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ORIGINAL ARTICLE

Natural history of achondroplasia: A retrospective review of longitudinal clinical data

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Abstract

There are limited data on the longitudinal frequency and severity of the symptoms and complications of achondroplasia. We undertook a retrospective electronic chart review of 114 patients to develop a more thorough understanding of the lifetime impact of achondroplasia. Craniocervical stenosis (involving the foramen magnum with or without cervical vertebrae C1 and/or C2) was noted in nearly 50% of patients with craniovertebral junction imaging; however, corrective decompression surgery was only needed in 6% of patients. No children in our cohort died at 4 years of age or under. Kyphosis was present in most patients but usually resolved in early childhood. Cervical and lumbar stenosis were diagnosed in children and adults while, genu varum, elbow contractures, and radial head dislocations were identified during childhood. Central sleep apnea and obstructive sleep apnea were present in children, while the diagnosis of obstructive sleep apnea was shown to recur in adulthood. Cardiovascular risk factors were present in only 7% of patients. A range of mental health disorders were identified, with most diagnoses being made before 18 years of age. Our data show that achondroplasia has a significant impact on patients' physical health, and complications continue to be reported and require intervention throughout patients' lifetimes. This highlights the need for continuous support beyond pediatric care, by adult care clinicians experienced with managing the long-term complications of achondroplasia.

KEYWORDS

achondroplasia, adult, child, natural history, retrospective study

1 | INTRODUCTION

Achondroplasia is the most common viable skeletal dysplasia and form of disproportionate stature, with an incidence of between 1 in 10,000 and 1 in 30,000 (Pauli, 2019; Unger, Bonafé, & Gouze, 2017; Waller et al., 2008) and a global prevalence of approximately 250,000 (Baujat, Legeai-Mallet, Finidori, Cormier-Daire, & Le Merrer, 2008; Horton, Hall, & Hecht, 2007; Ireland et al., 2014). Although achondroplasia may be inherited through autosomal dominant mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*) (Rousseau et al., 1994; Shiang et al., 1994), the majority of people with achondroplasia (~80%) carry de novo mutations (Orioli, Castilla, Scarano, & Mastroiacovo, 1995; Pauli, 2019), which are paternal in origin (Arnheim & Calabrese, 2016; Goriely & Wilkie, 2012).

Early diagnosis of achondroplasia is key to managing early complications in infants and children. Prenatal diagnosis can be carried out through molecular testing for mutations in *FGFR3*, when there is a family history or suspicion of a skeletal dysplasia on ultrasound, although most patients are diagnosed in the early postnatal period based on clinical characteristics and radiological features, such as short stature, short limbs, and abnormalities of the hands and skull (Pauli, 2019). In the last decade, most diagnoses have been confirmed by molecular mutation analysis.

Beyond the signs and symptoms of achondroplasia that present in early infancy, further skeletal features become apparent and additional complications begin to manifest as the patient grows older. People with achondroplasia retain a short stature throughout their lives, with mean adult heights of approximately 120 cm in women and 130 cm in men (Del Pino, Fano, & Adamo, 2018; Merker et al., 2018). Further typical complications are directly related to, or are secondary manifestations of, the abnormal size and shape of bones.

Craniocervical stenosis may cause cervical myelopathy. Outward signs or symptoms of compression of the brainstem/spinal cord at the craniocervical junction can include: sustained clonus, profound hypotonia, asymmetric reflexes, difficulty swallowing or gagging, and developmental delay beyond what is expected in achondroplasia (Pauli, 2019; Trotter, Hall,, & American Academy of Pediatrics Committee on Genetics, 2005). Stenosis of the jugular foramina may also be present and can cause hydrocephalus. Additional spinal manifestations such as thoracolumbar kyphosis and lumbar hyperlordosis develop (Pauli, 2019), and while these may resolve in childhood, they can contribute to spinal cord stenosis and require surgical intervention (Kopits, 1988b; Pauli, 2019). Signs and symptoms of spinal stenosis often begin in adolescence and become more severe in adulthood, resulting in pain, spinal claudication, and limited mobility (Ireland et al., 2014; Pauli, 2019).

Genu varum (Hunter, Bankier, Rogers, Sillence, & Scott Jr., 1998; Kopits, 1988a); joint hypermobility (Kashiwagi, Suzuki, Seto, & Futami, 2001; Pauli, 2019); and contracture of the elbow (Kopits, 1988a; Pauli, 2019) can all be present, resulting in reduced mobility and function, and, in some instances, pain.

Differences in the development of the facial bones (midface hypoplasia) and the skull base often cause obstructive sleep apnea, middle ear dysfunction, chronic otitis media and chronic sinusitis, as well as dental malocclusion (Collins & Choi, 2007; Hunter et al., 1998; Trotter et al., 2005; Wright & Irving, 2012). This middle ear dysfunction frequently results in hearing loss, which is often associated with speech delay (Hunter et al., 1998; Ireland et al., 2012, 2014; Pauli, 2019).

Although mortality rates are higher than in the general population across all age groups (Hashmi et al., 2018; Hecht, Francomano, Horton, & Annegers, 1987; Wynn, King, Gambello, Waller, & Hecht, 2007), mortality in patients under the age of 4 years is reducing due to increased awareness of risks associated with compression of the brainstem and cervical spine at the craniovertebral junction. Adults with achondroplasia are also at a high risk of mortality (Wynn et al., 2007), which is thought to be due to cardiovascular disease associated with decreased mobility and obesity (Hecht et al., 1987; Ireland et al., 2014).

