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How pain affect real life of children and adults with achondroplasia: A systematic review

Roberta Onesimo [a], Elisabetta Sforza [b,*], Maria Francesca Bedeschi [c], Chiara Leoni [a], Valentina Giorgio [a,b], Donato Rigante [a], Cristina De Rose [a], Eliza Maria Kuczynska [a], Domenico Marco Romeo [d,e], Osvaldo Palmacci [f], Luca Massimi [g,h], Matteo Porro [i], Michaela Veronika Gonfiantini [j], Angelo Selicorni [k], Anna Allegri [l], Mohamad Maghnie [l,m], Giuseppe Zampino [a]

[a] Center for Rare Diseases and Birth Defects, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168, Roma, Italy
[b] Università Cattolica Del Sacro Cuore, Rome, 00168, Italy
[c] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Medical Genetics Unit, Milan, Italy
[d] Pediatric Neurology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, 00168, Rome, Italy
[e] Pediatric Neurology Unit, Università Cattolica Del Sacro Cuore, 00168, Rome, Italy
[f] Department of Orthopaedics and Traumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica Del Sacro Cuore, Rome, Italy
[g] Neurochirurgia Pediatrica, Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy
[h] Dipartimento di Neuroscienze, Università Cattolica Del Sacro Cuore, Italy
[i] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Physical Medicine & Rehabilitation Service, Milan, Italy
[j] Rare Diseases and Medical Genetics Unit, IRCCS Bambino Gesù Children's Hospital, Rome, Italy
[k] Department of Paediatrics, Presidio S. Fermo, ASST Lariana, Como, Italy
[l] Pediatric Endocrinology Unit, Department of Pediatrics, IRCCS IstitutoGianninaGaslini, 16147, Genoa, Italy
[m] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, 16132, Genoa, Italy

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ABSTRACT

The clinical features of achondroplasia can cause acute self-limited pain that can evolve into chronic pain. Pain causes a low quality of life, in terms of physical, emotional, social, and school functioning in both adult and children with achondroplasia. We conducted a systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement to describe prevalence, assessment tools, causes and management strategies of pain in this rare disease. We found that shoulder and knee pain is typically referred during infancy, while knee pain is generally referred around 5–6 years of age. The prevalence of general pain in adolescence can be as high as 90%. Chronic pain in the achondroplasia population increases with age, with up to 70% of adults reporting general pain and back pain. Recognizing the multiple determinants of acute and chronic pain in patients with achondroplasia may enable physicians to better understand and manage this burden, particularly with the advent of new drugs that may modify some of the striking features of achondroplasia.

* Corresponding author
E-mail addresses: roberta.onesimo@policlinicogemelli.it (R. Onesimo), elisabetta.sforza@unicatt.it (E. Sforza), mariafrancesca.bedeschi@policlinico.mi.it (M.F. Bedeschi), chiara.leoni@policlinicogemelli.it (C. Leoni), valentina.giorgio@policlinicogemelli.it (V. Giorgio), Donato.Rigante@unicatt.it (D. Rigante), cristina.derose@guest.policlinicogemelli.it (C. De Rose), elizamaria.kuczynska@policlinicogemelli.it (E.M. Kuczynska), domenicomarco.romeo@policlinicogemelli.it (D.M. Romeo), osvaldo.palmacci@unicatt.it (O. Palmacci), luca.massimi@policlinicogemelli.it (L. Massimi), matteo.porro@policlinico.mi.it (M. Porro), mveronik.gonfiantini@opbg.net (M.V. Gonfiantini), angelo.selicorni@asst-lariana.it (A. Selicorni), annaallegri@gaslini.org (A. Allegri), Mohamad.Maghnie@unige.it (M. Maghnie), giuseppe.zampino@unicatt.it (G. Zampino).

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Abbreviations

ACEM-Symptom	Achondroplasia Child Experience Measures Symptom scale
ACH	achondroplasia
AS	ankylosing spondylitis
BMD	bone mineral denisty
BPI	Brief Pain Inventory
CHAQ	Childhood Health Assessment Questionnaire
LCH	Langerhans cell histiocytosis
MMPQ	Modified Mc Gill Pain Questionnaire
OSA	obstructive sleep apnea
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QOL	quality of life
SS	spinal stenosis
STEMS	Screening Tool for Everyday Mobility and Symptoms
TLK	thoracolumbar kyphosis

1. Background

The higher prevalence of pain and pain-related diseases is one of the root causes of disability and disease burden worldwide (GBD 2019 Diseases and and Injuries Collaborators, 2020). Striking clinical features of achondroplasia (ACH) can cause self-limited acute pain that can develop into a chronic, co-morbid illness interfering with daily activities (Tucker-Bartley et al., 2021; Maghnie et al., 2023). ACH arises from a mutation in the fibroblast growth factor receptor-3 (*FGFR3*) gene that leads to a defect in endochondral ossification, which results in rhizomelic limb-shortening and spinal column abnormalities (Bellus et al., 1995; Hong et al., 2011a; Pauli, 2019). Other manifestations of ACH include small stature, macrocephaly, midfacial retrusion, small chest, thoracolumbar kyphosis, lumbar hyperlordosis, limited elbow extension, short finger and trident configuration of the hands, hypermobile hips and knees, bowing of the mesial segment of the legs and hypotonia (Pauli, 2019). Oral findings include anterior open bite, malocclusion and protrusive maxillary incisors (Celenk et al., 2003; Karpagam et al., 2005; Brook and Winter 1970).

Functional performance across self-care and mobility skills, assessed through the WeeFIM-II scale, is commonly delayed up to the age of 7 years resulting in instensified physical caregiver support for everyday tasks (Ireland et al., 2011).

Although pain has been frequently reported especially in adulthood, a comprehensive analysis focused on this issue is lacking. Hence, due to its relevance, the present review aims to describe prevalence, assessment tools, causes and management strategies of pain in ACH.

2. Methods

This systematic review has been registered on the International prospective register of systematic reviews (PROSPERO) website (https://www.crd.york.ac.uk/prospero/; registration number:xx).

2.1. Search strategy

RO. and ES. conducted a thorough electronic literature search of the databases PubMed (MEDLINE), Scopus, Cochrane Library, and CINAHL (EBSCO). Text words and Medical Subject headings (MeSH) were used and Boolean operations including "AND", "OR", "NOT" were merged to form search phrases (Table 1). MeSH words contained two major components: terms pertaining to pain and terms referring to the target population, namely individuals suffering from ACH.

Table 1
Search methodology.

Database	Search strategy
PubMed	1. (pain [Text Word]) 2. (achondroplasia [MeSH Terms]) OR (skeletal dysplasia [Title/Abstract]) 3. (1) AND (2) 4. (3) AND English AND Humans
Scopus	1. (TITLE-ABS-KEY (pain) 2. (TITLE-ABS-KEY (achondroplasia) OR TITLE-ABS-KEY (skeletal AND dysplasia) 3. (1) AND (2) 4. (3) AND (LIMIT-TO (LANGUAGE, "English")
Cochrane Library	1. ("pain").mp. [mp = ti,ab,kw] 2. ("achondroplasia"):ti,ab, kw OR (skeletal dysplasia):ti,ab,kw 4. (1) AND (2)
CINAHL	1. TI pain 2. AB (achondroplasia OR skeletal dysplasia) 3. (1) AND (2) limited to English Language

2.1.1. Study eligibility

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist (Page et al., 2021) **(**Supplementary Table 1**)** and after removing duplicates, all full text articles were screened by two independent researchers; any discrepancies were solved in a consensus meeting. The articles were included if they reported on pain epidemiology, assessment and management in both the paediatric and adult ACH population, that were freely-available, and written in English. No date limit was set, to avoid excluding potentially useful publications.

3. Results

The initial literature search yielded 512 articles. Duplicates (n = 300) were excluded and the remaining 192 "full-text" manuscripts were reviewed. Agreement between the two independent researchers reviewing the articles was high (Cohen's Kappa >0.8). Of the total, 84 studies met the inclusion criteria (Supplementary Fig. 1).

A thematic synthesis of assessment instruments, causes of pain, allocation of pain, correlation with age, and possible management strategies is outlined as follows.

3.1. Assessment instruments

Numerous tools to assess the presence, distribution and intensity of pain in the ACH population from childhood to adulthood have been published in the English-language medical literature. Some of those instruments have been specifically developed for ACH population, while others were first intended for the general population and have since been adapted for this specific condition.

