasia, type Maroteaux (OMIM 602875).⁶⁹ Both CNP and NPR-B are expressed in the proliferative and prehypertrophic zones of the growth plate, setting up a potential autocrine or paracrine regulatory circuit.⁶⁹ Signals downstream of the two receptors intersect at the level of raf-1 such that the CNP-NPR-B signals antagonise MAPK signalling downstream of FGFR3 activation.^{70,71}

Consequences of mutations

Several mutation-specific mechanisms have been proposed to explain how activating mutations of FGFR3 enhance FGFR3 signals (figure 3).^{16,25} The trans-membrane achondroplasia mutation is thought to

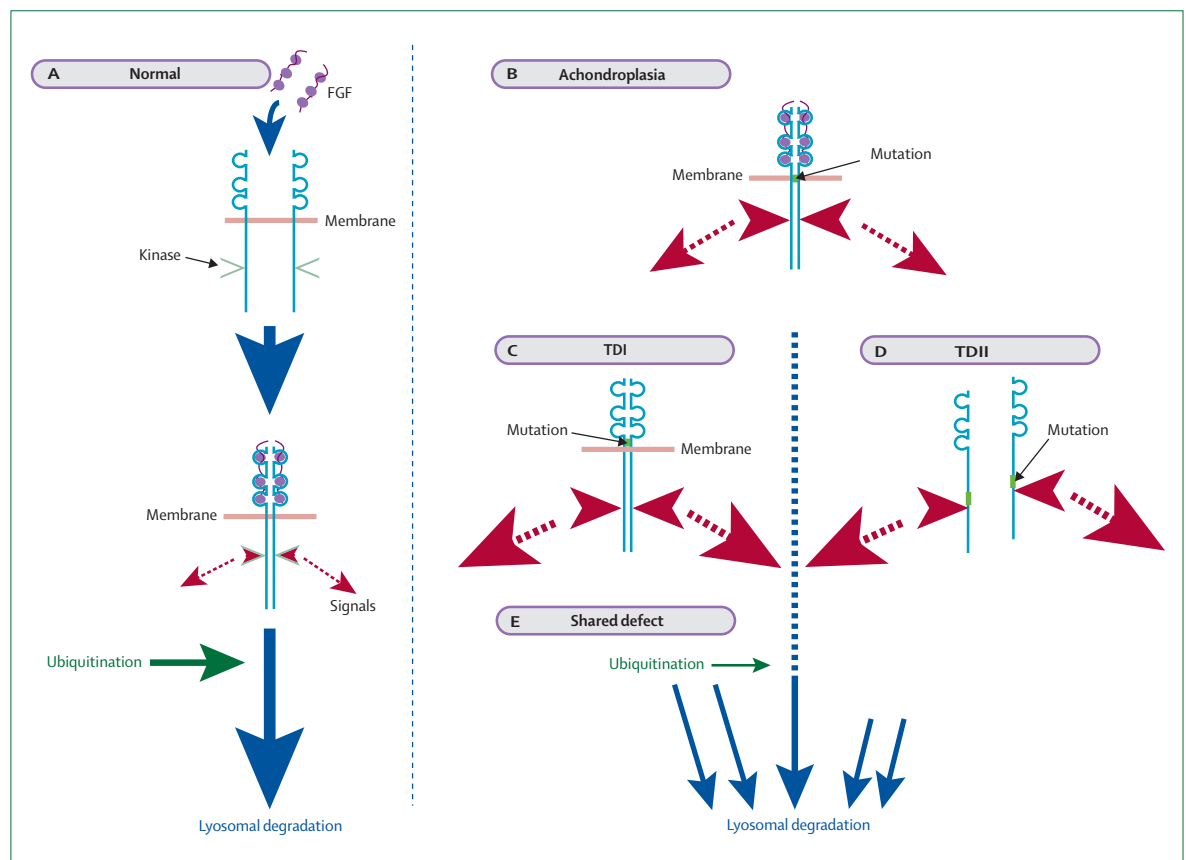


Figure 3: Proposed mechanisms by which mutations lead to gain of FGFR3 function

(A) Normally, ligand induces dimerisation of receptor monomers, which activates kinase and initiates propagation of FGFR3 signals. Activated FGFR3 is targeted by ubiquitination to the lysosomes, where they are degraded, terminating signal propagation soon after activation. (B) FGFR3 dimers are stabilised by mutation (arrow) in transmembrane domain of the receptor in achondroplasia. (C) FGFR3 dimers are induced by formation of disulphide bonds in the proximal extracellular domain (arrow) in thanatophoric dysplasia I. (D) Kinase is constitutively activated by mutation in thanatophoric dysplasia II (and to a lesser extent in severe achondroplasia with developmental delay and acanthosis nigricans and hypochondroplasia). (E) Disturbed ubiquitination, which slows lysosomal targeting and receptor degradation, is shared by mutations that activate FGFR3 kinase activity. Modified from reference 20 with permission.