The complex and diverse signs and symptoms of achondroplasia require a multidisciplinary approach throughout the lifetime of the patient (Ireland et al., 2014; Trotter et al., 2005). Regular monitoring, therapies and surgery can place a large clinical and treatment burden on patients over the course of their lifetime. Indeed, people with achondroplasia have been found to have lower physical and mental health scores than people without achondroplasia, indicating that this disorder has a negative impact on health-related quality of life (Fredwall et al., 2019; Gollust, Thompson, Gooding, & Biesecker, 2003; Mahomed, Spellman, & Goldberg, 1998).

People with achondroplasia also face daily social and environmental issues associated with small stature and skeletal abnormalities, which can lead to discrimination or harassment, contributing to reduced self-esteem (Gollust et al., 2003). Several complications of achondroplasia are associated with pain and reduced physical function (Hunter et al., 1998). This can lead to a decreased capacity to carry out activities of daily living, and impact across education, employment, and recreation (Fredwall et al., 2019; Gollust et al., 2003; Ireland et al., 2014; Nishimura & Hanaki, 2014). People with achondroplasia are also faced with the challenges associated with living in an environment designed for people of average height; although modifications can be made, there are other circumstances in which adaptations will be more limited or not present.

Despite these challenges, many people with achondroplasia are thriving. Many are able to gain a college degree, have a successful career, get married, raise a family, and participate in sports and other recreational activities. The Americans with Disabilities Act (1990) (United States Department of Justice Civil Rights Division, 1990) has contributed to improvements in physical access, and the growth in membership in support groups such as Little People of America (LPA) and the increased overall awareness of dwarfism and disabilities is helping to improve the quality of life of people with achondroplasia.

A further understanding of the frequency and severity of symptoms and complications could support improved clinical management strategies and planning across the patient's life. Indeed, there is a limited number of studies examining the full range of clinical implications or the longitudinal course of these clinical manifestations into adulthood (Fredwall et al., 2019; Horton et al., 2007).

The Regional Skeletal Dysplasia Program at Kaiser Permanente has provided comprehensive management and treatment of a range of rare skeletal dysplasias since 1997. The range of potential symptoms of achondroplasia is broad and complex, meaning that coordinated, multidisciplinary, expert input is required. As patients visit the program throughout their lifetime, the associated physical and mental health records provide a unique, longitudinal view of achondroplasia. These longitudinal data can improve understanding of the lifetime overall impact of physical and mental health manifestations that may be experienced by people with achondroplasia, and the effect of these manifestations on quality of life.

2 | METHODS

Data were collected by a retrospective electronic chart and medical history review of 114 patients in the Regional Skeletal Dysplasia Program in the Genetics Department of Kaiser Permanente Northern

California. Longitudinal data were collected on known signs, symptoms, and complications of achondroplasia, and mental health and chronic health statuses, throughout patients' lifetimes. A manual chart review was conducted in 2018 to determine the presence or absence of each sign or symptom for every patient. Data collection was not restricted according to age or the provider recording assessment of a sign or symptom, unless a specific care provider is detailed below.

Not all data were available for all patients. For each sign, symptom, or management characteristic, the number of patients with data recorded for that specific feature are shown; percentages are calculated based on numbers of patients with recorded data, where a symptom was recorded as present or absent, and do not include patients for whom data were missing. Analyses are descriptive.

3 | RESULTS

3.1 | Patient characteristics and diagnosis

Demographics and details of entry to and time in the Regional Skeletal Dysplasia Program are shown in Table 1. The mean period of follow-up in the program was 5.9 years. Ages at entry into the program, and mean years of follow-up by age group are shown in Table S1; cognitive, educational, and employment statuses are shown in Table S2. As expected, most patients were born to parents of average stature (84.6%); the remainder had one parent with achondroplasia (9.1%), two parents with achondroplasia (4.4%), or one parent with achondroplasia and one parent with another skeletal dysplasia (1.8%). A small percentage of patients were adopted (4.4%).

Diagnosis of achondroplasia was most frequently made using clinical and radiological assessments in the early postnatal period (Table 1). Geneticists were the most common specialists to make the diagnosis (66.7%), although pediatricians (2.6%), neonatologists (1.8%), and orthopedists (0.9%) were also involved (data were not recorded for 12 of the patients in the cohort). Of the patients with at least one parent with achondroplasia, all, but one, were diagnosed prenatally or on the day of birth. Diagnosis for the remaining child was confirmed at Day 186, although we expect that the family and doctors assumed she had achondroplasia prior to this. For the patients who did not have a family history of achondroplasia, age/period at diagnosis ranged from prenatal to 44 years. The difference between ages at diagnosis for patients with or without a family history of achondroplasia was significant (two-sided t-test, $p = .08$).

