Current Concept Review

JOURNAL OF CHILDREN'S ORTHOPAEDICS

Journal of Children's Orthopaedics
2024, Vol. 18(5) 461–476

DOI: 10.1177/18632521241269340
journals.sagepub.com/home/cho

Achondroplasia: Current concept of orthopaedic management

Gabriel T Mindler[1,2,3], Alexandra Stauffer[1,2], Catharina Chiari[1,2], Kiril Mladenov[4,5], and Joachim Horn[3,6,7]

Abstract

Achondroplasia, the most common form of inherited disproportionate short stature, is caused by mutations in the fibroblast growth factor receptor 3 gene. The typical clinical features of achondroplasia include short stature, rhizomelic disproportion, joint hyperlaxity, spinal deformity and deformity of the upper and lower limbs. The latter are among the challenges of state-of-the-art orthopaedic treatment plans and significantly contribute to the burden of the disease in individuals with achondroplasia. Multidisciplinary preoperative individual decision-making concerning surgical interventions should be considered. New medical treatments for achondroplasia have been developed and (some) have been approved for clinical use in several countries. While the number of research articles on achondroplasia is increasing rapidly, many unknown or controversial orthopaedic topics remain. Furthermore, in view of new medical developments with improvements in growth and potentially other effects, the timing and algorithms of orthopaedic treatments (e.g. guided growth, limb lengthening and deformity correction) need to be re-evaluated. While standing height is the primary research focus in medical therapy, it is crucial to comprehensively assess orthopaedic parameters in this multifactorial disease. The current treatment of patients with achondroplasia requires specialised multidisciplinary centres with transitional care and individual orthopaedic counselling.

Keywords: Deformity, achondroplasia, multidisciplinary, rare disease, transition

Introduction

Genetics/pathophysiology

Achondroplasia is the most common form of inherited disproportionate short stature with full penetrance caused by an autosomal dominant gain-of-function mutation in fibroblast growth factor receptor 3 (FGFR3).[1] This germline missense mutation results in ligand-independent activation of FGFR3 and its signalling pathways, with subsequent inhibition of chondrocyte proliferation and differentiation.[2,3] Other types of skeletal dysplasias are associated with missense mutations in FGFR3, ranging from mild, such as hypochondroplasia, to severe, such as severe achondroplasia with developmental delay, acanthosis nigricans syndrome or thanatophoric dysplasia, depending on localisation within the tyrosine kinase domain.[3]

Longitudinal bone growth not only requires bone elongation by chondrocyte proliferation and hypertrophy but also elongation of the perichondrium and periosteum.[4] In the endochondral bone, FGFR3 is expressed in the resting and proliferating zones of the growth plate and negatively regulates the proliferation and differentiation of chondrocytes when activated.[5,6] FGFR3 activation and its subsequent pathways lead to the inhibition of terminal hypertrophic differentiation of

[1]Department of Pediatric Orthopaedics and Foot Surgery, Orthopaedic Hospital Speising, Vienna, Austria
[2]Vienna Bone and Growth Center, Vienna, Austria
[3]EPOS Genetics and Metabolic Group, European Paediatric Orthopaedic Society, Rolle, Switzerland
[4]Altonaer Kinderkrankenhaus, Hamburg, Germany
[5]EPOS Spine Group, European Paediatric Orthopaedic Society, Rolle, Switzerland
[6]Division of Orthopedic Surgery, Oslo University Hospital, Norway
[7]Institute of Clinical Medicine, University of Oslo, Norway

Received 26 January 2024; accepted 25 June 2024

Corresponding Author:
Gabriel T Mindler, Department of Pediatric Orthopaedics and Foot Surgery, Orthopaedic Hospital Speising, Speisinger Strasse 109, Vienna 1130, Austria.
Email: gabriel.mindler@oss.at

chondrocytes, thus inhibiting endochondral ossification.[4] In calvarial mesenchymal or periosteal cells, no expression of FGFR3 was detected; therefore, these structures were not affected by the mutations.[6,7]

Clinical features

The typical clinical features of achondroplasia include short stature, rhizomelic disproportion, macrocephaly, midfacial retrusion, joint hyperlaxity, thoracic kyphosis and bony deformity of the upper and lower limbs.

Although body length at birth can be normal, linear growth is severely decreased in achondroplasia. The mean final standing height was approximately 130 cm in males and 125 cm in females with achondroplasia.[8]

Upper extremity deformities include hand abnormalities (short fingers and trident hand configuration), disproportion and a lack of elbow extension. Lower limb deformities include axis deviations, particularly varus deformities, maltorsion, hip flexion contracture, knee hyperextension and ligamentous instability.[8] Furthermore, disease-specific anatomical variants of the joints and other musculoskeletal areas have been described, especially in the spine, hip and knee. Lower limb shortening and deformity occur in all patients and consist predominantly of varus deformity of the legs, not only at the level of the knees (distal femur or proximal tibiae) but also at the ankle (distal tibiae), as well as internal maltorsion of the tibia/fibula. In many patients, ligamentous instability of the knee increases varus angulation owing to an increased lateral joint space angle. Further presentations of lower limb deformities include tibial recurvatum (tibial slope) and overgrowth of the fibula in relation to the tibia, resulting in joint problems of the knee and ankle and subsequent gait deviations.

The notable spinal obstacles in this hereditary skeletal dysplasia include foramen magnum stenosis (FMS), general stenosis of the spinal foramina, sagittal deformities, such as thoracolumbar kyphosis and increased sacral slope.

Disordered endochondral ossification resulting in premature fusion of the posterior elements, namely the pedicles to the vertebral body, at the level of the intervertebral disc, causes spinal dysplasia in achondroplasia.[9] While spinal bony changes, consisting of short thickened pedicles, facet hypertrophy, thick laminae, narrow anteroposterior and transverse canal diameters, and narrowed lateral recesses and nerve foramina, are well established in achondroplasia,[9,10] MRI analysis of the thoracic and lumbar spine shows various additional soft tissue alterations. The thoracic segments resent increased thoracic kyphosis angles, increased vertebral disc height and reduced vertebral body height and canal width. Similar changes have been observed in the lumbar segments with the addition of reduced interpedicular distance, abnormal sacral slope and degenerative changes, such as ossification of the posterior longitudinal ligament, ossification of the ligamentum flavum, osteoarthritis of the facet joints and intervertebral disc herniation.[11,12]

Overall, lower limb deformities lead to disease-specific kinematic and kinetic gait deviations in children with achondroplasia[13,14] as they display a flexion pattern, especially at the hip, knee and ankle in the sagittal plane. Kinematics deviated in all three planes from the unaffected control group, showing an increased peak anterior pelvic tilt, increased peak ankle dorsiflexion, increased knee flexion, increased peak hip abduction angle, increased peak knee varus angle during stance in the frontal plane and an increased range of motion in the pelvis. Increased external hip rotation and reduced tibial torsion are also observed. Walking speed is reduced, whereas cadence is increased in children with achondroplasia.[14]

Principles of management of achondroplasia

Interdisciplinary approach

Considering the multitude of possible paediatric, neurological, anaesthesiological and orthopaedic challenges during childhood, a multidisciplinary team plays a key role in the treatment of children with achondroplasia. Scheduling operations should involve close collaboration with other medical disciplines, as general anaesthesia may pose a risk for cervicomedullary compression or rather spinal cord ischaemia especially in younger children, increased incidence of sleep apnoea (obstructive and/or central) and increased cardiovascular risk especially in young adults.[15–18] Epidural anaesthesia is difficult because of spinal deformities, such as narrow spinal canal/stenoses, reduced epidural space, kyphoscoliosis and vertebral body deformities.[19,20]

The aforementioned perioperative complications should be considered, as well as an extensive preoperative evaluation in collaboration with paediatricians, otorhinolaryngologists and neurologists. Cardiopulmonary problems, including restrictive lung disease, pulmonary hypertension and heart disease necessitate lung function testing, ECG, echocardiography and thoracic radiography. Paediatricians are involved in the examination of chronic and current respiratory infections because treatment before scheduled surgeries may be necessary. Otorhinolaryngology consultation is especially important in cases of sleep apnoea, in addition to sleep laboratory and blood gas analyses. However, pre-existing neurological symptoms, such as hydrocephalus, cervicomedullary compression and spinal canal stenosis, are closely monitored by neurologists or neurosurgeons and often require MRI evaluation and/or surgical intervention.[21]

In surgical and nonsurgical settings, specialised nurses (trained in bone disease) are the key to good patient care, as patients often undergo deformity correction using external fixators. Further experience in this field is necessary when supervising patients to prevent complications. Furthermore, rehabilitation centres specialising in

paediatric rare bone diseases are necessary to improve function, mobility and well-being in age-adjusted groups. Physiotherapy is crucial in achondroplasia, for example, in cases of kyphosis, delayed motor milestones and perioperative and postoperative care, especially during bone-lengthening surgeries.

Another challenge in a multidisciplinary treatment setting is monitoring and early detection of obesity in children and adults with achondroplasia. Obesity has been recognised as a major health risk in achondroplasia due to the development of atypical visceral obesity, as it is believed to not only aggravate skeletal symptoms, such as lumbar spine issues, joint pain or lower limb deformity but also sleep apnoea and cardiovascular diseases. Thus, obesity should be treated as a chronic disease in patients with achondroplasia. Therefore, monitoring of macronutrients with respect to the total energy value, physical activity, growth and body proportions, as well as psychological support providing a feeling of emotional well-being and satisfaction with food, should be implemented as part of a health monitoring assessment protocol for achondroplasia.[17,22]

Movement and sports participation are important topics for many individuals with achondroplasia (e.g. world dwarf games or local sports clubs). However, universal recommendations for sports participation are critical. In the context of increased body mass index, lower limb deformities, disease-specific vulnerabilities (e.g. hyperlaxity and FMS), multidisciplinary counselling, and further mobility-focused research are necessary for adequate guidance.