stabilise FGFR3 dimers following ligand-induced dimerisation, although this mechanism has recently been challenged.^{38,72} The free cysteine residues introduced by the thanatophoric dysplasia I mutations are believed to form disulphide bonds, resulting in dimerisation, which in turn activates the receptor.^{35,73} The mutations of lysine residue 650 alter the conformation of the kinase domain, constitutively activating the intrinsic enzyme activity to different extents, which correspond with the severity of the clinical phenotype.^{16,55,74} The receptor tyrosine kinase is also activated by the common (Asp540Lys) hypochondroplasia mutation, but presumably to a low degree—ie, comparable with the Lys650Gln and Lys650Asp mutations that are associated with a hypochondroplasia phenotype.

Other mechanisms have been proposed that are not mutation specific, but probably reflect the increase in intrinsic receptor tyrosine kinase activity common to all achondroplasia FGFR3 mutations. Lievens and colleagues⁷⁵ have proposed that the high levels of intrinsic kinase activity interfere with biosynthesis and transport of the receptor to the cell surface. Another mechanism involves delayed turnover of activated receptors, which can lead to an increase in overall signal output. Monson-Orran and colleagues⁷⁶ have suggested that the achondroplasia mutation slows receptor internalisation, leaving it on the surface to signal. Cho and co-workers⁷⁷ have described a defect in c-Cbl-mediated receptor ubiquitination that delays trafficking of mutant FGFR3 to lysosomes for degradation. Similarly, Ben-Zvi and colleagues⁷⁸ have suggested that SOCS3 (suppressor of cytokine signalling 3) induced in response to exaggerated STAT1 signals might prolong the survival of mutant FGFR3.

Extraskelletal FGFR3

Most of the clinical features of achondroplasia are either direct or indirect consequences of increased FGFR3 signalling on endochondral bone growth. For instance, neurological manifestations in infants and adults with achondroplasia are typically the result of diminished growth of the base of the skull and vertebral pedicles, dental crowding is due to reduced growth of the midface, and hearing loss results from recurrent middle ear infection.

There are almost certainly manifestations that result from excess FGFR3 signalling in cells of other tissues. Unfortunately, except for tumours in which excess FGFR3 signalling has been identified, little is known about the function(s) of FGFR3 beyond early development, especially in adult tissues. Tissue surveys suggest that FGFR3 is expressed in the gastrointestinal tract, pancreatic islets of Langerhans, steroidogenic cells of the adrenal cortex, Schwann cells of sympathetic ganglia, and in the adult central nervous system, mostly in glial cells.^{79–83} These observations suggest that extraskelletal



Figure 4: Achondroplasia phenotype at different ages

(A) Infant with achondroplasia with macrocephaly, frontal bossing, midface hypoplasia, small chest, rhizomelic shortening of all the limbs, redundant skin folds, and extreme joint laxity. Note the trident hand with short fingers and abducted hips. (B) Typical radiograph findings from a child with achondroplasia. All of the tubular bones are short but the fibula is relatively long compared to the tibia. There is protrusion of the epiphysis into the metaphysis of the distal femur creating the so-called chevron deformity and to a lesser extent of the proximal tibia. The iliac bones are rounded, the acetabular roof is horizontal, and the sacrosciatic notches are small. (C) 3-year-old with achondroplasia with typical features listed in (A). Note that the redundant skin folds are no longer present and that joint laxity has improved. Rhizomelic shortening of the extremities is more pronounced and accompanied by tibial bowing.

overactivity of FGFR3 might contribute to the extraskelletal manifestations of achondroplasia, but too little is known to draw firm conclusions.