The *Achondroplasia Child Experience Measures Symptom scale* (ACEM-Symptom), along with the ACEM-Impact scale, was developed by Pfeiffer et al. as the first observer-reported outcome measures of physical symptoms/complications of ACH in children. The ACEM-Symptom comprises eight primary symptoms/complications including pain and can be administered to children between the age of 2–12 (Pfeiffer et al., 2021). In addition, for the pediatric population, the *Childhood Health Assessment Questionnaire* (CHAQ) version adapted for ACH, assesses the burden of pain through a 100 Visual Analogue Scale (VAS). Specifically, the CHAQ also measures the impact of the condition on physical functioning in eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). The CHAQ is advised for use with children 0–19 years old; self-report (PRO completion) is recommended for children aged ≥8 years, while caregiver report (ObsRO -Observer Reported Outcome-completion) is recommended for children <8 years old (Singh et al., 1994; Klepper, 2011; Aldhouse et al., 2022). Along with questionnaires specifically designed to measure pain,

the Quality of Life in Short Stature Youth (QoLISSY) questionnaire has been administered to better assess the health-related quality of life (HRQOL) in short stature youth (Aldhouse et al., 2022).

The burden of orthodontic pain resulting from craniofacial abnormalities intervention in ACH adolescents have been recently investigated (Meazzini et al., 2020). The authors used the *Modified Mc Gill Pain Questionnaire Short Form* (MMPQ-SF) (Iwasaki et al., 2013).

Alternatively, the *Screening Tool for Everyday Mobility and Symptoms* (STEMS) is a scale designed to record also pain and/or fatigue and their effects on daily activity levels and to provide a standardised screening tool to monitor pain in both children and adults with skeletal dysplasia (Ireland et al., 2021).

In the Fredwall et al. study on adults with ACH (Fredwall et al., 2020), pain location and intensity were measured using a pain drawing along with a 10-point Numeric Rating Scale (0 = no pain, 10 = worst pain you can imagine) derived from the *Norwegian Pain Society Minimum Questionnaire* (NOSF-MISS) [20. Using this assessment approach, patients are asked to score the highest severity for each pain site they experienced in the preceding week.

Ultimately, the *Brief Pain Inventory* (BPI), commonly used in average stature patients to assess pain intensity and interference with daily function (Cleeland and Ryan, 1994), has been actually used in the short stature skeletal dysplasia adult population in the Alade et al. study (Alade et al., 2013) (Table 2).

3.2. Causes of pain and management approaches (*Tables 3 and 4*)

3.2.1. Neurological issues

3.2.1.1. Spinal stenosis. Morphological anomalies of the spinal canal and the vertebrae are already present at birth and progressive narrowing of spinal canal in association with other factors leads to "spinal stenosis" (SS).

Symptomatic SS, with the compression of the spinal cord or nerve roots, occurs in 20%–50% of patients with ACH in adolescence or adulthood (Fano et al., 2022). The upper lumbar segment is most often affected (Chen et al., 2017). Characteristic symptoms of SS are back pain and/or radiating pain into the buttocks or the legs, exacerbated by prolonged walking, standing or lumbar extension, and resulting in decreased walking distance (Pauli, 2019; Fredwall et al., 2020; Schkrohowsky et al., 2007).

The delayed occurrence of clinical symptoms related to narrow thoracho-lumbar canal may be explained by the pathogenetic role of acquired cofactors as prolapse of intervertebral disks, hypertrophy of the ligamentum flavum, and for degenerative spondyloarthrosis (Fortuna et al., 1989; Ain et al., 2010). This condition rarely develops before the age of 15 years (Chen et al., 2017) and the prevalence of SS is known to increase with age (Fredwall et al., 2020).

There are currently no widely accepted quantitative criteria for the diagnosis of SS in the general population or in individuals with ACH (Suri et al., 2010). The North American Spine Society guidelines suggest applying a combination of characteristic symptoms and SS reports to establish the diagnosis of SS (Kreiner et al., 2013). In this regard, Calandrelli et al. recently suggested a reduction of upper lumbar canal width by more than 60% to be the critical point of SS, capable of predicting the development of neurological signs and symptoms in ACH adulthood (Calandrelli et al., 2022). SS is often initially managed using nonsurgical approaches (e.g., utilizing analgesics, non-steroidal anti--inflammatory drugs, epidural steroid injections, and physical therapy) (Comer et al., 2022). Surgical decompression is indicated when pain cannot be controlled, ambulation is severely compromised, or bowel/-bladder dysfunction occurs (Hoover-Fong et al., 2021; Baca et al., 2010; Hong et al., 2011b).

3.2.1.2. Cervical medullary compression. Ventral and dorsal cervical

Table 2
Description of included assessment instruments according to ages in the ACH population.

Instrument	Ages	Domain assessed	Scoring system
ACEM-s (Pfeiffer et al., 2021)	Infancy	Physical symptoms/ Complications including Pain	5-point Likert-type scale
CHAQ ObsRo completion (Singh et al., 1994; Klepper, 2011; Aldhouse et al., 2022)	Infancy	Physical functioning and Pain	0–100 VAS
CHAQ PRO completion (Singh et al., 1994; Klepper, 2011; Aldhouse et al., 2022)	Adolescence	Physical functioning and Pain	0–100 VAS
STEMS (Ireland et al., 2021)	All ages	Mobility aids usage and Pain	Combination of two number (1–5) and letter (A-C) Likert-type response scale
MMPQ-SF (Iwasaki et al., 2013)	Adolescence	Orthodontic pain	4-point Likert scale
NOSF-MISS (Fredheim et al., 2008)	Adulthood	Pain intensity	11 point (0–10) NRS
BPI (Cleeland and Ryan, 1994)	Adulthood	Intensity of pain Interference of pain in the patient's life	11 point (0–10) NRS

ACEM-Symptom: Achondroplasia Child Experience Measures Symptom scale; ACH: achondroplasia; BPI: Brief Pain Inventory; CHAQ: Childhood Health Assessment Questionnaire; MMPQ-SF: Modified Mc Gill Pain Questionnaire Short Form; NRS: numeric rating scale; STEMS: Screening Tool for Everyday Mobility and Symptoms; VAS: Visual analogue scale.

Table 3
List of the main causes of pain according to ages in the ACH population.

Ages	Reported causes of pain
Infancy	Cervical medullary compression (Ryken and Menezes, 1994) Thoracolumbar kyphosis (Bodensteiner, 2019; Engberts et al., 2012) Hydrocephalus (Kubota et al., 2020; King et al., 2009) Obstructive apnea (Pauli, 2019; Collins and Choi, 2007; Sisk et al., 1999; Loh et al., 1999; Zaffanello et al., 2017) Genu varum (Brooks et al., 2016; Lee et al., 2007) Treatments for small stature (NiMhurchadha et al., 2023; Donaldson et al., 2015; Kim et al., 2014; Correll, 1991; Kashiwagi et al., 2001; Lavini et al., 1990; Hosny, 2020; Al Harby, 2009)
Adolescence	Spinal stenosis (Fredwall et al., 2020; Singh et al., 1994; Chen et al., 2017) Cervical spinal cord infarction (NiMhurchadha et al., 2023) Genu varum (Brooks et al., 2016; Lee et al., 2007; Llerena et al., 2022; https://posna.org/physician-education/study-guide/achondroplasia; Kurian et al., 2019) Discoid lateral meniscus [55,56] Degenerative osteoarthritis (Karpagam et al., 2005; Ain et al., 2010; van den Broek et al., 2017a; Dhiman et al., 2017; Pfeiffer et al., 2022; Hunter et al., 1998) Treatments for small stature (NiMhurchadha et al., 2023; Donaldson et al., 2015; Kim et al., 2014; Correll, 1991; Kashiwagi et al., 2001; Lavini et al., 1990; Hosny, 2020; Al Harby, 2009)
Adulthood	Spinal stenosis (Fredwall et al., 2020; Fano et al., 2022; Chen et al., 2017) Obesity (Ceroni et al., 2018) Degenerative osteoarthritis (Karpagam et al., 2005; Ain et al., 2010; van den Broek et al., 2017a; Dhiman et al., 2017; Pfeiffer et al., 2022; Hunter et al., 1998) Ankylosis spondylitis (Randolph et al., 1988) Caesarean delivery (Melekoglu et al., 2017) Inguinal herniation (Mantle and Kingsnorth, 2003)

Table 4
List of the main signs and symptoms of pain according to pain site.