A thorough understanding of the lifetime impact of achondroplasia is crucial for ensuring optimal patient care and preventing emerging disease-related complications. Regular assessment of quality of life (QoL), physical activity and pain in both adults and children is recommended to properly evaluate the overall patient well-being. Adults present with significantly lower physical function scores than the general population,[23] whereas their mental component scores remain similar. However, children demonstrate not only reduced physical function scores but also delayed independence and a greater need for caregiver assistance, which may be attributed to the primary biomechanical and anatomical challenges in infants contributing to delays not only in reaching motor milestones but also in communication skill development.[17,24] Furthermore, the burden of disease increases in cases of medical and surgical complications, especially in cases of musculoskeletal and connective tissue involvement and neurological or otorhinolaryngological disorders.[24] Opposed to other skeletal dysplasias cervical instability is uncommon in achondroplasia.[25]

However, an increased risk of mortality in children and adults has been reported for several reasons. Foramen magnum stenosis resulting in cervicomedullary compression is associated with 50 times higher risk of sudden death in children aged below 5 years born with achondroplasia than in the general population and accounts for half of these excess deaths. The pathophysiological mechanisms of these events are believed to involve increased apnoeic events and decreased arousal responses. Sleep-disordered breathing remains a complication observed throughout the lifespan of patients with achondroplasia. In adults aged as early as 25 years, an increased number of deaths associated with cardiovascular events has been observed.[17,26]

In view of these considerations, even a simple orthopaedic procedure, such as guided growth, poses a challenge to orthopaedic surgeons and highlights the necessity for a multidisciplinary team for optimised patient care. This is even more evident in families that undergo repeated surgeries. Apart from extensive examinations by various medical disciplines before surgery, mental support in the form of psychological guidance allows for an efficient outcome, as the patient/parents' perspective can be considered when planning surgical interventions.

These disease-specific risks and complications emphasise the importance of optimised multidisciplinary patient care. Modern orthopaedic management of achondroplasia (and other diseases with short stature as the main clinical presentation) in a multidisciplinary setting, starting at birth, needs to primarily focus on the QoL, improvement of overall health, daily function, prevention of chronic diseases and patient-preferred treatment goals. The impact of the final standing height on the QoL of patients with achondroplasia remains unclear and requires further investigation.[24] Furthermore, in a study conducted by Maghnie et al.[24] parents of patients with achondroplasia reported worse QoL of their children than the children themselves. These authors state that there is a need to be cautious when using parent-reported scores.[24]

In our opinion, this also underlines the ethical dilemma in decision-making regarding surgical approaches in children with achondroplasia, especially considering lengthening procedures. There is no international consensus available on ethical decision-making in this regard.

The involvement of local patient organisations in the adaptation of clinical practice guidelines and scientific settings (study design) is recommended to respect patients' and parents' perspectives, which can differ significantly depending on culture/country values.

Guidelines for multidisciplinary management[27,28] need to be updated regularly to comprehensively guide the complexity of this rare disease and include new developments and medical achievements.

Advances in medical treatment

FGFR3 mutation in achondroplasia results in aberrant FGFR3 signalling, promoting sustained activation of extracellular signal-regulated (ERK) mitogen-activated protein (MAP) pathways, activation of signal transcription

pathways, remodelling of the chondrocyte cytoskeleton and interaction with autophagosome proteins, which, in turn, leads to inhibition of proliferation and differentiation of chondrocytes during endochondral growth, a reduction in hypertrophic chondrocytes, a loss of extracellular matrix and premature apoptosis. Drugs currently in clinical trials for the treatment of achondroplasia affect the aberrant FGFR3 pathway by neutralising FGF ligands (recifercept, RBM-007), inhibiting FGFR3 catalytic activity (infigratinib) and directly (meclozine) or indirectly (stable C-natriuretic peptide (CNP) ligands) inhibiting the RAS-ERK pathway. CNP and its receptor, natriuretic peptide receptor B (NPR-B), play key roles in the regulation of longitudinal bone growth by inhibiting the mitogen-activated protein kinases (MAPK) pathway via protein kinase G2-mediated inhibitory phosphorylation of rapidly accelerated fibrosarcoma proto-oncogene 1 (RAF-1). NPR-B binding increases chondrocyte proliferation and differentiation at the physis stage owing to indirect inhibition of the FGFR3 pathway at RAF-1 level. Unfortunately, wild-type CNPs are degraded by neutral enteropeptidase within 2 min of circulation, thus initiating the development of resistant CNP, namely BMN111, for proteolytic degradation due to N-terminal polyethylene glycol (PEG)ylation. In mice, the administration of this drug increased both axial and appendicular bone lengths and prevented the development of skeletal malformations associated with achondroplasia, such as skull flattening and bowing of the lower limbs.[29] Because clinical studies have shown promising results regarding growth velocity with good tolerance to the drug, BMN111 was registered as a vosoritide (Voxzogo) and approved by the European Medicines Agency (EMA) in 2021 for the treatment of children with genetically confirmed achondroplasia aged 2 or older by once-daily subcutaneous injection.[3] Voxzogo has since been approved by the EMA for use in younger patient populations and is now available for treatment in children as young as 4 months of age.

Apart from vosoritide, two additional variants of CNP, TransCon CNP and ASB20213, have been developed and approved for phase 2 and preclinical testing, respectively; however, no clinical results are yet available. TransCon CNP (conjugated to a PEG carrier via a cleavable linker) provides sustained systemic CNP levels upon weekly subcutaneous administration, resulting in greater stimulation of bone growth in a mouse model than intermittent levels of systemic CNP. The second CNP variant ASB20123 also stimulates skeletal growth in mice and has shown improved plasma half-life and retention in the physis compared to wild-type CNP.[29]

Meclozine, a histamine receptor antagonist, is an FDA-approved treatment for symptomatic motion sickness and is currently being evaluated in various clinical trials for multiple uses. It prevents ERK activation in the FGFR3-RAS-ERK pathway via the upstream kinase MAP kinase. In mice, meclozine administration improved bone volume and metaphyseal trabecular bone quality, increased body length, and reduced abnormalities in the long bones, cranium and vertebrae. This resulted in the approval of phase 1 clinical trials.[29]

Infigratinib, an FGFR3 tyrosine kinase inhibitor, interferes with adenosine triphosphate binding, resulting in the inhibition of the catalytic activity of FGFR3. In cultured chondrocytes and embryonic limb explants, inhibition of FGFR3 phosphorylation leads to the restoration of growth defects, rescue of growth arrest and impaired hypertrophic differentiation. It is currently approved for phase 2 clinical trials.[29]

These new developments in the potential medical treatment of achondroplasia underline the importance of a multidisciplinary approach with up-to-date paediatric treatment and surveillance. In addition to the important roles of paediatric endocrinologists and geneticists, many other disciplines are necessary to provide state-of-the-art therapy settings.

Orthopaedic management

The Achondroplasia Natural History Study (CLARITY) is the largest study reporting retrospective historic orthopaedic data of 1374 patients with achondroplasia from four centres. According to this study, 29.7% of patients underwent at least one orthopaedic intervention in the lower limbs or spine during their lifetime (spine surgery (12.7%) and lower extremity surgery (21.2%)). Malalignment was the primary reason for initial intervention.[30]

Spine

Foramen magnum stenosis. The base of the skull is formed by endochondral ossification and is therefore affected by FGFR3 mutation. This results in stenosis of the foramen magnum and subsequent cervicomedullary compression, contributing to morbidity and mortality in children with achondroplasia due to apnoea and sudden unexpected death. Presenting clinical symptoms consist of breathing difficulties, snoring, apnoea, lower cranial nerve dysfunction, swallowing problems or neurologic findings such as hyperreflexia, muscular weakness, paresis or clonus. Despite the narrowing of the cervicomedullary junction, most children develop normally and do not require surgical intervention; however, mortality due to FMS has been reported in 2%–5% of the patients with achondroplasia.[31] A sleep study is recommended immediately after the diagnosis of achondroplasia is established followed by an MRI imaging of the cranio-cervical junction. In most of the patients, symptomatic FMS is commonly treated in the first 2 years of life; however, some of the patients develop symptoms later in life.

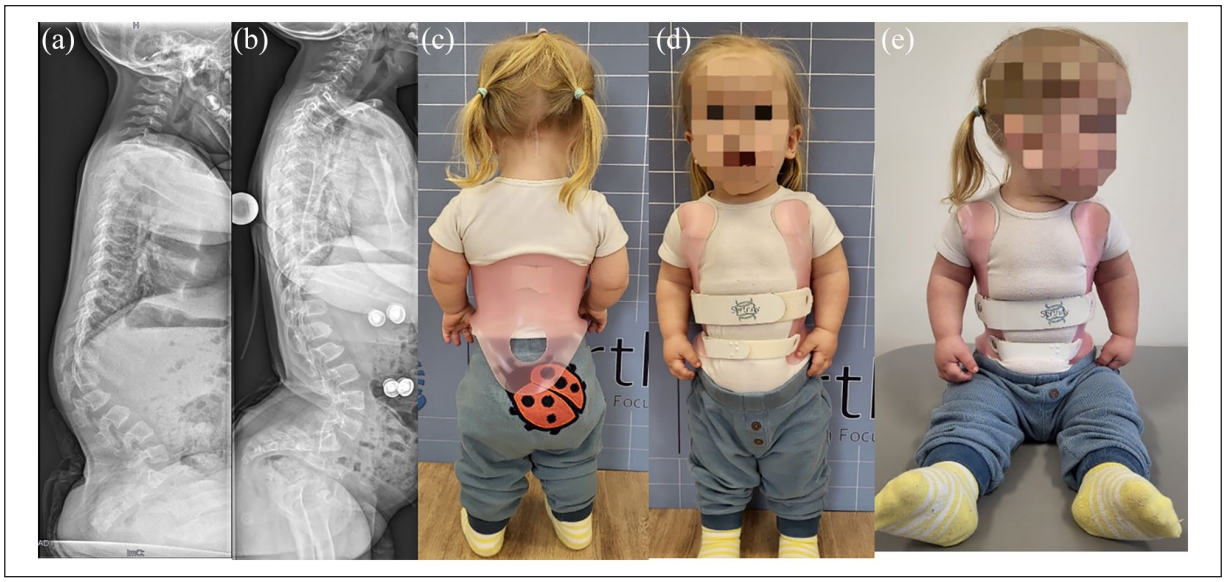


Figure 1. Three-year-old female with achondroplasia: (a) persistent lumbar kyphosis despite improvement of muscular trunk stability, (b) radiograph with a brace (note: severe lumbosacral lordosis with and without brace) and (c)–(e) clinical picture with a brace.