Clinical and radiological characteristics

The clinical features of achondroplasia are so distinctive they can easily be identified clinically and radiologically at birth, as well as later in life, so that confusion about the diagnosis should not occur.^{17–19,84} Nevertheless, about 20% of affected individuals are not recognised at birth.^{7,8,85}

With prenatal ultrasound becoming routine in developed countries, many affected fetuses are recognised in the third trimester of pregnancy, allowing families to be prepared for the birth of an affected child.^{86–89}

Achondroplasia is characterised by a long, narrow trunk and short limbs, especially in a proximal (rhizomelic) segment^{18,90} (figure 4). The head is large with frontal bossing,^{7,8,91} but the midface is hypoplastic, a result of the endochondral origin of the base of the skull.^{92,93} Hyperextensibility of joints, especially the knees and hands, is common, but full extension and rotation of the elbow is usually restricted.^{7,8} The hands are short and broad with fingers exhibiting a three-pronged (trident) appearance at birth due to an inability to fully oppose the third and fourth digits.^{5,19} Thoracolumbar gibbus might be present at birth and usually develops by 4 months.^{94–98} Mild to moderate hypotonia is common in infancy, often secondary to spinal cord compression at the cervical medullary junction, and contributes to motor milestone delay.^{99–102} Newborns usually lie with hips abducted after their mother lays them down.

Skeletal radiographs can be used to confirm the diagnosis with specific age-related criteria¹⁷ (figure 4). In the newborn period, when the diagnosis is usually suspected, the pelvis is abnormal with small and square iliac wings, the acetabular roof is horizontal, and there is narrowing of the sacrosciatic notch. The long bones are short, particularly proximally, and the metaphyses slope, resulting in a translucent area in the proximal ends of the femur. The cranium is large with prominent forehead, hypoplasia of the midface, and contraction of the base of the skull with a small foramen magnum. Vertebral bodies have a normal height and width; however, the pedicles are short and the interpedicular distance does not expand as it usually does in the caudal portion of the vertebral column. Typically, the spinal canal size decreases with age relative to the size of the spinal cord, leading to lumbar spinal stenosis. The distal femoral epiphyses develop a typical chevron appearance. These changes moderate with age but can be observed even after puberty, when closure of the epiphyses can be detected radiographically.

Although DNA testing is rarely needed for diagnosis, it is easily done and is available commercially.⁹⁰ DNA testing is more often done to confirm prenatal diagnosis of achondroplasia suspected from ultrasound examination or to assist couples in which both parents have achondroplasia and are at risk of having a baby with the much more severe homozygous achondroplasia, which for practical purposes is a lethal condition.^{103,104}

Natural history and management of complications

Primary and secondary skeletal complications

The complications of achondroplasia involve many organ systems, but in most instances they are the consequence of abnormal linear bone growth. Many, if not most, of

these complications evolve or appear at predicted ages including during adulthood, so that they can be anticipated and often minimised or even prevented if detected and treated early.^{7,8,105–107} Indeed, guidelines for health supervision for children with achondroplasia have been developed to aid primary care physicians in such anticipatory care.^{7,8,90} These guidelines also include growth curves specific to achondroplasia for length/height, weight, head circumference, and chest circumference.^{108–110} Thus, anticipating and testing for known complications at different ages is essential to the care and management of children and adults with achondroplasia.

In the newborn, the head is often large and the cranial-cervical junction is small.^{111–113} This can lead to internal hydrocephalus, mainly occurring because of increased venous pressure due to the narrowed jugular foramen.^{114,115} Although true megacephaly can occur in achondroplasia, the enlarged head size might represent communicating hydrocephalus or dilated ventricles without hydrocephalus.^{116–119} Head growth should be carefully monitored in the first few years with measurements and sonography.^{7,8} A rapid increase in head size, symptoms of increased pressure, or head size above the 95th percentile must be considered for shunting, preferably by a neurosurgeon familiar with achondroplasia. Some studies suggest that as many as 10% of individuals have ventricular shunts in place by their teen years.^{106,120}

Cervical cord compression at the cervical medullary junction is common and can require surgical decompression in infancy or early childhood.^{121–124} The best indicators of the need for decompression include: (1) lower limb hyper-reflexia, clonus, or both, (2) central apnoea demonstrated by polysomnography, and (3) foramen magnum measurements below the mean for achondroplasia.¹¹² When affected individuals are symptomatic, MRI imaging of the brain, cervical junction, and spinal cord should be done. About 5–10% of individuals have had cervical medullary decompression surgery, but this proportion varies depending on the source of affected individuals for the study.^{120,125}

Because of midface underdevelopment, the Eustachian tubes are short, the pharynx is small, and the tonsils and adenoids are large for the available space.^{92,93} Otitis media is common in infants, with at least 25% having chronic recurrent otitis media.¹⁰⁶ These complications need to be treated aggressively with tonsillectomy and ventilation tubes to prevent conductive hearing loss, which is seen in almost 40% of adults with achondroplasia. Speech delay and articulation problems are found in about 25% of patients, presumably related to the midface hypoplasia.¹⁰⁶ Additionally, orthodontic procedures to expand the maxillary area and to reduce the number of teeth in the mandible are often needed to achieve dental alignment.¹²⁶