	Site	Cause	Signs and symptoms	Management strategy
	Brain	Hydrocephalus	Headache, Lethargy, Irritability Anterior fontanelle bulging	Ventriculoperitoneal shunts (Kubota et al., 2020; King et al., 2009)
	Upper airway	OSA	Headache	Multilevel surgical interventions (Tenconi et al., 2017; Dehlink and Tan, 2016) Continuous positive airway pressure (CPAP) (Tenconi et al., 2017; Dehlink and Tan, 2016)
	Temporomandibular joint	Ankylosing spondylitis	Local pain	Pharmacological approaches (Randolph et al., 1988)
	Spinal cervical region	Cervical medullary compression	Hypotonia (infancy) Ataxia Apnoea	Surgical decompression (Ryken and Menezes, 1994)
	Spinal lumbar region	Lumbar spinal stenosis	Back pain Buttocks and leg pain Incontinence	Surgical decompression (Hoover-Fong et al., 2021) Pharmacological approaches (Comer et al., 2022)
	Spinal thoracolumbar region	Thoracolumbar kyphosis	Back pain Bilateral leg pain Claudication	Thoracolumbar orthosis (Misra and Morgan, 2003) Pharmacological approaches (Comer et al., 2022)
	Knee	Genu varum Discoid lateral meniscus Degenerative osteoarthritis Obesity	Local pain Instability	Physiotherapy (Kim et al., 2011) Orthosis (Kurian et al., 2019; Hoernschemeyer et al., 2016; Atanda et al., 2016; Zmerly et al., 2021; van den Broek et al., 2017b; Sewell et al., 2014) Surgical treatment (Kurian et al., 2019; Hoernschemeyer et al., 2016; Atanda et al., 2016; Zmerly et al., 2021; van den Broek et al., 2017b; Sewell et al., 2014)
	Limb	Small stature treatments	Pain due to injections Pain due to limb lengthening surgery	Pharmacological approaches (Lavini et al., 1990; Hosny, 2020; Al Harby, 2009)

medullary compression with or without basilar invagination and anterior pons indentation with upward brain stem displacement are frequent manifestations (Ryken and Menezes, 1994). Occipital-cervical pain is one of the symptoms, along with ataxia, incontinence and apnea. Symptoms are nonspecific in infancy, and young ACH patients with foramen magnum stenosis may only manifest hypotonia.

Surgery may reveal a marked dorsal and paramesial overgrowth of the rim of the foramen magnum, with thickening and invagination of the posterior atlantal arch and a dense fibrotic epidural band resulting in dorsal cervical medullary compression (Ryken and Menezes, 1994). Stanfontadard assessment comprises the imaging of the craniocervical junction along with neurologic examination and polysomnography (Pauli, 2019). Cervical medullary compression can be successfully treated with dorsal decompression of the craniovertebral junction (Ryken and Menezes, 1994).

3.2.1.3. Hydrocephalus. Headache can be a symptom of true hydrocephalus, namely ventricular enlargement accompanied by neurological symptoms. Other symptoms include lethargy, irritability or anterior fontanelle bulging. True hydrocephalus in ACH is rare and less than 4.3% of ACH patients require ventriculoperitoneal shunts (Kubota et al., 2020; King et al., 2009).

3.2.1.4. Headaches and obstructive sleep apnea. Obstructive sleep apnea (OSA) occurs in more than 30% of ACH individuals and can increase at any age (Collins and Choi, 2007). In children, one of the markers for OSA is morning headaches accompanied by other features of significance, including glottal stops and clinically observable apnea (Pauli, 2019; Sisk et al., 1999). These headaches are of brief duration, and their occurrence and severity increase with increasing OSA severity (Loh et al., 1999). ACH children have significant craniofacial and airway abnormalities that exacerbate OSA by restricting the naso-oropharyngeal cavity, that are not addressed by common upper airway surgery (Zaffanello et al., 2017). Hypotonia, thoracic kyphosis and pectus excavatum can further negatively contribute to OSA (Cleeland and Ryan, 1994). Drug-induced sleep endoscopy may be an appropriate first step to evaluate for multilevel collapse and surgical planning (Booth et al., 2020).

Previous reported findings suggest that adenoidectomy alone may be an ineffective first-line intervention for the ACH population, due to the need for further operations (Booth et al., 2020; Waters et al., 1996; Tenconi et al., 2017). Although it remains unclear which operations are most appropriate and management recommendations for OSA in ACH are still lacking, resolution of OSA after multilevel surgical interventions have been reported in multiple studies (Tenconi et al., 2017).

Due to the poor treatment outcomes and persistent nature of the OSA in this population and according to the current guidelines, postoperative polysomnography should be pursued following sleep surgery for children with ACH (Dehlink and Tan, 2016). Caregivers should additionally be counseled about the need for long term clinical monitoring (Dehlink and Tan, 2016).

3.2.2. Skeletal manifestations

3.2.2.1. Thoracolumbar kyphosis. Thoracolumbar kyphosis (TLK) is one of the most frequent skeletal manifestations in patients with ACH. TLK is found in nearly all ACH infants (Bodensteiner, 2019), although the natural history of TLK is unknown (Engberts et al., 2012). In combination with the narrow spinal canal, this kyphosis can easily result in compression of the medulla and/or the conus medullae. It produces low back pain and bilateral leg pain. For instance, Miyazaki et al. reported a 61-year-old ACH patient with low back pain, radiculopathy and neurogenic claudication. Plain radiographs revealed a high-grade thoracolumbar kyphotic deformity with diffuse degenerative changes in the lumbar spine (Miyazaki et al., 2017). Thoracolumbosacral orthosis is recommended in selected cases (Misra and Morgan, 2003). Specifically, thoracolumbosacral orthosis must be tailored to the individual and is indicated in case of appearance of anterior vertebral wedging, vertebral offset during the observation period or progression of the kyphosis to greater than or equal to 30°. Thoracolumbosacral orthosis must be tailored to the individual and modified as the correction proceeds. It is aimed at treating deformity and symptomatic improvement of thoracolumbar pain. (Misra and Morgan, 2003).

3.2.2.2. Genu varum. Genu varum is a prevalent orthopedic concern in

both children and adults with ACH (Brooks et al., 2016). It can be asymptomatic or may cause knee pain and instability compromising physical function (Ain et al., 2010). Particularly, knee and ankle musculoskeletal pain affects 70% of ACH children aged 4–10 years (Lee et al., 2007). Metaphyseal irregularities and joint laxity contribute to a common genu varum deformity and pain is caused by hypermobility rather than deformity (Llerena et al., 2022). According to the Pediatric Orthopaedic Society of North America, indications for surgical intervention include the presence of symptomatic deformity, lateral thrust, and/or severe malalignment (https://posna.org/physician-education/-study-guide/achondroplasia). Specifically, Lee et al. suggest early epiphysiodesis or partial excisional osteotomy of the proximal fibula to minimise the progression of the genu varum deformity in severe cases and monofocal or bifocal osteotomy before skeletal maturity at the proximal tibia and/or distal tibia when there is symptomatic malalignment (Lee et al., 2007). Mid-term results of valgus tibial and fibular osteotomies have been reported to be successful in the ACH population. The beneficial effects of fibular head resection and fibular epiphyseodesis surgery approach have not been proven yet (Kurian et al., 2019).

3.2.2.3. Discoid lateral meniscus. Knee pain in ACH patients is typically investigated for less uncommon causes such as genu varum, ligamentous instability, and neurogenic claudication. Although its occurrence in ACH population is still unknown, discoid lateral meniscus may also be added to the differential diagnosis to better understand the common complaints of leg pain.

A comprehensive history and physical examination, in combination with magnetic resonance imaging, can help making the diagnosis. Treatment with arthroscopic debridement, saucerization of the meniscus, and repair for unstable injuries has yielded positive outcomes (Hoernschemeyer et al., 2016; Atanda et al., 2016).

3.2.2.4. Degenerative osteoarthritis. Skeletal dysplasia in ACH can affect all body joints including the shoulder and knee and is prone to develop to degenerative osteoarthritis (OA). This may cause pain and mobility problems at young age, with consequent limit in practice sports or in engaging daily activities. Neurological signs in the arm, shoulder and neck have a prevalence of ~15% (Karpagam et al., 2005; Ain et al., 2010; van den Broek et al., 2017a; Dhiman et al., 2017; Pfeiffer et al., 2022; Hunter et al., 1998). Both conservative treatments, including pain medication and steroidal injections and surgery have been reported (Zmerly et al., 2021; van den Broek et al., 2017b). Although challenging, long-term satisfactory results after reverse shoulder (van den Broek et al., 2017b; Sewell et al., 2014) and knee arthroplasty accompanied by physiotherapy in terms of pain relief and functional improvement have been reported (Kim et al., 2011).