Treatment consists of surgical widening of the foramen magnum and upper cervical laminectomy with or without duraplasty.

Indications for Cervicomedullary decompression (CMD) are as follows:

- FMS with cord signal changes on MRI (myelopathy), especially when lack of cervicospinal fluid flow anterior to the spinal cord in neutral or flexion head position is present
- FMS with intracord lesions combined with abnormal neurological findings, such as central sleep apnoea, difficulty swallowing, hypertonia, paresis or clonus.[32,33] Resolution of symptoms was reported in 91% of patients after CMD; however, complication rate remains relatively high (21% – general complications, 9% – reoperation and 2% – perioperative mortality).[34]

Spinal stenosis. Spinal canal stenosis is observed in approximately 25% of the patients with achondroplasia. Initial evaluation is done using native X-rays with decreased interpedicular distance being a characteristic finding. In the presence of typical clinical symptoms such as neurologic claudication, back pain and sciatica, an MRI evaluation is advocated.[11] Most recently, imaging modalities have been well defined.[35] Surgical treatment is usually indicated in symptomatic cases comprising of posterior multilevel spinal canal and neuroforaminal decompression in combination with posterior spinal fusion to avoid the risk of postlaminectomy instability.[36–38] Excellent results with resolution of symptoms in 95% of the patients have been reported; however, 17% complication rate and 18% reoperation rate have been observed.[34]

Thoracolumbar kyphosis (TLK). TLK is a common finding in 80%–90% of newborns with achondroplasia. The deformity appears accentuated in the sitting position due to trunk muscle hypotonia in combination with head oversize (Figures 1 and 2). Unsupported sitting should be restricted in children <1 year of age to avoid worsening of TLK. Spontaneous resolution of TLK is observed in most of the patients during infancy as a result of increasing trunk control and ability to ambulate, with the reported incidence decreasing from 87% at age 2% to 11% at age 10 years old.[39] Recent studies report the positive influence of independent ambulation ability on TLK which resolved in 15% of the cases at walking age and in 58% 1 year after ambulation was achieved.[40] Further continuous improvement of TLK during growth was well documented in 64% of the patients post walking, 74% at 5 years and 88% of the cases at 10 years of age.[41] Persistent TLK into adulthood was reported in 10%–30% of the patients.[40,41] The most important negative factors for persistent TLK are apical vertebral translation, apical vertebral wedging and developmental delay during growth.

Evidence-based treatment protocols for persistent TLK in achondroplasia patients are not available but close monitoring of asymptomatic paediatric patients with mild to moderate persistent kyphosis between 20° and 40° Cobb is recommended. The benefit of brace treatment in children with achondroplasia is not clearly proven; however, it has been postulated that the progression of kyphosis could potentially be slowed, and even additional correction can

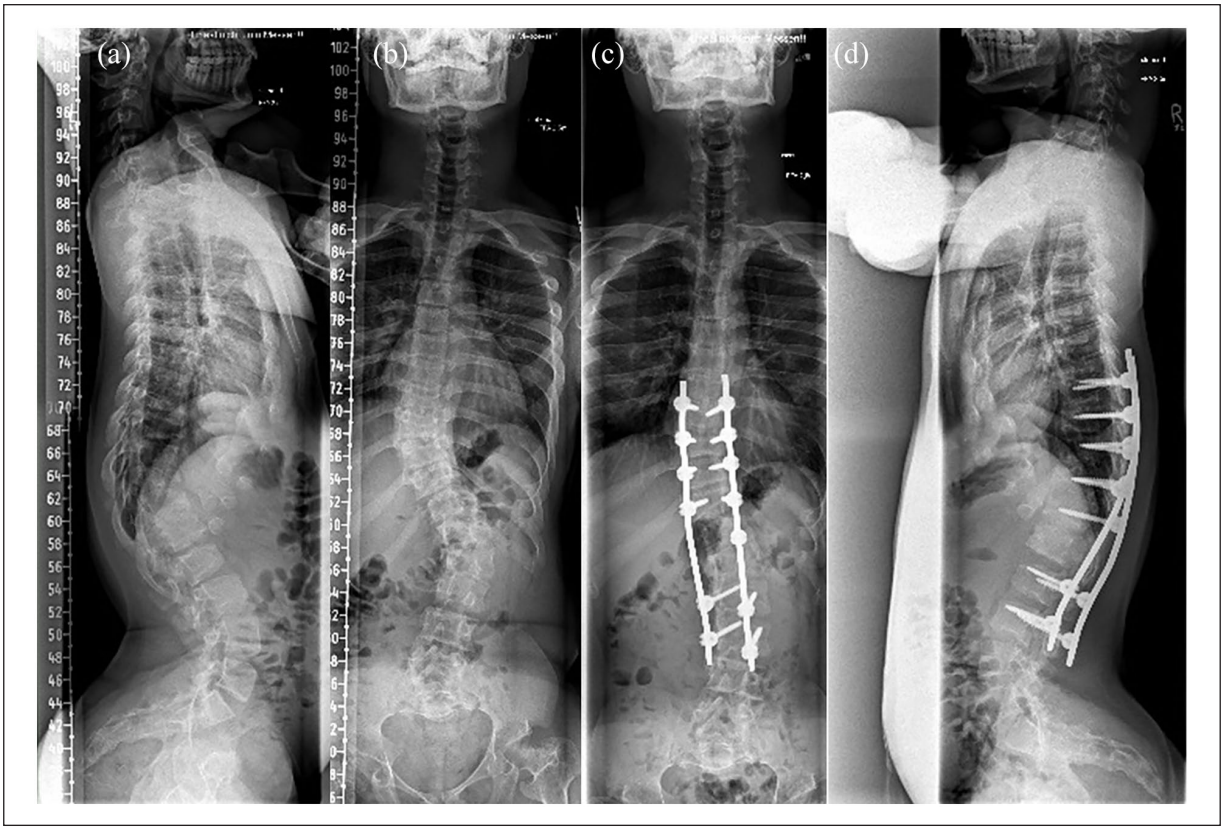


Figure 2. Symptomatic, thoracolumbar kyphosis and scoliosis in a 16-year-old patient with achondroplasia (a) and (b). Follow-up 1 year after posterior decompression, PSO L1 and posterior fusion Th8-L3 (c) and (d).

be promoted by early bracing. Even if the role of bracing remains unclear, it should be discussed as a treatment option especially in children with developmental motor delays since this is one of the factors negatively influencing spontaneous TLK improvement. Brace wear can be discontinued when no further correction under brace therapy is observed and after the formation of an edge-shaped anterior vertebral body.[42]

Surgical correction for persistent TLK should be considered in children with TLK >50° Cobb after 5 years of age since further spontaneous improvement is not to be expected.[42,43] Surgical correction is indicated in cases of anterior, symptomatic spinal cord compression even if TLK measures less than 50° Cobb.[40]

The aims of surgery for TLK are neurological improvement/preservation, deformity correction and stop of progression. Since the anterior portion of the vertebral body is very underdeveloped and the spinal canal is narrowed with predominant anterior spinal cord compression surgical techniques limited to the posterior vertebral elements such as Ponte osteotomies are not adequate to sufficiently correct kyphosis and decompress the spinal cord. Therefore, circumferential decompression is necessary, which can be achieved by pedicle subtraction osteotomy (PSO) and vertebral column resection (VCR). However, there are some limitations with PSO since segmental sagittal correction averages 35° Cobb and the posterior-only vertebral shortening with anteriorly located hinge may result in spinal cord 'kinking', limiting the indication for PSO for cases with moderate kyphotic deformity <50° Cobb. VCR, although technically demanding is the preferred surgical technique for severe deformities since it provides a wide circumferential decompression of the spinal canal without the need for posterior shortening. Furthermore, segmental correction of >50° Cobb in the sagittal as well as in the coronal plane if necessary is possible.[44]

Overall, planning surgical interventions for the lower limbs requires prior assessment and accurate integration of the spinal deformities in achondroplasia.

Severe lumbar hyperlordosis and extensive changes in the sacral slope are common spinal deformities in achondroplasia. Many aspects of the development of these spinal changes are compensatory; however, the exact interaction between pelvic and spinal parameters remains unclear and the relationship between hyperlaxity, muscular hypotension and specifically lower limb deformities (e.g. hip extension deficit and knee hyperextension) needs to be further examined.[45,46]

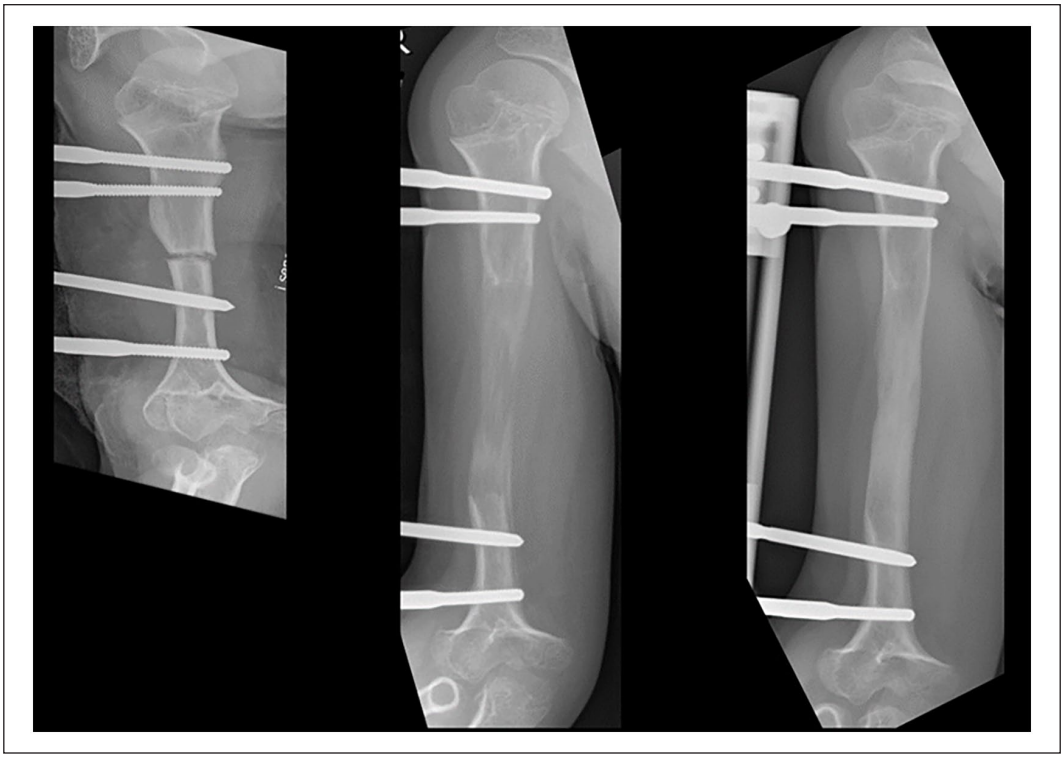


Figure 3. Ten-year-old female with achondroplasia and functional limitations due to shortening in the upper extremities. Bilateral simultaneous humeral lengthening of 8 cm was performed using an Orthofix© mono-lateral fixator.