Cardiorespiratory and sleep dysfunction, including snoring and apnoea both during the daytime and during sleep, are common. Initially, they are related to spinal cord compression and later to narrow breathing passages.^{127–134} At least 10% of patients have sleep apnoea by age 4 years and more than 16%, overall, report this problem.^{106,135,136} The causes of sleep apnoea and snoring fall into three general groups:¹³¹ (1) mid-facial hypoplasia resulting in relative adenoid and tonsil hypertrophy, (2) jugular foramen stenosis resulting in muscular upper airway obstruction because the neurological connections are compromised with progressive hydrocephalus due to jugular venous hypertension, and (3) muscular upper airway obstruction without hydrocephalus resulting from hypoglossal canal stenosis. The first group responds to removal of the adenoids and tonsils. The second group often requires surgical treatment of their hydrocephalus and nocturnal positive airway pressure. Since the third group can develop cor pulmonale, obstructive and central sleep apnoea, and gastro-oesophageal reflux, they might require several forms of therapy, including foramen magnum decompression.^{120,131} Disturbance of respiratory function and increased deep tendon reflexes or clonus at any age should raise the suspicion of central nervous system compromise requiring surgical intervention.

Sensory evoked potentials should be considered in infants with achondroplasia, especially in the presence of symptoms, since there is an increased risk of sudden unexpected deaths related to cervical cord compression.^{100,107} A small chest can be a problem in infancy, compounding the small respiratory passages and cervical compression, if present.^{106,121,129} By adulthood, there are usually no pulmonary problems related to the small chest. Increased sweating is seen in the newborn period and frequently throughout life. In the infant, it has been thought to be related to hypoxia, but seems to occur in all affected children whether hypoxic or not.^{7,8}

A thoracolumbar gibbus is often present at birth and usually develops by 4 months.^{96–98} It seems to be related to truncal hypotonia, which improves between 12 and 18 months. The gibbus might spontaneously resolve; however, until truncal strength is gained, achondroplastic infants should not be placed in a sitting position, but rather tipped back in an infant seat to avoid aggravating the gibbus.

About 10% of patients have tibial bowing by the age of 5 years.¹⁰⁶ It progresses during childhood, affecting 42% of adult patients.¹⁰⁶ Some of the bowing relates to fibular overgrowth. Osteotomies to correct bowing of the legs should be considered in childhood to straighten bones and realign the knees, since osteoarthritis can develop later in life related to the uneven distribution of weight on the joints.^{137,138}

Spinal stenosis and neurogenic claudication are common in older children and adult patients, especially those with persistent kyphosis.^{95,139,140} Problems related to cervical medullary junction compression tend to resolve

during childhood because the foramen magnum grows in size relative to the size of the spinal cord; however, the complications from spinal stenosis increase in adults. By age 10 years, nearly 10% of achondroplastic individuals have neurological signs with claudication and increased reflexes in their legs, and about 80% have these signs by the sixth decade.¹⁰⁶ About a third of patients require lumbar laminectomy surgery for symptomatic spinal stenosis.¹⁰⁵ Spinal laminectomy is best done by surgeons familiar with achondroplasia and before permanent damage to the spinal cord occurs.

Metabolic complications

Obesity is common in achondroplasia, but the reasons why are not understood.¹⁴¹ Hunter recommends that affected children and adults stay within one SD of the mean weight for height curves for achondroplasia.¹⁰⁶ Dietary management should begin early and be maintained throughout life.

Reproductive complications

In the past, reproduction was reduced mainly because of the social stigma associated with disproportionate short stature, which restricted choices of possible mates. However, with the development of lay organisations for individuals with short stature, such as Little People of America, individuals with disproportionate short stature have become more likely to marry and have children. Many couples with short stature choose to adopt a child with short stature rather than having their own biological children. Fertility seems to be normal in affected women who opt for childbearing, but caesarean section is required for delivery because of the small pelvis.¹⁴²

Prenatal detection of achondroplasia can be accomplished by ultrasound and DNA testing of amniocytes.^{86–89} When both parents have typical achondroplasia, homozygous achondroplasia can be prenatally diagnosed.¹⁰³ When prenatal diagnosis of achondroplasia is made to non-affected parents, consideration should be given to caesarean section since the large head of achondroplasia might not fit easily through the normal size pelvis, potentially leading to intracranial bleeding and secondary hydrocephalus.⁹¹ Most women with achondroplasia need general rather than spinal or epidural anaesthesia to avoid problems related to spinal stenosis.¹⁴³