3.2.2.5. Ankylosing spondylitis. Adults with ACH are as susceptible to other disorders as the general population. Specifically, a case of ankylosing spondylitis (AS) has been reported in a 41-year-old man. Temporomandibular joint pain and rigidity of the entire spine were experienced with images showing a complete fusion of the sacroiliac joints and fusion of the cervical vertebral bodies and apophyseal joints (Randolph et al., 1988). Inflammation and pathological new bone formation are the two most important pathological features of AS and therapies are still in the initial stage (Long et al., 2023).

3.2.2.6. Low bone mineral density. The majority of the reported ACH children and adults have below average bone mineral density (BMD) (Shirazi et al., 2017; Matsushita et al., 2016; Arita et al., 2013), likely due to the smaller achondroplasic limb length (Sims et al., 2019). BMD increases bone fragility and can lead to back pain and vertebral fractures (Matsushita et al., 2016; Sims et al., 2019). Therefore, BMD should carefully be monitored. Results on the positive effect of growth hormone therapy on BMD are not yet conclusive (Matsushita et al., 2016).

3.2.3. Small stature treatments

Two possible treatment approaches, namely pharmacological and surgical, exist for small stature in ACH patients. In the first scenario, the only pharmacologic therapy approved to date to increase linear growth is the C-Type Natriuretic Peptide analogue (called Vosoritide) (Paton, 2022; Duggan, 2021). If chosen, a recognized disadvantage will be daily subcutaneous injections with possible site pain (Pauli, 2019; NiMhurchadha et al., 2023).

Alternatively, extended limb lengthening is offered as an option for height enhancement.

A variety of techniques have been used for limb lengthening, generally through osteotomies and gradual distraction using external fixators (Donaldson et al., 2015). To note, limb lengthening in patients with ACH is controversial. Although psychosocial benefits of achieving functional height (Maghnie et al., 2023; Kim et al., 2014), risks for disability secondary to complications have to be accounted, including transient pain (Correll, 1991; Kashiwagi et al., 2001; Lavini et al., 1990). One complication can be premature consolidation of the regenerated bone due to irregular distraction of the osteotomy, especially in children. The treatment may be re-osteotomy or continuation of the distraction until the building force exceeds the resistance of the consolidation and the osteotomy opens once again, with severe pain (Hosny, 2020). Another complication reported inducing pain is sciatic nerve neuropraxia (Al Harby, 2009). According to Paley et al. the 4-segment lengthening offer advantages over 2-segment lengthening, reducing pain, risk of nerve injury and muscle contractures (Paley, 2021). Each patient is unique in his or her perception of pain allowing for many combinations of analgesic strategies. Multimodal pain management therapy should be used whenever possible (Garimella and Cellini, 2013). Anti-inflammatory drugs can be used to relieve mild to moderate pain (Fendrick and Greenberg, 2009). The recent metanalysis of Ghaddaf et al. found that adjuvant Botulinum toxin type A injection confers a significant improvement in pain during surgical limb lengthening and/or deformity without increasing the risk of adverse events (Ghaddaf et al., 2023).

3.2.4. Others

3.2.4.1. Obesity. Obesity is highly prevalent in the ACH population with potential neurologic and orthopedic sequela. Precisely, obesity further aggravates SS, sleep apnea and exacerbates joint pain, particularly knees (Ceroni et al., 2018). It results from a problem of energy balance due to excessive caloric intake and lack of physical activity due to the multiple specific challenges of the condition (Saint-Laurent et al., 2019). Obesity first of all requires prevention as well as an early clinical management (Comer et al., 2022; Hoover-Fong et al., 2021).

3.2.4.2. Postoperative pain. Although neglected, it is worth considering that patients may experience acute pain as a sequela after operations (De Benedittis et al., 1996). Most patients with ACH are eligible during their entire lifespan for otolaryngology or neurosurgery due to the striking clinical features of this condition. Moreover, since caesarean section for ACH expectant mothers is inevitable due to cephalopelvic disproportion, discomfort or pain in the first few days after delivery should be considered (Melekoglu et al., 2017).

3.2.4.3. Anecdotal cases associated with pain. Non-traumatic cervical spinal cord infarction with resulting quadriplegia with no apparent cause has been reported by Wieting et al. in a 12-year-old boy with ACH. The patient experienced a sudden onset of pain between his shoulder blades and in his left shoulder during running. A quickly development of numbness and weakness of legs and right arm was reported. Conservative was the choice, with methylprednisolone administration followed by comprehensive program of physical and occupational therapy (Wieting and Krach, 1994).

An unusual cause of back pain lower back pain radiating to left loin cause by inguinal herniation involving the ureter in a single ACH case (47-year-old man) have been reported by Mantle et al. (Mantle and Kingsnorth, 2003).

3.3. Ages

3.3.1. Pediatric age

In the Aldhouse et al. qualitative study on child experience of ACH, pain was found to be the most frequently mentioned symptom affecting physical functioning (Pfeiffer et al., 2021). Moreover, in the same study, children named pain along with difficulty reaching, short height and short limbs amongst the most bothersome aspects of ACH (Pfeiffer et al., 2021). The Maghnie et al. multinational observational study showed that ACH children experience a lower level of QoL if compared to their average statured peers also because of pain (Maghnie et al., 2023).

During childhood, main reported causes of pain are cervical medullary compression (Ryken and Menezes, 1994), thoracolumbar kyphosis (Bodensteiner, 2019; Engberts et al., 2012), hydrocephalus (Kubota et al., 2020; King et al., 2009), obstructive apnea (Pauli, 2019; Collins and Choi, 2007; Sisk et al., 1999; Loh et al., 1999; Zaffanello et al., 2017), genu varum (Brooks et al., 2016; Lee et al., 2007) and treatments for small stature (NiMhurchadha et al., 2023; Donaldson et al., 2015; Kim et al., 2014; Correll, 1991; Kashiwagi et al., 2001; Lavini et al., 1990; Hosny, 2020; Al Harby, 2009).

In several studies shoulder and knee pain was typically reported during infancy, while knee pain was generally reported around 5–6 years of age (Pauli, 2019; van den Broek et al., 2017a; van den Broek et al., 2017b). The study of Hunter et al. conducted on children showed a clear increase with age in the prevalence of back and leg pain with a higher prevalence of pain in the 5-to-18 years age-group versus the youngest (from 2 to 5 years) age group (Hunter et al., 1998).

3.3.2. Adolescence

In the Maghnie et al. multinational observational study, 58.6% of 41 ACH adolescents reported at least one pain site and 32.9% reported $\geq$3 pain sites with pain intensity ranging from little to medium. The knees and lower spine were the areas where discomfort was felt most frequently. Patients without limb lengthening experienced a greater mean number of pain sites and a slightly higher overall pain score (Maghnie et al., 2023). Moreover, Pfeiffer et al. found that 90% of the 19 adolescents participating in the study experienced general pain (Pfeiffer et al., 2022).

3.3.3. Adulthood

Recent studies conducted in multiple countries revealed common findings regarding the high prevalence of chronic pain in ACH adults. Specifically, 79.4% of Americans (Dhiman et al., 2017), and 70% of Norwegian suffer from moderate to severe chronic pain (Fredwall et al., 2020). Females report generally more pain than males (Alade et al., 2013), likewise the general population, although reasons of gender differences in pain experience remain still unclear (Bartley and Fillingim, 2013). Precisely, in the 3rd to 4th decade of life symptoms of SS usually occur (Dhiman et al., 2017). To note, although the high frequency of chronic pain, it has been observed that few American patients require a pain consultation, due to health insurance coverage of physician visits (Dhiman et al., 2017). In the Maghnie et al. study, 70.3% of 72 adults reported at least one pain site and 41.9% reported $\geq$3 pain sites with pain intensity ranging from little to medium. The knees and lower spine were the most common pain site locations. Adult patients who had limb lengthening surgeries reported greater severity and intensity scores (indicating worse pain) than those who had not (Maghnie et al., 2023).

4. Discussion

The Global Burden of Disease Study (2016) reaffirmed that the high importance of pain and pain-related diseases is the leading cause of disability and disease burden globally (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Similar to many rare diseases prone to chronic pain, the ACH community experiences higher rates of pain throughout the lifespan than their counterparts in the general population (Sieberg et al., 2021; Leoni et al., 2019).