Upper extremity

Deformities of the upper extremity, such as elbow flexion deformity, posterior bowing of the distal humerus, radial head deformity and/or dislocation, limited supination or pronation, cubitus varus and short ulna, are often observed in patients with achondroplasia. A positive correlation between 20° or more posterior bowing and flexion deformity has been reported previously.[16] Despite these limitations, surgical intervention is rarely indicated, apart from humeral lengthening due to reaching problems, especially in cases of reduced independence during personal hygiene[8] (Figures 3 and 4). When considering humeral lengthening, flexion deformity of the distal humerus should be considered and addressed accordingly.[47]

Unilateral or multiaxial external fixators can be used efficiently for humeral lengthening and angular and rotational deformity correction. However, circular fixators may be preferred in cases of severe deformity.[48,49] The lengthening of long bones can improve the overall proportion.

Although upper limb bone lengthening is known for its high complication rate,[50,51] humeral lengthening has been described to have an important role in the management of achondroplasia compared to lower limb lengthening.[52]

Laufer et al.[51] reported an improvement in self-reported scores after bilateral humeral lengthening, despite a high complication rate.

Although altered knee anatomy in achondroplasia has been described in studies using MRI or arthroscopy[53,54] and hip anatomy has been studied using ultrasound,[55] there are no detailed data (other than X-rays) on anatomic changes of the joints in the upper limb and whether possible anatomic changes of the shoulder, elbow and wrist have an impact on osteoarthritis, pain or function in achondroplasia.[56] Considering the high incidence of elbow contractures in achondroplasia,[8] predominantly occurring between the ages of 4 and 8 years,[47,57] structural analysis of anatomical structures could be helpful for treatment considerations, such as humeral lengthening.[58]

Lower extremity

Although genu varum is among the main clinical characteristics of achondroplasia, with reported rapid progression during childhood and affecting most adults, research regarding its natural history and prevalence is sparse. Currently, there are no consensus-based guidelines available regarding the surgical correction of genu varum, specifically when to operate, which type of surgery is preferred and what to expect from these procedures regarding function, pain and QoL.[17]

A shift from osteotomies to minimally invasive techniques for the surgical treatment of malalignments has been reported in patients with achondroplasia.[30] During

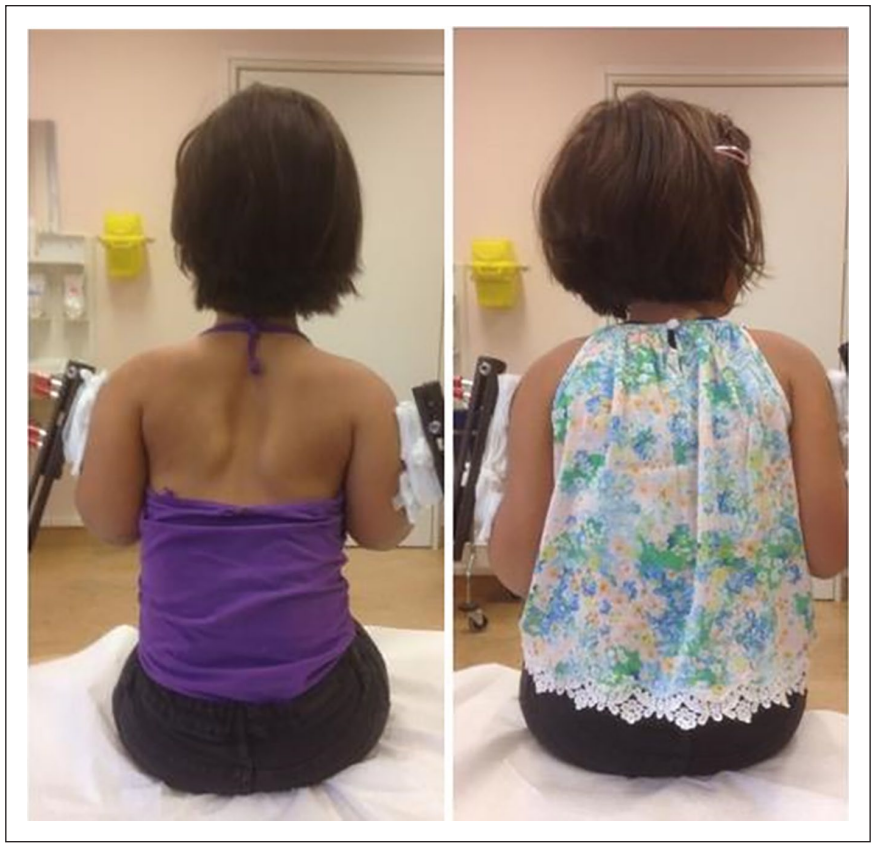


Figure 4. Ten-year-old female with achondroplasia who received bilateral simultaneous humeral lengthening. To the left: after 2 cm of lengthening; to the right: after 8 cm of lengthening.

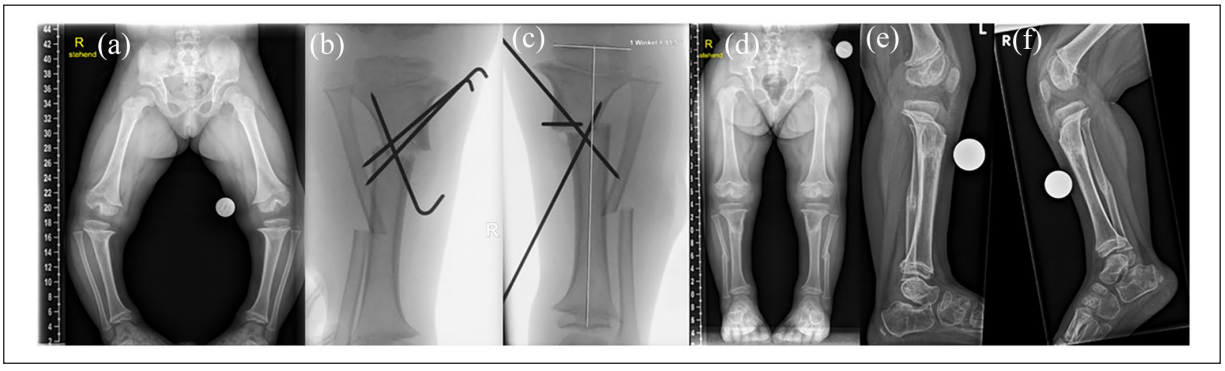
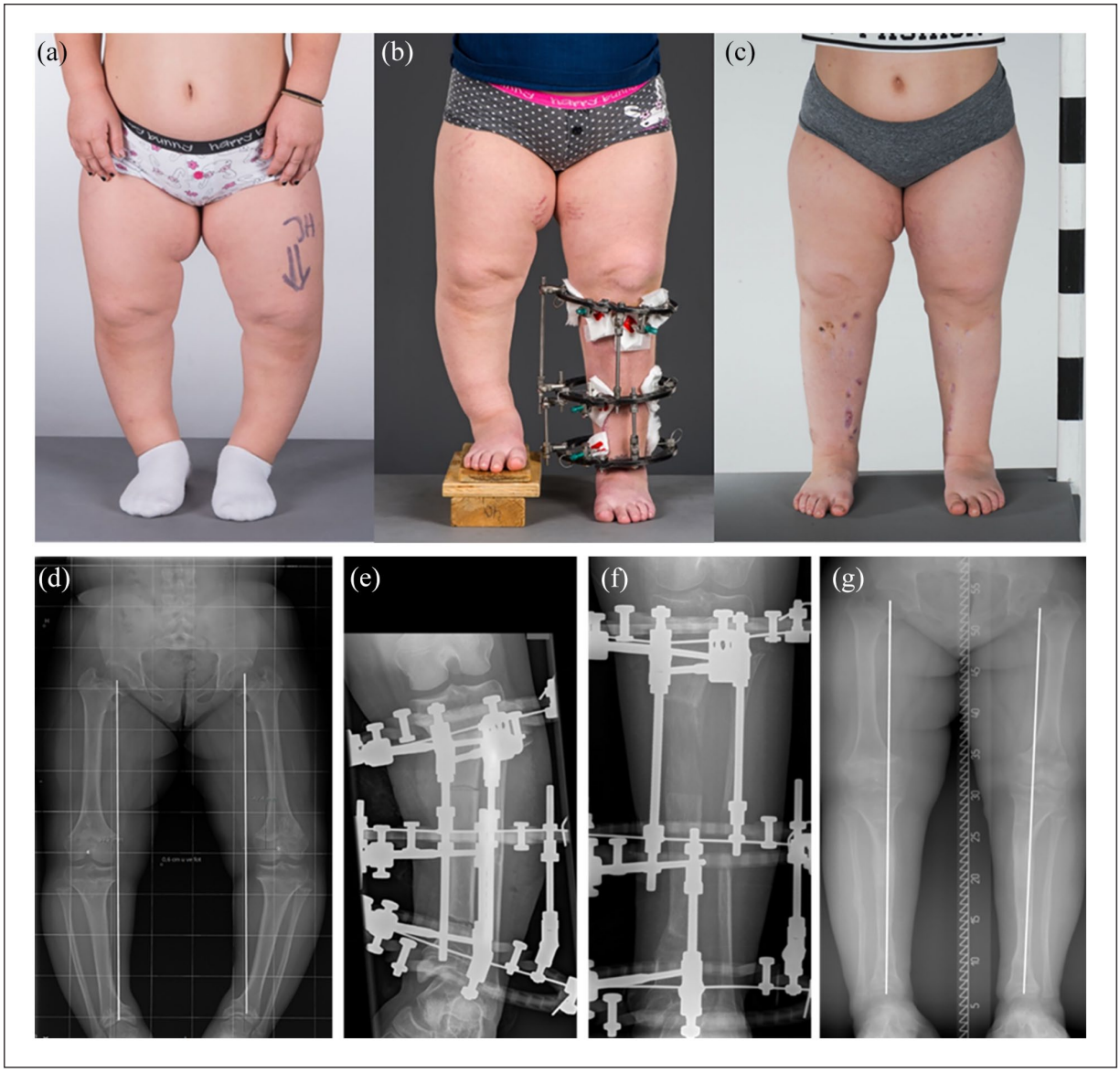