3.2 | Signs and symptoms, and treatment and management

3.2.1 | The brain and craniovertebral junction

Overall, 83% of patients (84/101) had undergone cross-sectional imaging of the brain and/or craniovertebral junction by magnetic resonance imaging (MRI) or computed tomography (CT), in order to evaluate for craniocervical stenosis, ventriculomegaly, and hydrocephalus (Table 2; mean age = 6.92 years; SD = 12.72 years). Most patients (46/78; 59.0%) were under the age of 2 years at first imaging, with a further 15 (19.2%) between the ages of 2 and 10 years. About 45.7% of patients (38/83) showed some degree of compression of the brainstem at the foramen magnum. However, only seven patients (7/112; 6.3%) had corrective decompression surgery involving the foramen magnum and upper cervical vertebrae at a mean age of 6.7 years (SD = 8.2 years). Surgeries were performed based on clinical symptoms: abnormal neurological examinations (3/7; 42.9%), tight foramen magnum on imaging (6/7; 85.7%), and/or sleep apnea (1/7; 14.3%); none were conducted based on increasing head circumference. Details of surgical resolution were recorded for six patients; the symptoms of craniocervical stenosis were resolved in three patients who received surgery (50.0%), although three patients (50%) experienced complications (2/3 required emergency tracheostomies) and two patients developed intellectual deficits. Only one of the decompression surgeries was performed at Kaiser Permanente; the other six were carried out before the patients joined the Regional Skeletal Dysplasia Program. Five patients (5/98; 5.1%) underwent ventriculoperitoneal shunt insertions to manage hydrocephalus. One patient who underwent decompression surgery and a second who had a ventriculoperitoneal shunt inserted each had surgery at a delayed stage, based on parental choice; these patients experienced significant complications, including paraplegia, neurogenic bladder, and bowel, and the requirement for a tracheostomy. Of the remaining four patients with shunts, one required multiple surgical revisions and developed a seizure disorder. The other three patients who had shunt insertions remained free of complications. Two of our young patients requiring shunts had extenuating circumstances (traumatic brain injury and coronal craniosynostosis).

3.2.2 | Spinal manifestations

Kyphosis was present in 83.1% of patients (74/89). Age at diagnosis, details of pediatric resolution, and management are shown in Table 3; locations of wedged vertebrae are reported in Table S3. Of the patients who were prescribed and wore a back brace, the youngest two were 18 months and the oldest was 10.3 years; of the four patients requiring surgery, the youngest was aged 10 years and the oldest was 19.5 years.

Of patients with recorded data, 17.9% (20/112) had cervical stenosis, while lumbar stenosis was more common, occurring in 42.3% of patients (47/111). Corrective decompression was carried out in 25% of patients with cervical stenosis (5/20; including one fusion surgery) and 36.2% of patients with lumbar stenosis (17/47; including two fusion surgeries). Ages at diagnosis and surgery are shown in Figure 1a,b (cervical; $n = 17$ and $n = 4$, respectively) and Figure 1c,d (lumbar; $n = 47$ and $n = 16$, respectively). Most cases of stenosis were reported prior to the age of 20 years; this was also the most common age group to undergo surgery. Locations of affected vertebrae and

TABLE 1 Patient characteristics and diagnosis

Characteristic (patients with recorded data)		
Age at entry, years (*n* = 114)	Mean (*SD*)	12.2 (16.0)
	Median (IQR)	5.1 (0.62–17.5)
	Total range	14 days to 57 years
Sex (female) (*n* = 114)		58 (50.9)
Ethnicity, *n* (%) (*n* = 114)	African American	4 (3.5)
	Asian	15 (13.2)
	Caucasian	52 (45.6)
	Hispanic	13 (11.4)
	Middle Eastern	1 (0.9)
	Mixed race	27 (23.7)
	Pacific Islander	2 (1.8)
Time in Regional Skeletal Dysplasia Program, *n* (%) (*n* = 114)	<1 year	34 (29.8)
	1 to <2 years	8 (7.0)
	2 to <4 years	8 (7.0)
	4 to <8 years	27 (23.7)
	8 to <12 years	18 (15.8)
	12–20 years	19 (16.7)
Age at last clinic visit, years (*n* = 114)	Mean (range)	18.2 (0.29–58.8)
Age/period at diagnosis, *n* (%) (*n* = 102)	Prenatal	12 (11.8)
	Postnatal, before discharge (0–3 days)	32 (31.4)
	Postnatal, within 1 month of birth	11 (10.8)
	1 to <6 months of age	3 (2.9)
	>6 months of age	27 (26.5)
	Postnatal, but date uncertain	17 (16.7)
Method of diagnosis, *n* (%) (*n* = 102)	At least clinically (*n* = 95)	88 (92.6)
	At least radiographically (*n* = 85)	70 (82.4)
	At least molecularly (*n* = 90)	31 (34.4)
	Clinically and radiographically (*n* = 70)	39 (55.7)
	Clinically, radiographically, and molecularly (*n* = 92)	24 (26.1)
Mean age at diagnosis (*n* = 102)	With at least one parent with achondroplasia (*n* = 14)	13.6 days
	Without a parent with achondroplasia (*n* = 71)	341 days

Abbreviations: IQR, interquartile range; *SD*, standard deviation.

associated symptoms are shown in Table S4. In only 1 case was there any involvement of the craniovertebral junction in patients with cervical stenosis. This patient had previously had craniocervical decompression and later required a more extensive decompression involving the craniovertebral junction and multiple levels of the cervical spine.

3.2.3 | Neurological manifestations

Fifty patients (50/111; 45.1%) had an abnormal neurological exam at some point during their follow-up at the Program. Ten patients experienced issues with neurogenic bladder (10/110; 9.1%) and six with neurogenic bowel (6/111; 5.4%). Paraplegia was reported in eight patients (8/111; 7.2%) and twelve were dependent on a mobility device (12/112; 10.7%).