Pain should be considered as a multifactorial problem and is best managed in individuals with ACH through a multidisciplinary approach including neurosurgeons, orthopaedic surgeons, general physicians, pain management specialists, physiotherapists, occupational therapists, psychologists and dieticians (Savarirayan et al., 2022). Neurological issues, including SS, cervical medullary compression, hydrocephalus and headaches caused by obstructive sleep apnea are frequently reported causes of pian and discomfort in the ACH population. These issues are also frequently associated with the common skeletal manifestations of ACH syndrome, namely thoracolumbar kyphosis, genu varum, discoid lateral meniscus, degenerative osteoarthritis, ankylosing spondylitis, osteoporosis and low bone mineral density. Moreover, pain can be exacerbated by obesity and lengthening interventions. Althought the pain-inducing causes have been clearly identified, shared guidelines for the assessment and management of pain are missing. For example, a widely accepted quantitative criteria for the diagnosis of SS and management recommendations for OSA in ACH are still lacking. Moreover, a review on post-operative limb lengthening pain management in the ACH population and any contraindications is needed.

All these aspects can make activity of daily living quite challenging for people with ACH.

In terms of quality of life (QOL), people with ACH can experience a lower level of QOL (Maghnie et al., 2023; Fredwall et al., 2020). Specifically, pain along with difficulty reaching and short height is one of the three most bothersome aspects of ACH (Aldhouse et al., 2022).

In terms of functional disability, pain affects also mobility performance across different settings (home, school/work and community) (Ireland et al., 2021). The maximum walking time is therefore often decreased. Among children, pain limits physical activities, social participation and classroom time (McGraw et al., 2022). Several cases are reported in which due to pain ACH adults stopped working or changed their type of work (Cleeland and Ryan, 1994). In terms of mental wellbeing, chronic pain has been linked to depression in a number of studies (Elliott et al., 2003; Yonko et al., 2021). Specifically, in the Ain et al. study, those with back pain associated with proximal and/or distal leg pain had more psychological distress (Fortuna et al., 1989). In terms of public health, the consequences of chronic pain lead to an increased healthcare utilization (Ain et al., 2010).

Given all these aspects and since pain is a commonly reported burden in people with ACH across the lifespan, it should be carefully monitored and assessed at every medical check-up (Savarirayan et al., 2019; McDonald and De Jesus, 2023). Additionally, a major focus is the implementation of management plans of pain in undertreated patients with ACH is warranted to improve their physical function (Maghnie et al., 2023; Alade et al., 2013).

5. Strengths and limitations

The present review systematically addressed the key determinants of pain in the ACH population. Strength of this review is the use of a rigorous and stringent methodology. In terms of publication bias, some potentially relevant articles may have been excluded due to language restrictions. Moreover, the methodological heterogeneity and limited number of included studies did not allow further statistical analysis.

6. Conclusions

Pain is by no means negligible and its systematic assessment in patients with ACH contributes to the optimal management of physical symptoms and their psychosocial correlates, which could enhance QoL.

In the future, multicentre clinical studies on pain as the primary endpoint should be conducted and the prevalence of the main causes of pain, including ligamentous laxity, should be further analysed. It is also essential to develop therapeutic interventions to provide more appropriate care. Recognizing the multiple determinants of acute and chronic pain in patients with ACH may enable physicians to better understand and manage this burden, particularly with the advent of new drugs that may change some of the known features of ACH.

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Authors contribution

Conceptualization, R.O., E.S., and G.Z.; Writing, review and editing: R.O., M.M and G.Z.; Supervision: M.F.B., C.L., V.G., D.R., C.D., E.M.K, D. M.R., O.P., L.M., M.P., M.V.G., A.S., A.A. All authors have read and agreed to the published version of the manuscript.

Availability of data and material

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Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Declaration of competing interest

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Data availability

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Appendix A. Supplementary data

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References

Ain, M.C., Abdullah, M.A., Ting, B.L., Skolasky, R.L., Carlisle, E.S., Schkrohowsky, J.G., Rigamonti, D., 2010. Progression of low back and lower extremity pain in a cohort of patients with achondroplasia. J. Neurosurg. Spine 13 (3), 335–340. https://doi.org/10.3171/2010.3.SPINE09629.

Al Harby, S.W., 2009. Reversible femoral distraction-induced sciatic neuropraxia in an achondroplasia patient. Journal of Taibah University Medical Sciences 4 (2), 174–177. https://doi.org/10.1016/s1658-3612(09)70107-6.

Alade, Y., Tunkel, D., Schulze, K., McGready, J., Jallo, G., Ain, M., Yost, T., Hoover-Fong, J., 2013. Cross-sectional assessment of pain and physical function in skeletal dysplasia patients. Clin. Genet. 84 (3), 237–243. https://doi.org/10.1111/cge.12045.

Aldhouse, N.V.J., Kitchen, H., Johnson, C., Marshall, C., Pegram, H., Pease, S., Collins, S., Baker, C.L., Beaverson, K., Crews, C., Massey, J., Wyrwich, K.W., 2022. Key measurement concepts and appropriate clinical outcome assessments in pediatric achondroplasia clinical trials. Orphanet J. Rare Dis. 17 (1), 182. https://doi.org/10.1186/s13023-022-02333-6.

Arita, E.S., Pippa, M.G., Marcucci, M., Cardoso, R., Cortes, A.R., Watanabe, P.C., Oliveira, J.X., 2013. Assessment of osteoporotic alterations in achondroplastic patients: a case series. Clin. Rheumatol. 32 (3), 399–402. https://doi.org/10.1007/s10067-012-2126-x.

Atanda Jr., A., Wallace, M., Bober, M.B., Mackenzie, W., 2016. Arthroscopic treatment of discoid lateral meniscus tears in children with achondroplasia. Journal of pediatric orthopedics 36 (5), e55–e58. https://doi.org/10.1097/BPO.0000000000000622.

Baca, K.E., Abdullah, M.A., Ting, B.L., Schkrohowsky, J.G., Hoernschemeyer, D.G., Carson, B.S., Ain, M.C., 2010. Surgical decompression for lumbar stenosis in pediatric achondroplasia. Journal of pediatric orthopedics 30 (5), 449–454. https://doi.org/10.1097/BPO.0b013e3181e00c66.

Bartley, E.J., Fillingim, R.B., 2013. Sex differences in pain: a brief review of clinical and experimental findings. Br. J. Anaesth. 111 (1), 52–58. https://doi.org/10.1093/bja/aet127.

Bellus, G.A., Hefferon, T.W., Ortiz de Luna, R.I., Hecht, J.T., Horton, W.A., Machado, M., Kaitila, I., McIntosh, I., Francomano, C.A., 1995. Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am. J. Hum. Genet. 56 (2), 368–373.

Bodensteiner, J.B., 2019. Neurological manifestations of achondroplasia. Curr. Neurol. Neurosci. Rep. 19 (12), 105. https://doi.org/10.1007/s11910-019-1008-x.

Booth, K.L., Levy, D.A., White, D.R., Meier, J.D., Pecha, P.P., 2020. Management of obstructive sleep apnea in children with achondroplasia: outcomes of surgical interventions. Int. J. Pediatr. Otorhinolaryngol. 138, 110332 https://doi.org/10.1016/j.ijporl.2020.110332.

Brook, A.H., Winter, G.B., 1970. Dental anomalies in association with achondroplasia. Report of two cases. Br. Dent. J. 129 (11), 519–520. https://doi.org/10.1038/sj.bdj.4802610.

Brooks, J.T., Bernholt, D.L., Tran, K.V., Ain, M.C., 2016. The tibial slope in patients with achondroplasia: its characterization and possible role in genu recurvatum development. Journal of pediatric orthopedics 36 (4), 349–354. https://doi.org/10.1097/BPO.0000000000000458.

Calandrelli, R., Pilato, F., Massimi, L., Onesimo, R., D'Apolito, G., Tenore, L., Leoni, C., Zampino, G., Colosimo, C., 2022. Thoracolumbar stenosis and neurologic symptoms: quantitative MRI in achondroplasia. J. Neuroimaging : official journal of the American Society of Neuroimaging 32 (5), 884–893. https://doi.org/10.1111/jon.13015.

Celenk, P., Arici, S., Celenk, C., 2003. Oral findings in a typical case of achondroplasia. J. Int. Med. Res. 31 (3), 236–238. https://doi.org/10.1177/147323000303100311.