Figure 5. (a)–(c): 4-year-old female with achondroplasia. (a) Severe varus deformity and internal torsion of both lower limbs. (b) and (c) Acute deformity correction against varus and internal tibial torsion with k-wire fixation. (d)–(f) 3-month follow-up.

childhood, specific lower limb deformities in achondroplasia can be treated minimally invasively with guided growth if planned adequately. Owing to reduced growth in achondroplasia, these guided growth procedures need to be performed considerably earlier. Children who require coronal plane deformity correction and are younger than 10 years at the initial guided growth surgery can be successfully treated with hemiepiphysiodesis, with an average treatment time of approximately 2 years.[59,60] However, children older than 10 years require a longer correction and implantation time of tension-band plates of approximately 3 years and full deformity correction may not be achieved.[60,61]

Although surgical interventions for achondroplasia are not mainly defined by lengthening procedures (Figure 5), multiple surgical bone lengthening techniques have been described[62,63] (Figures 6–8).

Bone lengthening in achondroplasia might be performed in combination with or without simultaneous deformity correction to achieve specific functional goals



Figures 6. (a)–(g) 11-year-old female with achondroplasia and severe knee and ankle varus causing pain and gait problems. Consecutive bilateral bi-focal axis correction combined with 7 cm of lengthening (5 cm proximal and 2 cm in distal tibia) in the lower leg using a classical Ilizarov frame was performed to achieve alignment in the knee and ankle joint.

of daily life (e.g. upper limb lengthening to enable personal hygiene, mono- or bifocal lower limb lengthening with axis correction), or bone lengthening might be performed repeatedly to increase height and obtain more normal-appearing proportions for functional and cosmetic reasons. Various surgical techniques (monolateral, circular frames and intramedullary nails) have been described for lengthening procedures, and progress in surgical hardware development (e.g. smaller nails) may lead to better lengthening outcomes concerning patient satisfaction and comfort as well as lengthening safety. There is currently no unanimous agreement on whether unilateral lengthening of the femur and tibia, simultaneous lengthening of both femora/tibiae, a crossover, or all simultaneously, is best suited for achondroplasia.

Recently, simultaneous bilateral femoral and tibial lengthening in patients with achondroplasia with external fixators has been described as feasible; however, it was associated with 76% of adverse events.[64] While an optimal approach to lengthening procedures needs to be developed, there is still insufficient evidence on how excessive lengthening can impair growth,[65] especially considering the medical therapies available. The question remains as to whether the burden of short stature is higher than that of repetitive surgical lengthening procedures during growth. However, the importance of height for

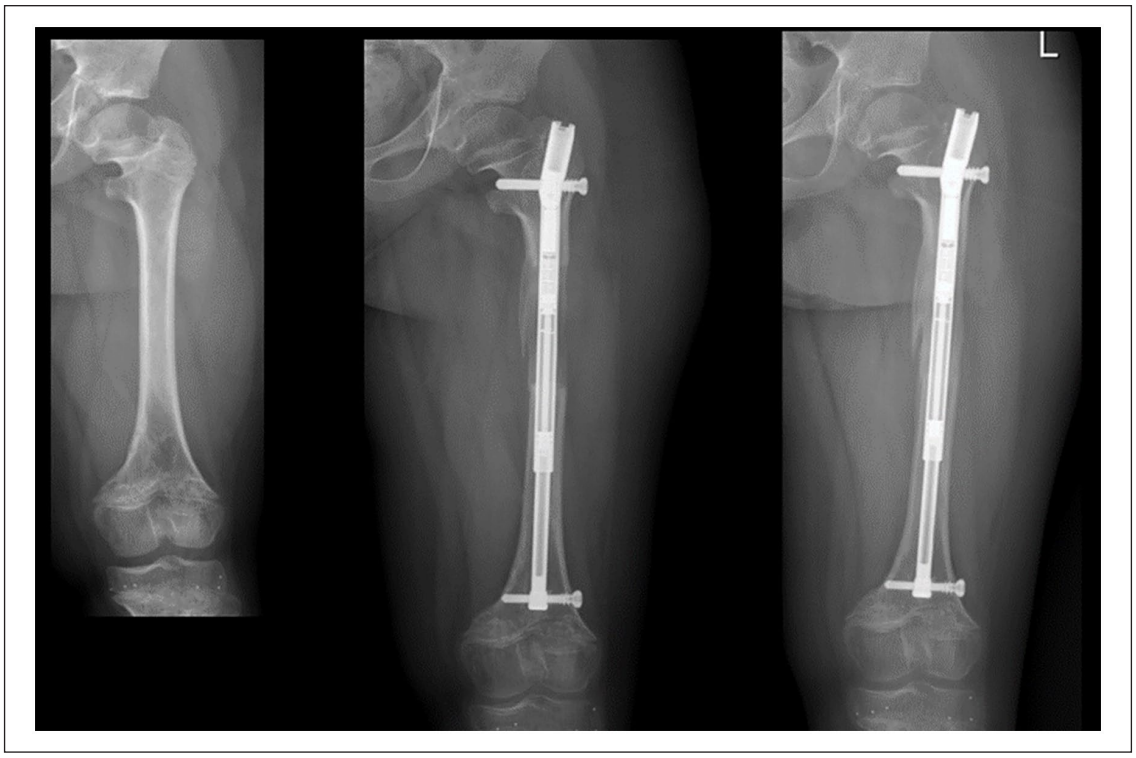


Figure 7. Eleven-year-old female with achondroplasia. Short femoral segment measuring 17 cm from the tip of the trochanter to the level of the distal femoral growth plate. 5 cm femoral lengthening was performed with an externally controlled intramedullary lengthening nail (length of 165 mm and a lengthening capacity of 5 cm).

physical functioning and QoL has not yet been assessed. Furthermore, the impact of limb lengthening on QoL remains inconclusive, despite some evidence in the literature suggesting an improvement in the physical QoL and performance of activities of daily living with greater height or upper limb length, as these parameters have been insufficiently discussed owing to the use of generic questionnaires (e.g. SF-36). Condition-specific instruments should be used to further our understanding of this relevant question.[66,67]

Furthermore, patients' general perspectives on limb-lengthening procedures might depend on local medical treatment concepts as well as the influence of local patient advocacy groups. Therefore, developing universally accepted concepts for limb lengthening and deformity correction in achondroplasia is almost impossible.

Surgical attempts have been made to restore the proportions of the fibula and tibia to improve knee and ankle stability. Definite recommendations for progress in these cases are not yet available.

Surgical distalisation of the fibula using frames or guided growth (epiphysiodesis) has also been discussed.[68] Epiphysiodesis of the proximal fibula is an option for minimally invasive distalisation of the fibula; however, to the best of our knowledge, no detailed data are available on the functional outcomes and exact timing. Furthermore, the distal varus deformity of the tibia is exceptionally difficult to address using minimally invasive techniques, and the distal tibial fibula length ratio (fibular overgrowth in relation to the tibia) and subtalar compensation (heel position and subtalar flexibility) must be considered in surgical planning.

Orthopaedic transition

Adults with achondroplasia are at a high risk of developing medical complications. The average life expectancy decreases by 10 years in adults with achondroplasia compared to unaffected individuals, and the primary causes of death include heart disease, neurological complications and accidents.[69]

One of the main challenges of multidisciplinary treatment for rare bone diseases is transition. A structured transition process for adults is often lacking as individuals with achondroplasia do not seamlessly transition to adult multidisciplinary care. Patients are increasingly lost to or decline follow-up upon adulthood when leaving paediatric care. A wide variety of specialties, including physicians, surgeons, physical therapists, allied professionals, mental health support and primary care professionals, are involved in the management of adults with achondroplasia. A well-coordinated transition from paediatric to adult care should