Neurocognitive development, life expectancy, and quality of life

Children with achondroplasia often have developmental delay,^{144,145} mainly motor, and may have lower IQ than do their siblings.^{146–149} Longevity studies of a large cohort of patients suggest that overall and age-specific mortality rates for achondroplasia are increased at all ages.¹⁰⁷ The increase comes mainly from cardiovascular disease for reasons that are not understood and to a lesser extent from accidents and neurological disease. The average life

expectancy for this cohort was decreased by 15 years compared with the US population. Although most adults live happy, productive lives, individuals with achondroplasia on average have lower annual incomes, less education, and are less likely to be married than people without achondroplasia.^{148,150,151}

Therapies to increase stature

There have been several trials of human growth hormone treatment in children with achondroplasia, mostly using pharmacological doses comparable with those used in Turner syndrome.^{152–160} Although there has been some increase in growth rate reported, especially early in the trials, no clear long-term benefit has been established and most experts do not recommend such treatment for achondroplasia.

Surgical limb lengthening is another approach that has been used to increase stature.^{157,161–166} It involves breaking bones, usually femurs, tibiae, and humeri, followed by slow stretching during the healing process by means of orthopaedic appliances. Although as much as 15–30 cm has been added to standing height, the procedure is controversial because of the need for repeated surgeries, the extended time that orthopaedic appliances must be in place, superficial wound infections, and complications related to stretching of non-skeletal tissues including nerves and blood vessels.

Future directions

As the molecular pathways involved in the pathogenesis of achondroplasia and related disorders have become clearer, a number of potential therapeutic strategies have emerged. Most of these approaches have been patterned after those used to treat cancer. This might seem peculiar because the physiological disturbances are in opposite directions—ie, excessive growth in cancer versus inadequate growth in achondroplasia. However, at the molecular level, the mechanisms are quite similar—excessive receptor tyrosine kinase activity.

Most attention has been directed at inhibiting the FGFR3 tyrosine kinase through small chemical inhibitors. This strategy has a strong rationale because all of the cellular and higher level physiological disturbances that interfere with bone growth seem to be driven by the excess in tyrosine kinase activity. Selective FGFR3 kinase inhibitors have been developed and show promise in cell and organ culture experiments, but to date none has worked effectively in whole animals.¹⁶⁷ An alternative approach has involved generating antibodies to block FGFR3 activation. Highly specific humanised antibodies have been developed.^{167,168} Although these antibodies block receptor activation in cell culture, in-vivo studies have yet to be done.

The therapeutic use of CNP or a CNP analogue that could activate the NPR-B signalling pathway to counter excessive FGFR3 signals has been proposed.^{169,170} This approach is appealing because other natriuretic peptides

have been used clinically for their haemodynamic effects in adults and even in children.^{170,171} Although they seem to be safe, at least in the short term, a major drawback is their very short half-life, which requires them to be administered by continuous infusion. A variation of this approach involves therapeutically targeting NPR-C, another natriuretic peptide receptor that binds to CNP. NPR-C, which is present on hypertrophic chondrocytes in the growth plate,⁶⁹ lacks the ability to increase intracellular cGMP and has been proposed to function as a clearance receptor to down-regulate the effects of natriuretic peptides.¹⁷⁰ Theoretically, blocking NPR-C would lead to an increase in CNP available to bind to NPR-B, which would be expected to antagonise FGFR3 signals in the growth plate.

There are two considerations with regard to molecular treatment of achondroplasia that deserve special attention. The first is that treatment would need to be long term, probably starting soon after birth when the diagnosis is made and lasting through puberty. Because skeletal size is usually only mildly reduced at birth, there would potentially be ample time for catch-up growth. However, this long period of treatment adds challenges to any therapeutic approach.

The second consideration involves targeting therapeutic agents to the cartilaginous growth plate. Compared with most tissues, cartilage is avascular and the dense and highly charged extracellular matrix that surrounds chondrocytes represents a formidable barrier for drug delivery. Indeed, these factors might explain, at least in part, why treatments that have worked in cell and organ culture experiments have failed in whole animals. Agents given systemically might need to be administered in higher doses than those used for most other tissues to achieve therapeutic levels in the growth plate, and this could lead to side-effects in the other tissues. Accordingly, it might be necessary to develop means to target agents to growth plate chondrocytes to reach effective doses of drugs and to avoid adverse effects in other tissues.

Contributors

JGH and JTH wrote the initial drafts of the clinical aspects sections and WAH wrote the initial draft of the aetiology and genetics, pathophysiology, and future directions sections. All authors contributed to the overall revisions and final manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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