Ceroni, J.R.M., Soares, D.C.Q., Testai, L.C., Kawahira, R.S.H., Yamamoto, G.L., Sugayama, S.M.M., Oliveira, L.A.N., Bertola, D.R., Kim, C.A., 2018. Natural history of 39 patients with Achondroplasia. Clinics 73, e324. https://doi.org/10.6061/clinics/2018/e324.

Chen, J., Yu, C., Zhao, Y., Niu, Y., Zhang, L., Yu, Y., Wu, J., He, J., 2017. A novel non-invasive detection method for the FGFR3 gene mutation in maternal plasma for a fetal achondroplasia diagnosis based on signal amplification by hemin-MOFs/PtNPs. Biosens. Bioelectron. 91, 892–899. https://doi.org/10.1016/j.bios.2016.10.067.

Cleeland, C.S., Ryan, K.M., 1994. Pain assessment: global use of the brief pain inventory. Ann. Acad. Med. Singapore 23 (2), 129–138.

Collins, W.O., Choi, S.S., 2007. Otolaryngologic manifestations of achondroplasia. Arch. Otolaryngol. Head Neck Surg. 133 (3), 237–244. https://doi.org/10.1001/archotol.133.3.237.

Comer, C., Ammendolia, C., Battié, M.C., Bussières, A., Fairbank, J., Haig, A., Melloh, M., Redmond, A., Schneider, M.J., Standaert, C.J., Tomkins-Lane, C., Williamson, E., Wong, A.Y., 2022. Consensus on a standardised treatment pathway algorithm for lumbar spinal stenosis: an international Delphi study. BMC Muscoskel. Disord. 23 (1), 550. https://doi.org/10.1186/s12891-022-05485-5.

Correll, J., 1991. Surgical correction of short stature in skeletal dysplasias. Acta Paediatr. Scand. Suppl. 377, 143–148. https://doi.org/10.1111/apa.1991.80.s377.143.

De Benedittis, G., Lorenzetti, A., Migliore, M., Spagnoli, D., Tiberio, F., Villani, R.M., 1996. Postoperative pain in neurosurgery: a pilot study in brain surgery. Neurosurgery 38 (3), 466–470. https://doi.org/10.1097/00006123-199603000-00008.

Dehlink, E., Tan, H.L., 2016. Update on paediatric obstructive sleep apnoea. J. Thorac. Dis. 8 (2), 224–235. https://doi.org/10.3978/j.issn.2072-1439.2015.12.04.

Dhiman, N., Albaghdadi, A., Zogg, C.K., Sharma, M., Hoover-Fong, J.E., Ain, M.C., Haider, A.H., 2017. Factors associated with health-related quality of life (HRQOL) in adults with short stature skeletal dysplasias. Qual. Life Res. : an international journal of quality of life aspects of treatment, care and rehabilitation 26 (5), 1337–1348. https://doi.org/10.1007/s11136-016-1455-7.

Donaldson, J., Aftab, S., Bradish, C., 2015. Achondroplasia and limb lengthening: results in a UK cohort and review of the literature. J. Orthop. 12 (1), 31–34. https://doi.org/10.1016/j.jor.2015.01.001.