3.2.4 | Orthopedic manifestations in limbs and joints

Manifestations in the upper and lower limbs were frequent, and in some cases corrective surgery was carried out, involving a range of

TABLE 2 Craniocervical stenosis, ventriculomegaly, and hydrocephalus

Craniovertebral junction characteristic (patients with recorded data)	Patients affected, *n* (%)
Craniocervical stenosis (*n* = 83)	38 (45.7)
Ventriculomegaly (*n* = 82)	27 (32.9)
Hydrocephalus (*n* = 98)	17 (17.3)

TABLE 3 Kyphosis

Kyphosis, *n* (%) (patients with recorded data)		
Age at diagnosis of kyphosis (*n* = 63)	0 to <3 months	10 (15.9)
	3 months to <6 months	11 (17.5)
	6 months to <12 months	17 (27.0)
	12 months to <24 months	12 (19.0)
	≥24 months	13 (20.6)
Resolution of kyphosis (*n* = 64)	As a toddler	50 (78.1)
	No resolution	14 (21.9)
Treatment of kyphosis (*n* = 74)	Back brace	7 (9.5)
	Surgical requirement	4 (5.4)

procedures with varying levels of success (Table 4 and Table S5). Physical therapy and occupational therapy were frequently used as nonsurgical options. No patient had arthritis or joint degeneration that required joint replacement.

Genu varum was most commonly identified in patients under 4 years of age (*n* = 63), although corrective surgery was mostly frequently carried out between the ages of 10 and 15 years (*n* = 23; Figure 2). The most common type of corrective surgery was tibial osteotomy with Taylor spatial frame (16/25; 64%), followed by tibial osteotomy without frame (4/25; 16%) and eight-plate/guided growth (3/25; 12%). Two patients (8%) received other types of corrective surgery. Frequencies of elbow contractures and radial head dislocations by age are shown in Figure 3.

3.2.5 | Respiratory manifestations

As expected, both central and obstructive sleep apnea were reported, and were resolved or managed through a range of strategies (Table 5 and Table S6). Central sleep apnea was diagnosed in children (19/114; 16.7%), whereas obstructive sleep apnea was diagnosed in both children and adults (79/114; 69.3%), including patients over the age of 50 years.

3.2.6 | Ear, nose, and throat (ENT) and dental manifestations

Most patients experienced otitis media and conductive hearing loss at some point, and dental manifestations were also common (Table 6). Both children with intellectual disabilities and six of the eight children with learning disabilities had conductive hearing loss (Table S2). In four of these patients, hearing loss has been persistent. Hearing loss was resolved in 59.1% of patients (39/66) following the placement of pressure equalization tubes. Overall, 19.6% of the cohort (18/92) experienced chronic sinusitis.

3.2.7 | Cardiovascular manifestations

We looked at a range of cardiovascular risk factors and events in our study population. Of 112 patients with recorded data, risk factors or events were reported in only 8 patients (7.1%); 2 patients (1.8%) had type 2 diabetes, 4 (3.6%) had hypertension, and 5 (4.5%) had hyperlipidemia. One patient with type 2 diabetes mellitus also had both hypertension and hyperlipidemia. No patients had type 1 diabetes. None of these were recorded in patients under the age of 20 or over the age of 60 years. One patient (0.9%) had a stroke and also experienced a myocardial infarction; this patient also had hypertension and hyperlipidemia.

3.2.8 | Mental health

Thirty-one patients (31/100; 31.0%) had attended a mental health visit, at which a range of mental health disorders were diagnosed. In addition, 4.7% of patients (4/85) had also undergone neuropsychiatric testing. Self-esteem issues were reported in 23 patients (23/85; 27.1%), attention deficit disorder or attention deficit hyperactivity disorder in 13 patients (13/89; 14.6%), and suicidal ideation in 3 patients (3/94; 3.2%). Thirty patients received a diagnosis of at least one mental health disorder. Although the first diagnosis of a mental health disorder occurred most commonly before the age of 12 years, the diagnosis of a second disorder occurred most frequently between the ages of 12 and 18 years and diagnoses continued into patients over the age of 40. The most common diagnoses were depression, attention deficit disorder (with or without hyperactivity), anxiety, and adjustment disorder.

3.2.9 | Other

Overall, 32.7% of patients (34/104) experienced chronic headaches and 17.1% (18/105) required daily analgesia for over 6 months, suggesting issues with chronic pain. Chronic headaches were present in patients of all ages, from children under the age of 5 years to adults over the age of 60 (*n* = 28; Table 7). In spite of almost 15% (17/114) of the total study population reporting chronic headaches under the age of 15 years, it seems that daily analgesia was not considered until the later teenage years (Table 7). The increased number of patients starting daily analgesia between 40 and 60 years probably relates to the worsening of spinal stenosis symptoms in that age group.

The numbers of patients who were pregnant while managed by the Regional Skeletal Dysplasia Program are shown in Table S7. All