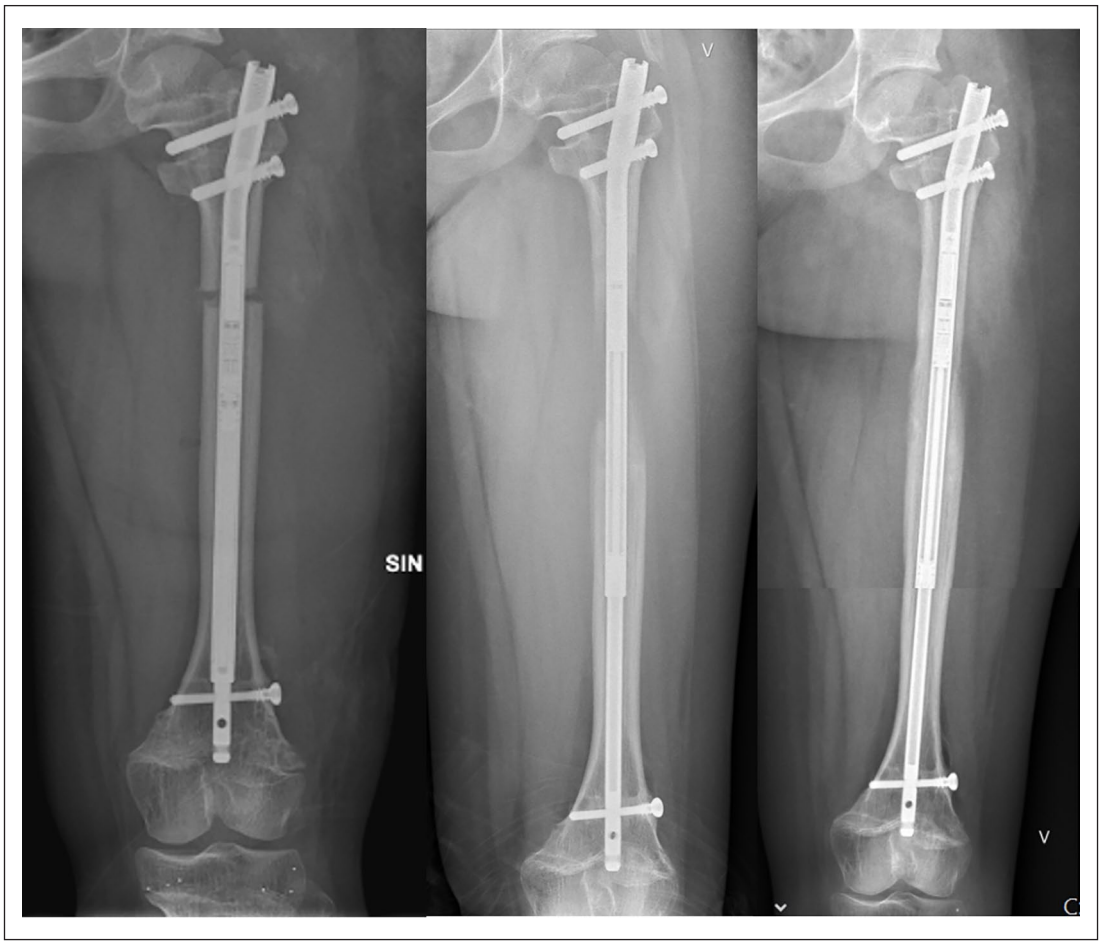


Figure 8. Repeated lengthening of the same patient as shown in Figure 7: The lengthening nail from the first lengthening was removed and a new nail with a lengthening capacity of 8 cm was implanted. The total gain of length in both femora was 13 cm in this patient.

be implemented in the clinical management of patients with achondroplasia.[70]

Recurrence of FMS can occur at any time during growth, and although recurrence rates of approximately 10% have been observed in children, no data are available for adults. Clinical symptoms of cervicomedullary compression in adults may mimic those of cervical myelopathy. Adults with restenosis of the foramen magnum experience symptoms, such as pain, weakness, lack of overall movement, asymmetric limb motion, swallowing, coughing, worsening obstructive apnoea and central apnoea. Patients with new neurological symptoms should be carefully evaluated for foraminal magnum restenosis. Surgical management remains challenging.[33]

Up to 79% of adults with achondroplasia,[56] especially females,[71] have reported pain, and the prevalence of pain increases with age. During childhood, the main causes of pain have been reported to be cervical medullary compression, thoracolumbar kyphosis, hydrocephalus, obstructive apnoea, genu varum, discoid meniscus and bone lengthening treatment. In adolescent and adult patients, the main areas of pain are the knee and lumbar region, as well as general pain.[56]

In an orthopaedic surgical setting, the transition of adolescents with achondroplasia to adult orthopaedic care requires a specialised team for optimal care consisting of at least an adult spine surgeon and an arthroplasty specialist focusing on small implants and hyperlaxity/deformity issues.

The degenerative process of lumbar spinal stenosis often leads to surgical intervention because of the progression of symptoms even at rest, urinary retention and severe claudication.[16] However, posterior decompression in achondroplasia is associated with complications, such as durotomy, new neurological symptoms, and infection requiring irrigation and debridement.[72]

Despite these anatomical variants, frequency and severity of lower limb deformity, total knee arthroplasty cases are rare. Careful preoperative planning and consideration

of revision-style implants in severe cases, as well as thorough patient counselling, are required prior to TKA.[73] Varus deformity and ligament laxity at the knee pose challenges for surgeons when planning TKA. Meticulous technical consideration by arthroplasty specialists focusing on rare bone diseases is required because arthroplasty without deformity correction, prior frontal plane correction or concomitant valgisation osteotomy with TKA may be considered for achondroplasia.[74,75] Intraoperative and postoperative complications secondary to altered anatomical circumstances and short stature should be carefully considered and managed in a specialised multidisciplinary setting.

However, skeletal dysplasia is also associated with premature degenerative osteoarthritis.[76,77] The onset of hip osteoarthritis, which results in decreased mobility and QoL, is a problem in patients with achondroplasia. However, total hip replacement in these patients remains challenging, as it is associated with a high rate of intra- and postoperative complications.[77] Extensive preoperative planning by arthroplasty specialists educated in skeletal dysplasia in a multidisciplinary setting, as well as intraoperative radiographic imaging, is recommended because of disease-specific anatomical changes, as standard surgical landmarks may be altered or absent.[79] The smaller anatomy poses a challenge to the successful engagement of the femoral implant as well as proper placement of the acetabular implant resulting in possible dislocation, implant malpositioning, periprosthetic fractures and aseptic loosening.[76,78,79] Furthermore, conditions, such as varus deformity and ligamentous laxity, contribute to the demand for total hip arthroplasty (THA) in achondroplasia. The odds for postoperative infection within 90 days of surgery are three times higher; however, the successful implant survival rate in achondroplasia after 5 years is comparable to that in non-affected individuals at 95%.[76] These studies underline the importance of orthopaedic transition in achondroplasia.

Owing to the high rate of mental comorbidities and the severe burden of disease in adults, healthcare providers should focus on improving QoL.[66] Interventions in childhood should be considered in light of the long-term effects on the QoL of patients with achondroplasia. Murton et al. reported that only studies with self-help and patient education interventions resulted in improved health related quality of life (HRQoL) compared to studies examining vosoritide, limb lengthening or other surgical procedures.[80]

Combined treatment

The current concept of orthopaedic treatment protocols may have to be revised in the near future owing to the development of new medical treatments.

Paediatric orthopaedics focuses on guidance during the growth period; thus, all medical treatments that alter growth can potentially change our paediatric orthopaedic treatment algorithms (Figure 9).

Preliminary studies evaluating the growth potential in children with achondroplasia undergoing vosoritide therapy showed increased growth (up to 1.57 cm per year) compared with an age-matched placebo control group.[81,82]

The primary outcome parameter in most vosoritide studies is standing height. However, lower-limb deformities, which clearly influence standing height, were not assessed in these initial studies. Furthermore, the assessment of spinal deformities, such as kyphosis, with regard to standing height is lacking.

Improved growth in achondroplasia can influence the timing of the guided growth procedures. New medical therapies available for other rare bone diseases[83] implicate increased correction rate with guided growth.

Normally, guided growth procedures for the correction of lower limb deformities in children with achondroplasia are performed significantly earlier than in unaffected children because of restricted growth potential.[60,61] However, all the available published data on this topic date before the administration of vosoritide (and other medical developments).

Further research is required to extensively evaluate the effect of medication on the potential and rate of frontal deformity correction using hemiepiphysiodesis in patients with achondroplasia. A suitable age for guided growth in patients with achondroplasia should be recommended in comprehensive prospective clinical studies.

In addition to growth and medical modulations of growth, deformity development is another important topic. Achondroplasia is known for disease-specific skeletal deformities, which are congenital or can develop during growth; therefore, it is of great interest to observe how these deformities develop with FGFR pathway-modulating medication. Comprehensive data on the improvement in proportions with medication are needed to fully evaluate the efficacy of these treatments.

The definition of the possible impact of medical therapy (vosoritide) on the development of FMS, thus possibly reducing the need for cervicomedullary surgical interventions, has been attempted in recent studies[84]; however, to the best of our knowledge, no such data are available for upper and lower limb deformities.

Bone healing after osteotomies and bone-lengthening procedures combined with new medical treatments have not yet been reported. Currently, it remains unclear whether our paediatric orthopaedic surgical deformity reconstruction algorithm should be reassessed with regard to medical treatment. No universally accepted treatment standards are available; thus, it remains an obligation of multidisciplinary centres to individually discuss the benefits and risks of orthopaedic surgeries and concomitant medical therapy. Questions arise regarding the necessity of pausing