Duggan, S., 2021. Vosoritide: first approval. Drugs 81 (17), 2057–2062. https://doi.org/10.1007/s40265-021-01623-w.
Elliott, T.E., Renier, C.M., Palcher, J.A., 2003. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain medicine (Malden, Mass 4 (4), 331–339. https://doi.org/10.1111/j.1526-4637.2003.03040.x.
Engberts, A.C., Jacobs, W.C., Castelijns, S.J., Castelein, R.M., Vleggeert-Lankamp, C.L., 2012. The prevalence of thoracolumbar kyphosis in achondroplasia: a systematic review. Journal of children's orthopaedics 6 (1), 69–73. https://doi.org/10.1007/s11832-011-0378-7.
Fano, V., Kim, C.A., Rosselli, P., Dib, R.E., Shediac, R., Magalhães, T., Mesojedovas, D., Llerena Jr., J., 2022. Impact of achondroplasia on Latin American patients: a systematic review and meta-analysis of observational studies. Orphanet J. Rare Dis. 17 (1), 4. https://doi.org/10.1186/s13023-021-02142-3.
Fendrick, A.M., Greenberg, B.P., 2009. A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. Osteopathic medicine and primary care 3, 1. https://doi.org/10.1186/1750-4732-3-1.
Fortuna, A., Ferrante, L., Acqui, M., Santoro, A., Mastronardi, L., 1989. Narrowing of thoraco-lumbar spinal canal in achondroplasia. J. Neurosurg. Sci. 33 (2), 185–196.
Fredheim, O.M., Borchgrevink, P.C., Landmark, T., Schjødt, B., Breivik, H., 2008. Et nytt skjema for kartlegging av smerter [A new schedule for the inventory of pain]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke 128 (18), 2082–2084.
Fredwall, S.O., Steen, U., de Vries, O., Rustad, C.F., Eggesbø, H.B., Weedon-Fekjær, H., Lidal, I.B., Savarirayan, R., Månum, G., 2020. High prevalence of symptomatic spinal stenosis in Norwegian adults with achondroplasia: a population-based study. Orphanet J. Rare Dis. 15 (1), 123. https://doi.org/10.1186/s13023-020-01397-6.
Garimella, V., Cellini, C., 2013. Postoperative pain control. Clin. Colon Rectal Surg. 26 (3), 191–196. https://doi.org/10.1055/s-0033-1351138.
GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (London, England) 390 (10100), 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2.
GBD 2019 Diseases and Injuries Collaborators, 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England) 396 (10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9.
Ghaddaf, A.A., Alsharef, J.F., Alomari, M.S., Al Qurashi, A.A., Abdulhamid, A.S., Alshehri, M.S., Alosaimi, M., 2023. Botulinum toxin type A for lower limb lengthening and deformity correction: a systematic review and meta-analysis. J. Orthop. Sci. : official journal of the Japanese Orthopaedic Association 28 (4), 806–813. https://doi.org/10.1016/j.jos.2022.04.011.
Hoernschemeyer, D.G., Atanda Jr., A., Dean-Davis, E., Gupta, S.K., 2016. Discoid meniscus associated with achondroplasia. Orthopedics 39 (3), e498–e503. https://doi.org/10.3928/01477447-20160427-06.
Hong, J.Y., Suh, S.W., Modi, H.N., Park, J.W., Park, J.H., 2011a. Analysis of sagittal spinopelvic parameters in achondroplasia. Spine 36 (18), E1233–E1239. https://doi.org/10.1097/BRS.0b013e3182063e89.
Hong, J.Y., Suh, S.W., Modi, H.N., Park, J.W., Park, J.H., 2011b. Analysis of sagittal spinopelvic parameters in achondroplasia. Spine 36 (18), E1233–E1239. https://doi.org/10.1097/BRS.0b013e3182063e89.
Hoover-Fong, J.E., Schulze, K.J., Alade, A.Y., Bober, M.B., Gough, E., Hashmi, S.S., Hecht, J.T., Legare, J.M., Little, M.E., Modaff, P., Pauli, R.M., Rodriguez-Buritica, D. F., Serna, M.E., Smid, C., Liu, C., McGready, J., 2021. Growth in achondroplasia including stature, weight, weight-for-height and head circumference from CLARITY: achondroplasia natural history study-a multi-center retrospective cohort study of achondroplasia in the US. Orphanet J. Rare Dis. 16 (1), 522. https://doi.org/10.1186/s13023-021-02141-4.
Hosny, G.A., 2020. Limb lengthening history, evolution, complications and current concepts. J. Orthop. Traumatol. : official journal of the Italian Society of Orthopaedics and Traumatology 21 (1), 3. https://doi.org/10.1186/s10195-019-0541-3.
https://posna.org/physician-education/study-guide/achondroplasia.
Hunter, A.G., Bankier, A., Rogers, J.G., Sillence, D., Scott Jr., C.I., 1998. Medical complications of achondroplasia: a multicentre patient review. J. Med. Genet. 35 (9), 705–712. https://doi.org/10.1136/jmg.35.9.705.
Ireland, P.J., McGill, J., Zankl, A., Ware, R.S., Pacey, V., Ault, J., Savarirayan, R., Sillence, D., Thompson, E.M., Townshend, S., Johnston, L.M., 2011. Functional performance in young Australian children with achondroplasia. Dev. Med. Child Neurol. 53 (10), 944–950. https://doi.org/10.1111/j.1469-8749.2011.04050.x.
Ireland, P.J., Savarirayan, R., Pocovi, T., Tate, T., Coussens, M., Tofts, L., Munns, C., Pacey, V., 2021. Development of the screening tool for everyday mobility and symptoms (STEMS) for skeletal dysplasia. Orphanet J. Rare Dis. 16 (1), 40. https://doi.org/10.1186/s13023-021-01681-z.
Iwasaki, L.R., Freytag, L.E., Schumacher, C.A., Walker, M.P., Williams, K.B., 2013. Validation of a modified McGill Pain Questionnaire for orthodontic patients. Angle Orthod. 83 (5), 906–912. https://doi.org/10.2319/110812-859.1.
Karpagam, S., Rabin, K., George, M., Santhosh, K., 2005. Correction of anterior open bite in a case of achondroplasia. Indian J. Dent. Res. 16 (4), 159–166. https://doi.org/10.4103/0970-9290.29903 official publication of Indian Society for Dental Research.
Kashiwagi, N., Suzuki, S., Seto, Y., Futami, T., 2001. Bilateral humeral lengthening in achondroplasia. Clin. Orthop. Relat. Res. (391), 251–257. https://doi.org/10.1097/00003086-200110000-00029.
Kim, R.H., Scuderi, G.R., Dennis, D.A., Nakano, S.W., 2011. Technical challenges of total knee arthroplasty in skeletal dysplasia. Clin. Orthop. Relat. Res. 469 (1), 69–75. https://doi.org/10.1007/s11999-010-1516-0.
Kim, S.J., Pierce, W., Sabharwal, S., 2014. The etiology of short stature affects the clinical outcome of lower limb lengthening using external fixation. A systematic review of 18 trials involving 547 patients. Acta Orthop. 85 (2), 181–186. https://doi.org/10.3109/17453674.2014.899856.
King, J.A., Vachhrajani, S., Drake, J.M., Rutka, J.T., 2009. Neurosurgical implications of achondroplasia. J. Neurosurg. Pediatr. 4 (4), 297–306. https://doi.org/10.3171/2009.3.PEDS08344.
Klepper, S.E., 2011. Measures of pediatric function: child health assessment questionnaire (C-HAQ), juvenile arthritis functional assessment scale (JAFAS), pediatric outcomes data collection instrument (PODCI), and activities scale for kids (ASK). Arthritis Care Res. 63 (Suppl. 11) https://doi.org/10.1002/acr.20635. S371–S382.
Kreiner, D.S., Shaffer, W.O., Baisden, J.L., Gilbert, T.J., Summers, J.T., Toton, J.F., Hwang, S.W., Mendel, R.C., Reitman, C.A., North American Spine Society, 2013. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). Spine J. : official journal of the North American Spine Society 13 (7), 734–743. https://doi.org/10.1016/j.spinee.2012.11.059.
Kubota, T., Adachi, M., Kitaoka, T., Hasegawa, K., Ohata, Y., Fujiwara, M., Michigami, T., Mochizuki, H., Ozono, K., 2020. Clinical practice guidelines for achondroplasia. Clin. Pediatr. Endocrinol. : case reports and clinical investigations : official journal of the Japanese Society for Pediatric Endocrinology 29 (1), 25–42. https://doi.org/10.1297/cpe.29.25.
Kurian, B.T., Belthur, M.V., Jones, S., Giles, S.N., Fernandes, J.A., 2019. Correction of bowleg deformity in achondroplasia through combined bony realignment and lateral collateral ligament tightening. Strategies in Trauma and Limb Reconstruction 14 (3), 132–138. https://doi.org/10.5005/jp-journals-10080-1441.
Lavini, F., Renzi-Brivio, L., de Bastiani, G., 1990. Psychologic, vascular, and physiologic aspects of lower limb lengthening in achondroplastics. Clin. Orthop. Relat. Res. (250), 138–142.
Lee, S.T., Song, H.R., Mahajan, R., Makwana, V., Suh, S.W., Lee, S.H., 2007. Development of genu varum in achondroplasia: relation to fibular overgrowth. J. Bone Jt. Surg. Br. Vol. 89 (1), 57–61. https://doi.org/10.1302/0301-620X.89B1.18223.
Leoni, C., Triumbari, E.K.A., Vollono, C., Onesimo, R., Podagrosi, M., Giorgio, V., Kuczynska, E., Veltri, S., Tartaglia, M., Zampino, G., 2019. Pain in individuals with RASopathies: prevalence and clinical characterization in a sample of 80 affected patients. Am. J. Med. Genet. 179 (6), 940–947. https://doi.org/10.1002/ajmg.a.61111.
Llerena Jr., J., Kim, C.A., Fano, V., Rosselli, P., Collett-Solberg, P.F., de Medeiros, P.F.V., Del Pino, M., Bertola, D., Lourenço, C.M., Cavalcanti, D.P., Félix, T.M., Rosa-Bellas, A., Rossi, N.T., Cortes, F., Abreu, F., Cavalcanti, N., Ruz, M.C.H., Baratela, W., 2022. Achondroplasia in Latin America: practical recommendations for the multidisciplinary care of pediatric patients. BMC Pediatr. 22 (1), 492. https://doi.org/10.1186/s12887-022-03505-w.
Loh, N.K., Dinner, D.S., Foldvary, N., Skobieranda, F., Yew, W.W., 1999. Do patients with obstructive sleep apnea wake up with headaches? Arch. Intern. Med. 159 (15), 1765–1768. https://doi.org/10.1001/archinte.159.15.1765.
Long, Z., Deng, Y., He, Q., Yang, K., Zeng, L., Hao, W., Deng, Y., Fan, J., Chen, H., 2023. Efficacy and safety of Iguratimod in the treatment of Ankylosing Spondylitis: a systematic review and meta-analysis of randomized controlled trials. Front. Immunol. 14, 993860 https://doi.org/10.3389/fimmu.2023.993860.
Maghnie, M., Semler, O., Guillen-Navarro, E., Selicorni, A., Heath, K.E., Haeusler, G., Hagenäs, L., Merker, A., Leiva-Gea, A., González, V.L., Raimann, A., Rehberg, M., Santos-Simarro, F., Ertl, D.A., Gregersen, P.A., Onesimo, R., Landfeldt, E., Jarrett, J., Quinn, J., Rowell, R., et al., 2023. Lifetime impact of achondroplasia study in Europe (LIAISE): findings from a multinational observational study. Orphanet J. Rare Dis. 18 (1), 56. https://doi.org/10.1186/s13023-023-02652-2.
Mantle, M., Kingsnorth, A.N., 2003. An unusual cause of back pain in an achondroplastic man. Hernia : the journal of hernias and abdominal wall surgery 7 (2), 95–96. https://doi.org/10.1007/s10029-002-0097-6.
Matsushita, M., Kitoh, H., Mishima, K., Kadono, I., Sugiura, H., Hasegawa, S., Nishida, Y., Ishiguro, N., 2016. Low bone mineral density in achondroplasia and hypochondroplasia. Pediatr. Int. : official journal of the Japan Pediatric Society 58 (8), 705–708. https://doi.org/10.1111/ped.12890.
McDonald, E.J., De Jesus, O., 2023. Achondroplasia. In: StatPearls. StatPearls Publishing.
McGraw, S.A., Henne, J.C., Nutter, J., Larkin, A.A., Chen, E., 2022. Treatment goals for achondroplasia: a qualitative study with parents and adults. Adv. Ther. 39 (7), 3378–3391. https://doi.org/10.1007/s12325-022-02190-6.
Meazzini, M.C., Tortora, C., Mazzoleni, F., Autelitano, L., 2020. Comparison of pain perception in patients affected by cleft and cranio facial anomalies treated with traditional fixed appliances or invisalign. Cleft Palate-Craniofacial J. 57 (1), 35–42. https://doi.org/10.1177/1055665619861780 official publication of the American Cleft Palate-Craniofacial Association.
Melekoglu, R., Celik, E., Eraslan, S., 2017. Successful obstetric and anaesthetic management of a pregnant woman with achondroplasia. BMJ Case Rep. https://doi.org/10.1136/bcr-2017-221238, 2017, bcr2017221238.
Misra, S.N., Morgan, H.W., 2003. Thoracolumbar spinal deformity in achondroplasia. Neurosurg. Focus 14 (1), e4. https://doi.org/10.3171/foc.2003.14.1.5.
Miyazaki, M., Kanezaki, S., Notani, N., Ishihara, T., Tsumura, H., 2017. Spondylectomy and lateral lumbar interbody fusion for thoracolumbar kyphosis in an adult with achondroplasia: a case report. Medicine 96 (49), e8983. https://doi.org/10.1097/MD.0000000000008983.