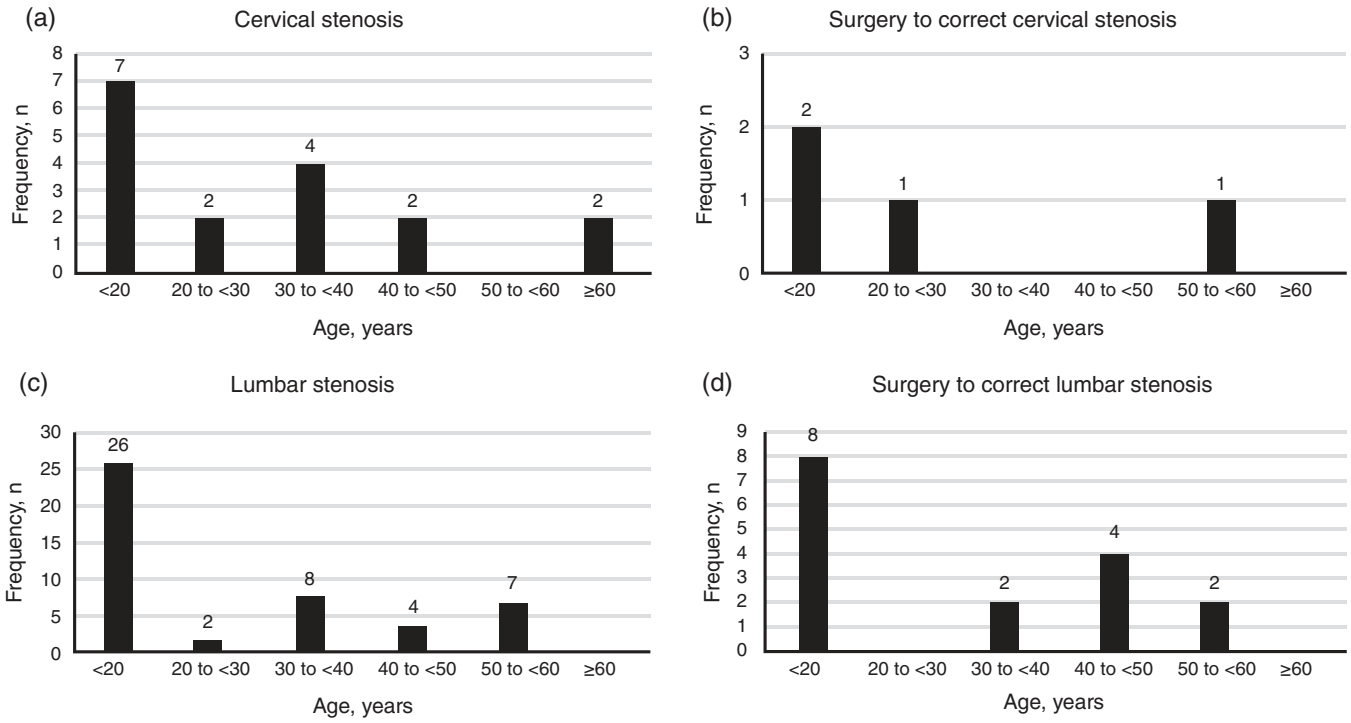

FIGURE 1 Spinal stenosis in achondroplasia: Frequencies of diagnoses and corrective surgeries by age group for cervical stenosis (*n* = 17 or 4; a and b) and lumbar stenosis (*n* = 47 or 16; c and d)

patients with data recorded on methods of delivery had babies delivered by cesarean section (*n* = 8) and no complications were reported (*n* = 4).

3.3 | Mortality

Three attendees of the Regional Skeletal Dysplasia Program have died. The first was a 7-year-old girl who had Down syndrome in addition to achondroplasia. The cause is unknown, as she was no longer in the Program at her time of death. The second was aged 24 years old and died of respiratory failure. He was severely affected by achondroplasia throughout his lifetime and had experienced an anoxic brain injury in infancy, which resulted in quadriplegia, a neurogenic bladder, epilepsy, and a requirement to be chronically ventilated since the age of 2 years. The third was a 24-year-old woman; the cause of death is unknown, although she was not severely affected by achondroplasia as a child.

TABLE 4 Orthopedic manifestations in the knee and elbow

Orthopedic characteristic, *n* (%) (patients with recorded data)		
Lower limb—Knee	Knee instability (*n* = 91)	15 (16.5)
	Genu varum (*n* = 105)	88 (83.8)
	Surgery recommended for genu varum (*n* = 85)	30 (35.3)
	Surgery carried out for genu varum (*n* = 50)	27 patients[a] (54%)
Upper limb—Elbow	Elbow contracture (*n* = 93)	64 (68.8)
	Radial head dislocation (*n* = 91)	30 (33.0)
Surgery	Extensive limb lengthening (*n* = 110)	0
	Other lower extremity orthopedic surgery (excluding joint replacements) (*n* = 111)	4 (3.6)
Physiotherapy or occupational therapy (*n* = 101)		67 (66.3)

[a]About 54% of patients with recorded data, or 90% of patients for whom surgery was recommended.

4 | DISCUSSION

The data from the care provided to 114 patients over the last 20 years adds further evidence on how achondroplasia affects individuals throughout their lifetime.

Over 80% of patients had documented imaging of their brain and craniovertebral junction at some time in their lives. This is significant because for more than 5 years the Regional Skeletal Dysplasia Program had not routinely imaged infants with achondroplasia because of the risks of radiation from CT and sedation during MRI. Infants were only imaged when there were clinical symptoms of spinal compression or increased intracranial pressure (e.g., abnormal sleep study, abnormal neurological exam, or increasing head