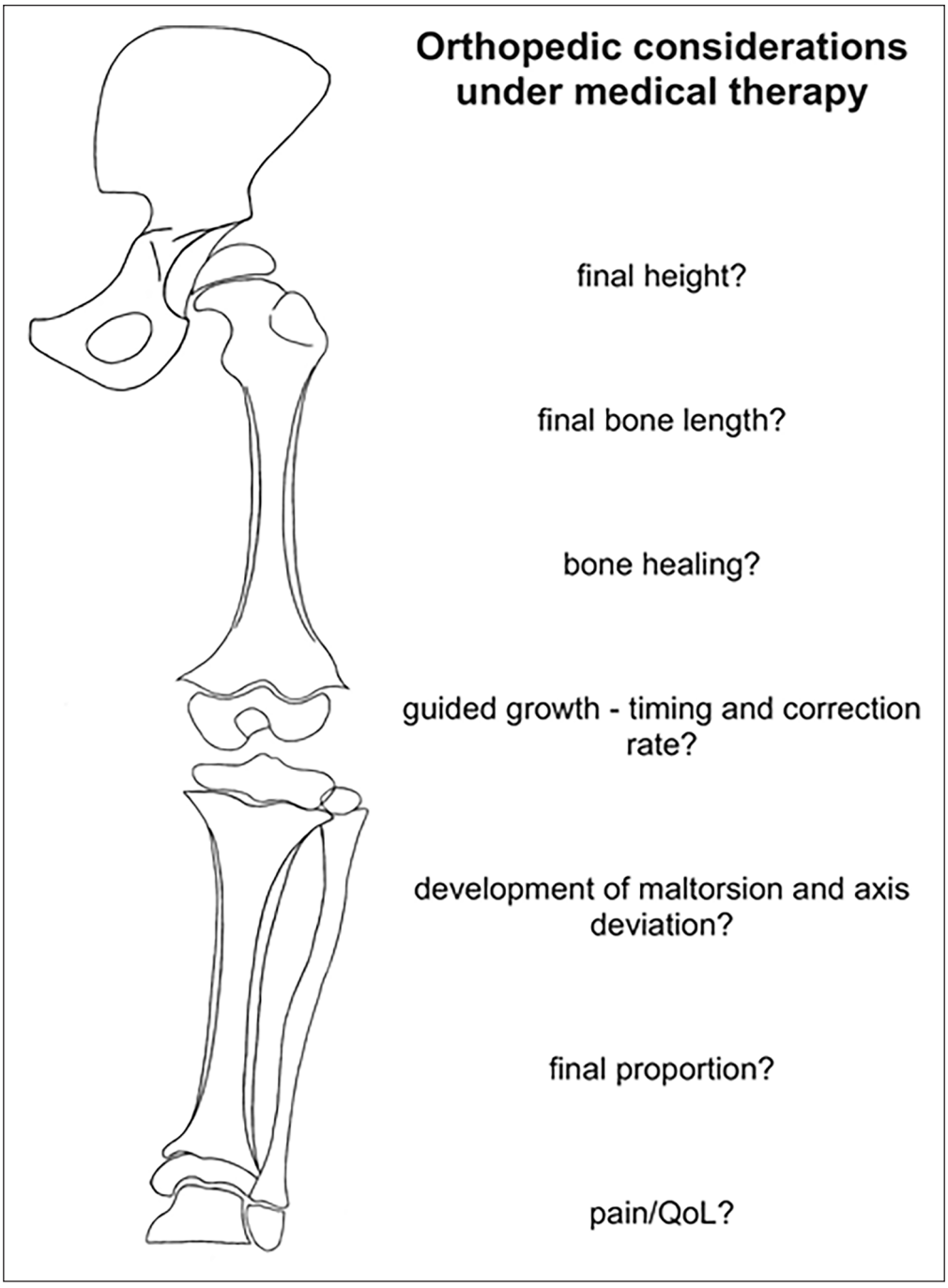


Figure 9. Orthopaedic consideration under medical therapy: Schematic representation of lower limb deformities in a child with achondroplasia with highlights on topics lacking clinical data, specifically, the effect of medical therapy on these factors. Further studies are necessary to fully evaluate the effect of vosoritide, and other agents undergoing clinical testing, on factors, such as final height and proportions, bone healing during surgical intervention, the implications for guided growth regarding timing of surgery and correction rate, as well as the development of lower limb deformities. Furthermore, the effect on QoL, especially patient-reported pain, should be evaluated with novel medical treatment options. See Section 4.5.

treatment for scheduled surgeries and the need to postpone such surgeries to continue treatment. Prospective data and multidisciplinary expert discussions that include patients and families are required to develop efficient treatment algorithms.

Furthermore, improvement in growth in achondroplasia could change our approach to limb reconstruction procedures, as well as the timing. With fewer limb-lengthening procedures, patients might be able to reach a height within 2–3 standard deviations of normal height. Initially, longer

bones before first limb lengthening might allow the use of lengthening nails with a larger stroke (possible maximum amount of lengthening), further reducing the number of lengthening procedures.

Hyperlaxity is an important and sometimes burdensome symptom of achondroplasia. It is not yet clear whether hyperlaxity resulting in possible joint instability correlates with reported joint pain in children and adults with achondroplasia.[56] While it is clinically difficult to measure, it will be interesting to observe whether this parameter is influenced by new treatments and subsequently joint pain.

Future research on the orthopaedic treatment of achondroplasia needs to reconsider which orthopaedic interventions will result in increased musculoskeletal function and a higher QoL.

Conclusion

From a paediatric orthopaedic standpoint, new medical treatment options have the potential to revolutionise treatment algorithms for achondroplasia. However, aspects related to deformity, function and daily activity/QoL must be assessed further to evaluate the orthopaedic benefits of novel medical treatments.

Adaptations and re-evaluation of current treatment concepts in view of changing medical treatment options are necessary for optimal patient care. Orthopaedic surgeons must adapt to new treatment developments and actively participate in the implementation of multidisciplinarity and transition, inclusion of patients' opinions, and consensus regarding concomitant medical treatment and surgical interventions.

Acknowledgments

This article focuses on orthopaedic treatment of patients with achondroplasia in a multidisciplinary setting. While the article was written by the orthopaedic surgeons, the multidisciplinary treatment of rare diseases is a team effort. The authors want to thank their multidisciplinary teams and local patient organisations for their valuable clinical and scientific impact on the orthopaedic treatment and this manuscript.

Author contributions

GM did the conception and design of this article. GM and AS wrote the first draft of the manuscript. AS and GM did literature research. JH and KM wrote sections of the manuscript. JH, KM and CC did a review of the article. All authors contributed to the article and approved the submitted version.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: G.T.M received non-related honoraria from Kyowa Kirin, Alexion and Biomarin for consultancy and/or scientific presentations. A.S, C.C and K.M have no conflict of interest. J.H. has a consultant agreement with NuVasive (lengthening nails) for teaching activities.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Ethical statement

Current concept review – not applicable.

ORCID iD

Gabriel T Mindler https://orcid.org/0000-0002-8533-2164

Supplemental material

Supplemental material for this article is available online.

References

1. Legare JM. Achondroplasia. 1998 Oct 12 [updated 2023 May 11]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A (eds.) *GeneReviews®[Internet]*. Seattle (WA): University of Washington, Seattle, 1993–2024.
2. Di Martino E, L'Hôte CG, Kennedy W, et al. Mutant fibroblast growth factor receptor 3 induces intracellular signaling and cellular transformation in a cell type- and mutation-specific manner. *Oncogene* 2009; 28: 4306–4316.
3. Legeai-Mallet L and Savarirayan R. Novel therapeutic approaches for the treatment of achondroplasia. *Bone* 2020; 141: 115579.
4. Ornitz DM and Legeai-Mallet L. Achondroplasia: development, pathogenesis, and therapy. *Dev Dyn* 2017; 246: 291–309.
5. Ornitz DM. FGF signaling in the developing endochondral skeleton. *Cytokine Growth Factor Rev* 2005; 16: 205–213.
6. Foldynova-Trantirkova S, Wilcox WR and Krejci P. Sixteen years and counting: the current understanding of fibroblast growth factor receptor 3 (FGFR3) signaling in skeletal dysplasias. *Hum Mutat* 2012; 33: 29–41.
7. Ornitz DM and Marie PJ. FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev* 2002; 16: 1446–1465.
8. Pauli RM. Achondroplasia: a comprehensive clinical review. *Orphanet J Rare Dis* 2019; 14: 1.
9. Jeong ST, Song HR, Keny SM, et al. MRI study of the lumbar spine in achondroplasia. A morphometric analysis for the evaluation of stenosis of the canal. *J Bone Joint Surg Br* 2006; 88: 1192–1196.
10. Kumar CP, Song HR, Lee SH, et al. Thoracic and lumbar pedicle morphometry in achondroplasia. *Clin Orthop Relat Res* 2007; 454: 180–185.
11. Calandrelli R, Pilato F, Massimi L, et al. Thoracolumbar stenosis and neurologic symptoms: quantitative MRI in achondroplasia. *J Neuroimaging* 2022; 32: 884–893.
12. Huet T, Cohen-Solal M, Laredo JD, et al. Lumbar spinal stenosis and disc alterations affect the upper lumbar spine in adults with achondroplasia. *Sci Rep* 2020; 10: 4699.