NiMhurchadha, S., Butler, K., Argent, R., Palm, K., Baujat, G., Cormier-Daire, V., Mohnike, K., 2023. Parents' experience of administering vosoritide: a daily injectable for children with achondroplasia. Adv. Ther. 40 (5), 2457–2470. https://doi.org/10.1007/s12325-023-02496-z.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst. Rev. 10 (1), 89. https://doi.org/10.1186/s13643-021-01626-4.

Paley, D., 2021. Extensive limb lengthening for achondroplasia and hypochondroplasia. Children 8 (7), 540. https://doi.org/10.3390/children8070540.

Paton, D.M., 2022. Efficacy of vosoritide in the treatment of achondroplasia. Drugs of today (Barcelona, Spain : 1998 58 (9), 451–456. https://doi.org/10.1358/dot.2022.58.9.3422313.

Pauli, R.M., 2019. Achondroplasia: a comprehensive clinical review. Orphanet J. Rare Dis. 14 (1), 1. https://doi.org/10.1186/s13023-018-0972-6.

Pfeiffer, K.M., Brod, M., Smith, A., Gianettoni, J., Viuff, D., Ota, S., Charlton, R.W., 2021. Assessing physical symptoms, daily functioning, and well-being in children with achondroplasia. Am. J. Med. Genet. 185 (1), 33–45. https://doi.org/10.1002/ajmg.a.61903.

Pfeiffer, K.M., Brod, M., Smith, A., Viuff, D., Ota, S., Charlton, R.W., 2022. Functioning and well-being in older children and adolescents with achondroplasia: a qualitative study. Am. J. Med. Genet. 188 (2), 454–462. https://doi.org/10.1002/ajmg.a.62534.

Randolph, L.M., Shohat, M., Miller, D., Lachman, R., Rimoin, D.L., 1988. Achondroplasia with ankylosing spondylitis. Am. J. Med. Genet. 31 (1), 117–121. https://doi.org/10.1002/ajmg.1320310113.

Ryken, T.C., Menezes, A.H., 1994. Cervicomedullary compression in achondroplasia. J. Neurosurg. 81 (1), 43–48. https://doi.org/10.3171/jns.1994.81.1.0043.

Saint-Laurent, C., Garde-Etayo, L., Gouze, E., 2019. Obesity in achondroplasia patients: from evidence to medical monitoring. Orphanet J. Rare Dis. 14 (1), 253. https://doi.org/10.1186/s13023-019-1247-6.

Savarirayan, R., Irving, M., Bacino, C.A., Bostwick, B., Charrow, J., Cormier-Daire, V., Le Quan Sang, K.H., Dickson, P., Harmatz, P., Phillips, J., Owen, N., Cherukuri, A., Jayaram, K., Jeha, G.S., Larimore, K., Chan, M.L., Huntsman Labed, A., Day, J., Hoover-Fong, J., 2019. C-type natriuretic Peptide analogue therapy in children with achondroplasia. N. Engl. J. Med. 381 (1), 25–35. https://doi.org/10.1056/NEJMoa1813446.

Savarirayan, R., Ireland, P., Irving, M., Thompson, D., Alves, I., Baratela, W.A.R., Betts, J., Bober, M.B., Boero, S., Briddell, J., Campbell, J., Campeau, P.M., Carl-Innig, P., Cheung, M.S., Cobourne, M., Cormier-Daire, V., Deladure-Molla, M., Del Pino, M., Elphick, H., Fano, V., et al., 2022. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. Nature.

Schkrohowsky, J.G., Hoernschemeyer, D.G., Carson, B.S., Ain, M.C., 2007. Early presentation of spinal stenosis in achondroplasia. Journal of pediatric orthopedics 27 (2), 119–122. https://doi.org/10.1097/01.bpb.0000248570.50875.28.

Sewell, M.D., Al-Hadithy, N., Higgs, D., Bayley, I., Falworth, M., Lambert, S., 2014. Complex shoulder arthroplasty in patients with skeletal dysplasia can decrease pain and improve function. J. Shoulder Elbow Surg. 23 (10), 1499–1507. https://doi.org/10.1016/j.jse.2014.01.003.

Shirazi, M., Golshahi, F., Teimoory, N., 2017. Successful delivery in a woman with achondroplasia: a case report. Acta Med. Iran. 55 (8), 536–537.

Sieberg, C.B., Lebel, A., Silliman, E., Holmes, S., Borsook, D., Elman, I., 2021. Left to themselves: time to target chronic pain in childhood rare diseases. Neurosci. Biobehav. Rev. 126, 276–288. https://doi.org/10.1016/j.neubiorev.2021.03.008.

Sims, D., Onambélé-Pearson, G., Burden, A., Payton, C., Morse, C., 2019. Whole-body and segmental analysis of body composition in adult males with achondroplasia using dual X-ray absorptiometry. PLoS One 14 (3), e0213806. https://doi.org/10.1371/journal.pone.0213806.

Singh, G., Athreya, B.H., Fries, J.F., Goldsmith, D.P., 1994. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum. 37 (12), 1761–1769. https://doi.org/10.1002/art.1780371209.

Sisk, E.A., Heatley, D.G., Borowski, B.J., Leverson, G.E., Pauli, R.M., 1999. Obstructive sleep apnea in children with achondroplasia: surgical and anesthetic considerations. Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 120 (2), 248–254. https://doi.org/10.1016/S0194-5998(99)70414-6.

Suri, P., Rainville, J., Kalichman, L., Katz, J.N., 2010. Does this older adult with lower extremity pain have the clinical syndrome of lumbar spinal stenosis? JAMA 304 (23), 2628–2636. https://doi.org/10.1001/jama.2010.1833.

Tenconi, R., Khirani, S., Amaddeo, A., Michot, C., Baujat, G., Couloigner, V., De Sanctis, L., James, S., Zerah, M., Cormier-Daire, V., Fauroux, B., 2017. Sleep-disordered breathing and its management in children with achondroplasia. Am. J. Med. Genet. 173 (4), 868–878. https://doi.org/10.1002/ajmg.a.38130.

Tucker-Bartley, A., Lemme, J., Gomez-Morad, A., Shah, N., Veliu, M., Birklein, F., Storz, C., Rutkove, S., Kronn, D., Boyce, A.M., Kraft, E., Upadhyay, J., 2021. Pain phenotypes in rare musculoskeletal and neuromuscular diseases. Neurosci. Biobehav. Rev. 124, 267–290. https://doi.org/10.1016/j.neubiorev.2021.02.009.

van den Broek, M., Verborgt, O., Declercq, G., 2017a. Reverse shoulder arthroplasty in young patient with achondroplasia - ten year follow up: case report. Orthopaedics & traumatology, surgery & research : OTSR 103 (7), 1127–1130. https://doi.org/10.1016/j.otsr.2017.07.004.

van den Broek, M., Verborgt, O., Declercq, G., 2017b. Reverse shoulder arthroplasty in young patient with achondroplasia - ten year follow up: case report. Orthopaedics & traumatology, surgery & research : OTSR 103 (7), 1127–1130. https://doi.org/10.1016/j.otsr.2017.07.004.

Waters, K.A., Kirjavainen, T., Jimenez, M., Cowell, C.T., Sillence, D.O., Sullivan, C.E., 1996. Overnight growth hormone secretion in achondroplasia: deconvolution analysis, correlation with sleep state, and changes after treatment of obstructive sleep apnea. Pediatr. Res. 39 (3), 547–553. https://doi.org/10.1203/00006450-199603000-00026.

Wieting, J.M., Krach, L.E., 1994. Spinal cord injury rehabilitation in a pediatric achondroplastic patient: case report. Arch. Phys. Med. Rehabil. 75 (1), 106–108.

Yonko, E.A., Emanuel, J.S., Carter, E.M., Raggio, C.L., 2021. Quality of life in adults with achondroplasia in the United States. Am. J. Med. Genet. 185 (3), 695–701. https://doi.org/10.1002/ajmg.a.62018.

Zaffanello, M., et al., 2017. Sleep disordered breathing in children with achondroplasia. World Journal Of Pediatric 13 (1), 8–14. https://doi.org/10.1007/s12519-016-0051-9.

Zmerly, H., Russo, M., Moscato, M., Akkawi, I., 2021. Total knee arthroplasty in a young patient with achondroplasia. BMJ Case Rep. 14 (7), e242909 https://doi.org/10.1136/bcr-2021-242909.