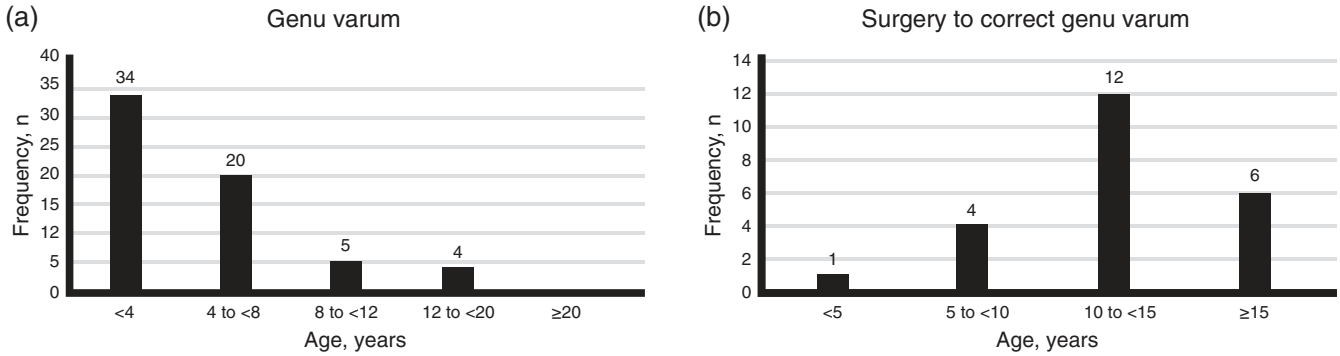

FIGURE 2 Genu varum: Ages at diagnosis of genu varum (a) and age at time of corrective surgery (b)

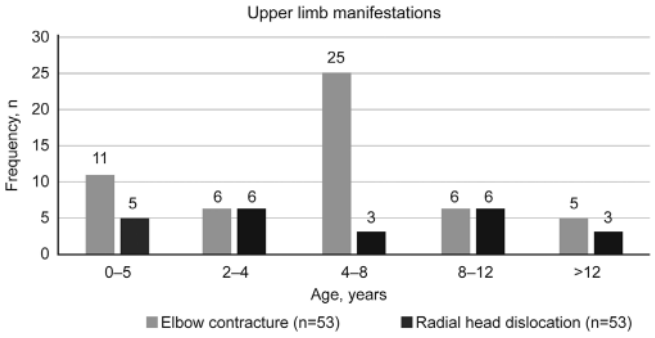

FIGURE 3 Upper limb manifestations: Ages at which either elbow contracture (n = 53) or radial head dislocation (n = 23) were reported

circumference). A publication by the Skeletal Dysplasia Management Consortium in 2019 has suggested that imaging should be carried out in all infants because physical and sleep examinations do not adequately predict compression of the spinal cord (Sanders, Sheldon, & Charrow, 2019). In our population, 59% of patients had undergone imaging evaluations before the age of 2 years, and 78% before the age of 10 years, indicating the extent of the population considered to be at risk of spinal compression and raised intracranial pressure. Despite universal narrowing of the foramen magnum, only a small percentage of children with achondroplasia required decompression surgery. Our study has reported that 45.7% of patients had craniocervical stenosis, and 6.3% went on to have decompression surgery; this figure is comparable with the 5–10% of patients reported in previous studies (Hunter et al., 1998; Pauli, 2019; Rimoin, 1995). Of note, only one of the seven patients had decompression surgery while being followed in the Regional Skeletal Dysplasia Program; all six other patients had decompression surgery prior to care in the Kaiser Permanente system. This may represent the variation of thresholds that different neurosurgeons have for deciding when to proceed with this difficult surgical procedure. Complications of stenosis of the jugular foramina—ventriculomegaly and hydrocephalus—were present in our population, although insertion of a ventriculoperitoneal shunt was only required in 5.1%. This was lower than in Hunter et al. in 1998 (10.5%) and a report by King et al. in 2009 (41.4% of children with achondroplasia [Hunter et al., 1998; King, Vachhrajani, Drake, & Rutka, 2009]).

Kyphosis was present in over 80% of patients but resolved in early childhood in 78% of cases. This is in agreement with previous literature that reported that kyphosis is present in more than 90% of infants but only 10–30% of adults (Ireland et al., 2014; Kopits, 1988b; Pauli, 2019). A small number of patients (n = 4) required surgical correction because of severe kyphosis.

Spinal stenosis is one of the most commonly reported complications in adults with achondroplasia (Hecht, Bodensteiner, & Butler, 2014; Hunter et al., 1998; Kahanovitz, Rimoin, & Sillence, 1982); indeed, we identified patients diagnosed with either cervical and/or lumbar stenosis across a broad age range (from under 20 years to over 50 years) as in the Hunter study (Hunter et al., 1998). Similar to the Hunter study, surgery continued in patients aged over 40 years in our cohort. Our data show that cervical and lumbar stenosis can clearly affect individuals in late childhood/teenage years. Therefore, it is imperative that this age group continues to have annual neurological evaluations to rule out spinal stenosis. As the proportion of people with stenosis rises with the aging population, clinicians must manage the consequences of this condition; we have identified patients with neurological abnormalities, neurogenic bladder and/or bowel, paraplegia, and dependence on mobility devices. Although there are only limited data on the consequences of stenosis beyond weakness and sensory changes, our study provides important information not only on complications that are likely to have a negative impact on quality of life but also on the types of complications that clinicians should be prepared to manage across the age spectrum of achondroplasia. We have also reported that 36% of patients with lumbar stenosis require decompression surgery; this result is similar to that identified by Sciubba et al. (2007), indicating that surgery remains a key strategy in the management of this complication.