13. Inan M, Thacker M, Church C, et al. Dynamic lower extremity alignment in children with achondroplasia. *J Pediatr Orthop* 2006; 26: 526–529.
14. Broström EW, Antonissen L, Von Heideken J, et al. Gait in children with achondroplasia – A cross-sectional study on joint kinematics and kinetics. *BMC Musculoskelet Disord* 2022; 23: 397.
15. Humble AGR, Phu T and Ryan K. Emergency front of neck access after a can't intubate can't oxygenate scenario in a patient with achondroplasia. *Can J Anaesth* 2020; 67: 779–780.
16. Kitoh H, Matsushita M, Mishima K, et al. Disease-specific complications and multidisciplinary interventions in achondroplasia. *J Bone Miner Metab* 2022; 40: 189–195.
17. Hoover-Fong J, Cheung MS, Fano V, et al. Lifetime impact of achondroplasia: current evidence and perspectives on the natural history. *Bone* 2021; 146: 115872.
18. Monedero P, Garcia-Pedrajas F, Coca I, et al. Is management of anesthesia in Achodroplastic dwarfs really a challenge?. *J Clin Anesth* 1997; 9: 208–212.
19. Morrow MJ and Black IH. Epidural anaesthesia for caesarean section in an achondroplastic dwarf. *Br J Anaesth* 1998; 81: 619–621.
20. Melekoglu R, Celik E and Eraslan S. Successful obstetric and anaesthetic management of a pregnant woman with achondroplasia. *BMJ Case Rep* 2017; 2017: bcr-2017.
21. Wynn J, King TM, Gambello MJ, et al. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A* 2007; 143A: 2502–2511.
22. Saint-Laurent C, Garde-Etayo L and Gouze E. Obesity in achondroplasia patients: from evidence to medical monitoring. *Orphanet J Rare Dis* 2019; 14: 253.
23. Matsushita M, Kitoh H, Mishima K, et al. Physical, mental, and social problems of adolescent and adult patients with achondroplasia. *Calcif Tissue Int* 2019; 104: 364–372.
24. Maghnie M, Semler O, Guillen-Navarro E, et al. Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study. *Orphanet J Rare Dis* 2023; 18: 56.
25. Mohindra S, Tripathi M and Arora S. Atlanto-axial instability in achondroplastic dwarfs: a report of two cases and literature review. *Pediatr Neurosurg* 2011; 47(4): 284–287.
26. Nakano Y, Kubota T, Ohata Y, et al. Assessment of body fat mass, anthropometric measurement and cardiometabolic risk in children and adolescents with achondroplasia and hypochondroplasia. *Endocr J* 2023; 70: 435–443.
27. Savarirayan R, Ireland P, Irving M, et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. *Nat Rev Endocrinol* 2022; 18: 173–189.
28. Hoover-Fong J, Scott CI, Jones MC, et al. Health supervision for people with achondroplasia. *Pediatrics* 2020; 145: e20201010.
29. Fafilek B, Bosakova M and Krejci P. Expanding horizons of achondroplasia treatment: current options and future developments. *Osteoarthr Cartil* 2022; 30: 535–544.
30. Nahm NJ, Mackenzie WGS, Mackenzie WG, et al. Achondroplasia natural history study (Clarity): 60-year experience in orthopedic surgery from four skeletal dysplasia centers. *Orphanet J Rare Dis* 2023; 18: 139.
31. Trotter TL, Hall JG and American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. *Pediatrics* 2005; 116(3): 771–783.
32. Kashanian A, Stadler JA and Danielpour M. Neurosurgical evaluation and management of children with achondroplasia. *Neurosurg Clin N Am* 2022; 33: 17–23.
33. Groves ML, Kashanian A, Danielpour M, et al. Neurosurgical evaluation and management of adults with achondroplasia. *Neurosurg Clin N Am* 2022; 33: 25–35.
34. Akinnusotu O, Isaacs AM, Stone M, et al. Neurosurgical management of cervicomedullary compression, spinal stenosis, and hydrocephalus in pediatric achondroplasia: a systematic review. *J Neurosurg Pediatr* 2023; 32(5): 597–606.
35. Wright J, Cheung M, Siddiqui A, et al. Recommendations for neuroradiological examinations in children living with achondroplasia: a European Society of Pediatric Radiology and European Society of Neuroradiology opinion paper. *Pediatr Radiol* 2023; 53(12): 2323–2344.
36. Hallan DR, Mrowczynski OD, McNutt S, et al. Postlaminectomy kyphosis in achondroplasia patients: to concurrently fuse or not. *Cureus* 2020; 12(5): e7966.
37. Agabegi SS, Antekeier DP, Crawford AH, et al. Postlaminectomy kyphosis in an achondroplastic adolescent treated for spinal stenosis. *Orthopedics* 2008; 31(2): 168.
38. Ain MC and Browne JA. Spinal arthrodesis with instrumentation for thoracolumbar kyphosis in pediatric achondroplasia. *Spine* 2004; 29(18): 2075–2080.
39. Kopits SE. Orthopedic aspects of achondroplasia in children. *Basic Life Sci* 1988; 48: 189–197.
40. Margalit A, McKean G, Lawing C, et al. Walking out of the curve: thoracolumbar kyphosis in achondroplasia. *J Pediatr Orthop* 2018; 38: 491–497.
41. da Silva LCA, Asma A, Ulusaloglu AC, et al. Walking status and spinopelvic parameters in young children with achondroplasia: 10-year follow-up. *Spine Deform* 2023; 11(6): 1477–1483.
42. Shirley ED and Ain MC. Achondroplasia: manifestations and treatment. *J Am Acad Orthop Surg* 2009; 17(4): 231–241.
43. McDonald EJ and De Jesus O. Achondroplasia. 2023 Aug 23. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing, 2024.
44. Tanaka M, Chan TT, Misawa H, et al. Long-term results of posterior vertebral column resection for severe thoracolumbar kyphosis with achondroplastic patients: a case series. *Medicina (Kaunas)* 2022; 58(5): 605.
45. Cai H, Omara C, Castelein R, et al. Sagittal balance parameters in achondroplasia. *Brain Spine* 2023; 3: 102670.
46. Abousamra O, Shah SA, Heydemann JA, et al. Sagittal spinopelvic parameters in children with achondroplasia. *Spine Deform* 2019; 7(1): 163–170.
47. Kitoh H, Kitakoji T, Kurita K, et al. Deformities of the elbow in achondroplasia. *J Bone Joint Surg Br* 2002; 84: 680–683.
48. Hosny GA. Humeral lengthening and deformity correction. *J Child Orthop* 2016; 10: 585–592.

49. Malot R, Park KW, Song SH, et al. Role of hybrid monolateral fixators in managing humeral length and deformity correction. *Acta Orthop* 2013; 84: 280–285.
50. Farr S, Mindler G, Ganger R, et al. Bone lengthening in the pediatric upper extremity. *J Bone Joint Surg Am* 2016; 98: 1490–1503.
51. Laufer A, Rölfing JD, Gosheger G, et al. What are the risks and functional outcomes associated with bilateral humeral lengthening using a monolateral external fixator in patients with achondroplasia? *Clin Orthop Relat Res* 2022; 480: 1779–1789.
52. Kim SJ, Agashe MV, Song SH, et al. Comparison between upper and lower limb lengthening in patients with achondroplasia: a retrospective study. *J Bone Joint Surg Br* 2012; 94: 128–133.
53. Akyol Y, Averill LW, Atanda A, et al. Magnetic resonance evaluation of the knee in children and adolescents with achondroplasia. *Pediatr Radiol* 2015; 45: 888–895.
54. Del Pilar Duque Orozco M, Record NC, Rogers KJ, et al. Arthroscopic knee anatomy in young achondroplasia patients. *J Child Orthop* 2017; 11: 169–174.
55. De Pellegrin M and Moharamzadeh D. Ultrasound hip evaluation in achondroplasia. *J Pediatr Orthop* 2008; 28: 427–431.
56. Onesimo R, Sforza E, Bedeschi MF, et al. How pain affect real life of children and adults with achondroplasia: a systematic review. *Eur J Med Genet* 2023; 66: 104850.
57. Okenfuss E, Moghaddam B and Avins AL. Natural history of achondroplasia: a retrospective review of longitudinal clinical data. *Am J Med Genet A* 2020; 182: 2540–2551.
58. Arenas-Miquelez A, Arbeloa-Gutierrez L, Amaya M, et al. Upper limb lengthening in achondroplasia using unilateral external fixation. *J Pediatr Orthop* 2021; 41: e328–e336.
59. Makarewich CA, Zhang E and Stevens PM. Hemiepiphysiodesis for lower extremity coronal plane angular correction in the distal femur and proximal tibia in children with achondroplasia. *J Pediatr Orthop* 2023; 43(8): e639–e642.
60. Ulusaloglu AC, Asma A, Silva LC, et al. Growth modulation by tension band plate in achondroplasia with Varus Knee deformity: comparison of gait analysis measurements. *J Pediatr Orthop* 2023; 43: 168–173.
61. McClure PK, Kilinc E and Birch JG. Growth modulation in achondroplasia. *J Pediatr Orthop* 2017; 37: e384–e387.
62. Mindler GT, Stauffer A and Ganger R. Leg lengthening and deformity correction in rare bone diseases: a multidisciplinary approach. *Wien Med Wochenschr* 2021; 171: 126–132.
63. Schiedel F and Rödl R. Lower limb lengthening in patients with disproportionate short stature with achondroplasia: a systematic review of the last 20 years. *Disabil Rehabil* 2012; 34: 982–987.
64. Shabtai L, Jauregui JJ, Herzenberg JE, et al. Simultaneous bilateral femoral and tibial lengthening in achondroplasia. *Children (Basel)* 2021; 8: 749.
65. Song SH, Agashe MV, Huh YJ, et al. Physeal growth arrest after tibial lengthening in achondroplasia: 23 children followed to skeletal maturity. *Acta Orthop* 2012; 83: 282–287.
66. Yonko EA, Emanuel JS, Carter EM, et al. Quality of life in adults with achondroplasia in the United States. *Am J Med Genet A* 2021; 185: 695–701.
67. Constantinides C, Landis SH, Jarrett J, et al. Quality of life, physical functioning, and psychosocial function among patients with achondroplasia: a targeted literature review. *Disabil Rehabil* 2022; 44: 6166–6178.
68. Beals RK and Stanley G. Surgical correction of bowlegs in achondroplasia. *J Pediatr Orthop B* 2005; 14: 245–249.
69. Fredwall SO, Maanum G, Johansen H, et al. Current knowledge of medical complications in adults with achondroplasia: a scoping review. *Clin Genet* 2020; 97: 179–197.
70. Fredwall S, Allum Y, Alsayed M, et al. Optimising care and follow-up of adults with achondroplasia. *Orphanet J Rare Dis* 2022; 17: 318.
71. Alade Y, Tunkel D, Schulze K, et al. Cross-sectional assessment of pain and physical function in skeletal dysplasia patients. *Clin Genet* 2013; 84: 237–243.
72. Shafi K, Lovecchio F, Sava M, et al. Complications and revisions after spine surgery in patients with skeletal dysplasia: have we improved? *Glob Spine J* 2023; 13: 268–275.
73. Stancil R, Goldberg M, Bouchard M, et al. Complex primary total knee arthroplasty in a patient with achondroplasia, osteoarthritis, and severe coronal instability. *Arthroplast Today* 2021; 8: 24–28.
74. Zmerly H, Russo M, Moscato M, et al. Total knee arthroplasty in a young patient with achondroplasia. *BMJ Case Rep* 2021; 14: e242909.
75. Walter SG, Schwering T and Preiss S. Two-staged bilateral, femoral alignment osteotomy with concomitant total knee arthroplasty in an achondroplasia patient – A case report. *J Orthop Case Rep* 2017; 7: 33–36.
76. Moore HG, Schneble CA, Kahan JB, et al. Total joint arthroplasty in patients with achondroplasia: comparison of 90-day adverse events and 5-year implant survival. *Arthroplast Today* 2021; 11: 151–156.
77. Van Den Broek M, Verborgt O and Declercq G. Reverse shoulder arthroplasty in young patient with achondroplasia – Ten year follow up: case report. *Orthop Traumatol Surg Res* 2017; 103: 1127–1130.
78. Gautam D and Malhotra R. Bilateral simultaneous total hip replacement in Achondroplasia. *J Clin Orthop Trauma* 2017; 8(Supplement 1): S76–S79.
79. Malcolm TL, Phan DL and Schwarzkopf R. Concomitant achondroplasia and developmental dysplasia of the hip. *Arthroplast Today* 2015; 1: 111–115.
80. Murton MC, Drane ELA, Goff-Leggett DM, et al. Burden and treatment of achondroplasia: a systematic literature review. *Adv Ther* 2023; 40: 3639–3680.
81. Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet* 2020; 396: 684–692.
82. Savarirayan R, Tofts L, Irving M, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. *Genet Med* 2021; 23: 2443–2447.
83. Mindler GT, Stauffer A, Kranzl A, et al. Persistent lower limb deformities despite amelioration of rickets in X-linked hypophosphatemia (XLH) – A prospective observational study. *Front Endocrinol* 2022; 13: 866170.
84. Savarirayan R, Irving M, Maixner W, et al. Rationale, design, and methods of a randomised, controlled, open-label clinical trial with an open-label extension to investigate the safety of vosoritide in infants and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery. *Sci Prog* 2021; 104: 00368504211003782.