The limbs were also frequently affected in our cohort, with over 80% of patients experiencing genu varum and 35.3% requiring corrective surgery. Although the prevalence of genu varum in our study is at the higher end of the range previously reported (42–93%) (Horton et al., 2007; Hunter et al., 1998; Kopits, 1988a; Pauli, 2019), the frequency of surgical correction is similar (23.7%) (Kopits, 1988a). Although genu varum was commonly first diagnosed before the age

TABLE 5 Respiratory manifestations

Apnea characteristic, *n* (%) (patients with recorded data)		
Central sleep apnea		
Central sleep apnea present (*n* = 114)		19 (16.7)
Severity (*n* = 19)	Mild	6 (31.6)
	Moderate	0
	Severe	4 (21.1)
	Unsure	9 (47.4)
Age at diagnosis (*n* = 16)	0–6 months	4 (25.0)
	6 months to <1 year	8 (50.0)
	1 year to <2 years	2 (12.5)
	≥2 years	2 (12.5)
Treatment (*n* = 7)	CPAP	2 (28.6)
	BiPAP	2 (28.6)
	Oxygen	5 (71.4)
Resolution (*n* = 8)	Patient "grew out of" central sleep apnea	7 (87.5)
	Decompression surgery	1 (12.5)
Obstructive sleep apnea		
Obstructive sleep apnea present (*n* = 114)		79 (69.3)
Age at diagnosis (*n* = 72)	<1 year old	16 (22.2)
	1 to <3 years old	14 (19.4)
	3 to <5 years old	8 (11.1)
	5 to <10 years old	8 (11.1)
	10 to <20 years old	13 (18.1)
	20 to <30 years old	3 (4.2)
	30 to <40 years old	5 (6.9)
	40 to <50 years old	4 (5.6)
	>50 years old	1 (1.4)
Type of surgery (*n* = 50)	Adenoidectomy	46 (92.0)
	Tonsillectomy	42 (84.0)
	Revision of adenoidectomy or tonsillectomy	14 (28.0)
	Different or additional surgery	12 (24.0)
Nonsurgical treatment	CPAP (*n* = 74)	20 (27.0)
	BiPAP (*n* = 76)	8 (10.5)
	Oxygen (*n* = 75)	11 (14.7)

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

of 4 years, the majority of corrective surgeries were carried out between the ages of 10 and 15 years, similar to a previously reported age range (Baujat et al., 2008). Elbow contractures were most commonly reported (documented by a healthcare professional) between the ages of 4 and 8 years, in concordance with a previous study (Kopits, 1988a). Identifying radial head dislocations became a focus in our clinic after two to three patients had attempted relocations after attending the emergency room with arm pain. We counseled families that when dislocations were identified, they should not allow physicians inexperienced with achondroplasia to attempt relocation. Extensive limb-lengthening surgery is considered to be inappropriate in the majority of patients (Pauli, 2019) and not socially accepted in the United States, and was not performed in our cohort. Approximately two thirds of patients were managed by physical therapists or occupational therapists at some time during their care, usually in early childhood to help progress developmental skills or after surgeries for rehabilitation. Of note, none of our patients required joint replacement surgery (hips, knees, or shoulders), providing longitudinal evidence that joint degeneration is not a common feature of achondroplasia. This result is consistent with a study of a mouse model of achondroplasia, in which surgically induced arthritis occurred to a lesser extent than in wild-type mice (Okura et al., 2018).

Obstructive sleep apnea was more common than central sleep apnea in our cohort (69.3 vs. 16.7%) and continued to be diagnosed into adulthood. The prevalence of central sleep apnea in achondroplasia has not previously been reported, whereas obstructive sleep apnea

TABLE 6 ENT and dental manifestations

Characteristic, *n* (%) (patients with recorded data)			
Middle ear	Recurrent (≥3 episodes) otitis media (*n* = 99)		73 (73.7)
	ENT-diagnosed history of chronic middle ear effusion (*n* = 85)		60 (70.6)
	Pressure equalization tubes required	Ever (*n* = 102)	66 (64.7)
		1 time (*n* = 62)	19 (30.6)
		2–3 times (*n* = 62)	25 (40.3)
		4 or more times (*n* = 62)	18 (29.0)
Tympanic membrane perforations (*n* = 91)			24 (26.4)
Conductive hearing loss	Ever (*n* = 106)		79 (74.5)
	Resolved with pressure equalization tubes (*n* = 66)	Yes	39 (59.1)
		No	20 (30.3)
		Further audiometry not performed[a]	7 (10.6)
	Hearing aids recommended (*n* = 104)		10 (9.6)
	Hearing aids used (*n* = 9)		6 (66.7)
	Speech therapy required (*n* = 85)		40 (47.1)
Dental	Malocclusion (*n* = 61)		33 (54.1)
	Dental crowding (*n* = 57)		21 (36.8)

Abbreviations: ENT, ear, nose, and throat.
[a]Due to patient leaving the Regional Skeletal Dysplasia Program, no follow-up audiometry performed, or ongoing treatment.

TABLE 7 Ages at which chronic headaches were reported (*n* = 28) and daily analgesia initiated (*n* = 13)

Age, years	Chronic headaches, *n* (%)	Daily analgesia, *n* (%)
0 to ≤5	3 (10.7)	1 (7.7)
>5 to ≤10	8 (28.6)	1 (7.7)
>10 to ≤15	6 (21.4)	1 (7.7)
>15 to ≤20	5 (17.9)	3 (23.1)
>20 to ≤40	2 (7.1)	1 (7.7)
>40 to ≤60	3 (10.7)	6 (46.2)
>60	1 (3.6)	0

is known to occur in 10–87% of patients (Horton et al., 2007; Sisk, Heatley, Borowski, Leverson, & Pauli, 1999; Tenconi et al., 2017). As well as the burden of reduced sleep quality, many patients required surgery to manage obstructive sleep apnea, and in several cases further surgeries or some type of respiratory assistance [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or oxygen] was required.

We report recurrent middle ear dysfunction in over 70% of patients, and hearing loss in a similar percentage of patients at some timepoint during their follow-up in the program, which was associated with a need for pressure equalization tubes and/or speech therapy in 64.7 or 47.1% of patients, respectively. These figures are similar to those previously reported for middle ear dysfunction and the requirement for pressure equalization tubes (Collins & Choi, 2007; Horton et al., 2007). We do, however, report a higher percentage of patients with conductive hearing loss (74.5%) at any point during their time in the program, compared with a previous report that showed a cumulative percentage of 40% in patients aged 20 or younger (Hunter et al., 1998). While conductive hearing loss was resolved in almost 60% of patients using pressure equalization tubes, almost 50% of individuals required speech therapy, and in earlier studies most patients have been reported to have a speech or language disorder (Galasso et al., 2019). All patients with intellectual disabilities and most patients who had learning disabilities in our population had conductive hearing loss, indicating the importance of this complication in understanding the full impact of achondroplasia. Dental and orthondontic complications were similar in frequency to previous reports (Hunter et al., 1998).

In contrast with previous studies of mortality in achondroplasia that suggested a link with cardiovascular events (Hecht et al., 1987; Wynn et al., 2007), we did not identify an increased number of patients with cardiovascular risk factors (such as type 2 diabetes and hyperlipidemia), and the reason for increased mortality is not apparent in our cohort.

The topic of mental health disorders in achondroplasia has not previously undergone a detailed longitudinal analysis. In our cohort, we identified patients with multiple mental health diagnoses, ranging from self-esteem issues, to attention deficit hyperactivity disorder (ADHD). The frequency of ADD and ADHD (14.6%) is similar to that reported in a study of children in the United States (11%) (Visser et al., 2014). Even though a diagnosis of a mental health disorder was more common before the age of 18 years, such disorders could occur in patients over the age of

40 years, highlighting the need to remain vigilant throughout a patient's lifetime.

Chronic headaches and the need for daily analgesia were reported in approximately 30 and 17% of patients, respectively, which had a further negative impact on quality of life. Our study is the first to describe the potential impact throughout patients' lives. Both the total number of patients affected and the number of children with chronic headaches indicate that clinicians should be highly aware of the potential for chronic headaches. Aside from chronic headaches, pain is associated with multiple signs and symptoms of achondroplasia (Ceroni et al., 2018; Hunter et al., 1998; Pauli, 2019). In spite of this, daily analgesia was only used by a limited number of patients, and was not usually initiated until adulthood. This may be of particular note given the occurrence of chronic headaches in children, and may indicate there is some parental hesitation in starting long-term, daily analgesia in children.

All pregnancies in women with achondroplasia that had a documented mode of delivery were delivered by cesarean section. No complications were reported during delivery. There is limited information on pregnancy in people with achondroplasia (Fredwall et al., 2019; Pauli, 2019), and schemes such as the Regional Skeletal Dysplasia Program have a key role to play in collating information to support optimal management of pregnancy and delivery.

5 | SUMMARY AND CONCLUSIONS

Our study is one of the largest to date to provide a longitudinal picture over the lifetime of patients with achondroplasia. Such studies are often limited by patient age groups; babies have the potential to contribute a large volume of data in the future, although currently they have provided only a small amount. Older patients might have limited recorded medical histories, aside from the details of surgeries, and may not be able to remember the specifics of any assessments or treatments they received in childhood. The types of assessment used to monitor patients have also changed significantly in recent decades. For example, prior to the 1990s, sleep studies were not used frequently, whereas currently these assessments may be in routine use; therefore, a much larger volume of data is available for younger patients. Despite these limitations, our population highlights the need for continuous assessment of patients throughout their lifetimes by clinicians with experience in managing the symptoms and complications of achondroplasia. We show that cervical stenosis, lumbar stenosis, and obstructive sleep apnea all continue to be diagnosed into adulthood, and given the potential severity of each of these, adults with achondroplasia should continue to be regularly monitored when they leave pediatric care and enter adult healthcare systems. Hearing loss may also persist or recur in adulthood. Beyond this lifetime monitoring requirement, a wide range of surgeries were conducted in our cohort, including decompressions to resolve craniocervical stenosis or stenosis of the spine, insertion of ventriculoperitoneal shunts, placement of pressure equalization tubes, surgeries to correct kyphosis or genu varum, adenoidectomies, tonsillectomies, and cesarean sections.

Despite the clinical, surgical, and social challenges of achondroplasia, and the need for continued assessment, people with achondroplasia often overcome these difficulties to live full lives in terms of achieving success in education and employment, and getting married and having children (biologically or through adoption). Our study provides a wealth of information to support clinicians in understanding the lifetime impact of achondroplasia and in ensuring clinical resources are ready to minimize the impact of new symptoms that arise or longer-term symptoms that may become severe.

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CONFLICT OF INTEREST

AA and EO have received grants from BioMarin Pharmaceutical during the conduct of the study. BM has no disclosures.

DATA AVAILABILITY STATEMENT

Patient-level data are not publicly available due to privacy and ethical restrictions. Any investigator interested in collaborations using this data may contact the corresponding author directly.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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