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ORIGINAL ARTICLE

Medical complications in children with achondroplasia

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Abstract

Aim: To determine the rates of medical investigations, complications, interventions, and outcomes in children with achondroplasia.

Method: Children and adolescents with achondroplasia born between 2000 and 2019, aged between 0 and 18 years of age, and seen at The Children's Hospital at Westmead skeletal dysplasia clinic were included. Data were collected retrospectively from clinical records. Standard descriptive statistics were used for analysis.

Results: The study included 108 participants, 58 males and 50 females. Ninety-nine participants (91.7%) entered the study at birth. The other nine (8.3%) participants entered the study after birth (mean age = 2 years 4 months, SD = 1 year 8 months). The median age of exit from the study was 8 years 8 months (IQR = 8 years 9 months) with a median follow-up of 8 years 8 months (IQR = 8 years 9 months). Fifty-two (48%) participants presented with craniocervical stenosis, 15 (13.9%) with hydrocephalus, 66 (61.1%) with hearing impairment, 44 (40.7%) with sleep-disordered breathing, 46 (42.6%) with lower-limb malalignment, 24 (22.2%) with thoracolumbar kyphosis, 10 (9.3%) with symptomatic spinal stenosis, 12 (11.1%) with obesity, and 16 (14.8%) who had at least one admission for respiratory illness. Two children died during the study period.

Interpretation: We report contemporary rates of medical complications in an Australian population of children with achondroplasia. Recommendations for surveillance in clinical practice are discussed. This information will help guide clinicians with their expectant management of achondroplasia and provide prognostic information to the families of children with achondroplasia.

Achondroplasia is the most common skeletal dysplasia causing short stature in humans.[1] An autosomal dominant condition, it is usually diagnosed clinically at birth and confirmed with radiological and/or genetic investigations. The prevalence of achondroplasia in Australia is increasing, with 1 in 20 000 children affected;[2] 80% are born to parents of average stature and 99% have the same *FGFR3* mutation.[2]

In 1995, the American Academy of Paediatrics (AAP) Committee on Genetics published guidelines on Health Supervision for Children with Achondroplasia,[3] which were updated in 2005 and 2020.[4,5] They outline optimal management for children with achondroplasia, including surveillance and management of complications. A targeted pharmaceutical therapy for achondroplasia is now approved in Europe with other drugs currently in clinical trials; the impact of treatment on medical complications is not yet known.[6]

Clinical features of achondroplasia include short stature, short limbs (proximal more than distal), macrocephaly, midfacial retrusion, small thorax, thoracolumbar kyphosis, exaggerated lumbar lordosis, limited elbow extension, short fingers, hip and knee laxity, and lower-leg bowing and weakness.[7] These have an impact on children's motor development

Abbreviation: AAP, American Academy of Paediatrics

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and physical functioning, resulting in mild to moderate physical disability. Medical complications may also arise, including craniofacial complications (hydrocephalus, craniosynostosis, craniocervical stenosis, subdural haematomas), ear, nose, and throat complications (hearing impairment, sleep-disordered breathing), orthopaedic complications (lower-limb malalignment, spinal stenosis, thoracolumbar kyphosis), respiratory complications, obesity, and death.[7]

Recent studies reported the rate of medical complications in achondroplasia.[8–10] However, diagnostic method, follow-up length, medical record variability, and reliance on participant recall, limit the findings. According to the AAP guidelines,[3] the impact of changes in patient management have not always been described clearly and there are limited reports on the outcomes of interventions and service use in achondroplasia.

We provide a contemporary account of medical investigations, complications, interventions, outcomes, and service use in a defined Australian population of children with achondroplasia.

What this paper adds

- Children with achondroplasia have a high burden of medical complications and interventions.
- The rate of death in childhood is high at 2% (1 in 54).
- Fifteen per cent of our study group required hospital admission for intercurrent respiratory illnesses.

METHOD

We conducted a retrospective cohort study of medical complications in children with achondroplasia known to the Children's Hospital at Westmead, Sydney, Australia. The hospital hosts the only specialist clinic covering the state of New South Wales and the Australian Capital Territory, which together comprise 33.5% of the total Australian population.[11] The clinic has been providing multidisciplinary care to all children with achondroplasia in New South Wales and the Australian Capital Territory for over three decades and has a well-established comprehensive referral network. Children attend clinic review several times in the first year of life, then annually. All caregivers are educated on a delayed seating protocol to reduce the risk of thoracolumbar kyphosis. Ethics approval and a waiver of consent for retrospective data collection was granted by the Sydney Children's Hospitals Network Human Research Ethics Committee (ref. no. 2020/ETH001198).

Participants

All children with achondroplasia born between 1st January 2000 and 31st December 2019, who had at least two achondroplasia-related episodes of care at the hospital, were identified from electronic medical records and databases. Clinical diagnosis was confirmed with either a radiological diagnosis, a molecular diagnosis, or by having a first-degree relative with a molecular diagnosis. Radiological diagnosis was confirmed by skeletal survey reviewed by a clinical geneticist or paediatric radiologist with expert knowledge of bone dysplasia. Children were excluded if they had coexisting conditions that would affect the course of their disease. Participant data were excluded from the start date of active pharmaceutical treatment in clinical trials or from 18 years of age onwards.

Data collection

Retrospective data were collected from electronic and paper medical records for activity between 1st January 2000 and 31st December 2019. These included records of investigations and interventions carried out at the Children's Hospital at Westmead and correspondence verifying investigations and interventions performed at other centres.

Demographic data

Date and country of birth, sex, presence of parental achondroplasia, and date of death were collected. Date and method of initial diagnosis and presence of shortened bones on prenatal ultrasound were also recorded.

Craniofacial data

Number and timing of craniofacial investigations

Head ultrasound, head computerized tomography, head magnetic resonance imaging (MRI), and cervical spine (including base of skull) MRI scans were collected. The diagnosis of craniocervical complications including hydrocephalus, craniosynostosis, subdural haematomas, or craniocervical stenosis, as documented from these investigations, was recorded. Craniofacial interventions including ventriculoperitoneal shunt insertion, orthodontic procedures, maxillary advancement, and craniocervical decompression surgery were recorded; the outcomes of interventions documented on craniofacial imaging were also recorded.

Ear, nose, and throat data

The number and timing of polysomnography carried out at the Children's Hospital at Westmead and other tertiary paediatric hospitals were recorded. Sleep-disordered breathing was defined as a total apnoea–hypopnea index score greater than 1.[12] Hearing impairment was determined from audiology test results. Interventions including apnoea monitors,

non-invasive ventilation, supplemental oxygen, adenoidectomy, tonsillectomy, and insertion of tympanostomy tubes (grommets), and their outcomes were recorded.

Orthopaedic data

Lower-limb X-rays, whole-spine X-rays, and whole-spine MRI scans were recorded. Diagnosis of clinically significant lower-limb malalignment, clinically significant thoracolumbar kyphosis, and symptomatic spinal stenosis were recorded. Lower-limb malalignment and thoracolumbar kyphosis were deemed clinically significant when radiographic investigation was required. Interventions of lower-limb orthopaedic surgery, spinal bracing, and spinal decompression were collected. Intervention outcomes on relevant medical imaging were recorded.

Obesity data

Growth data collected included head circumference, height, and weight approximately every 3 months in the first year of life, then annually, with reference centiles from local achondroplasia-specific growth charts.[13] Growth data from children born preterm were excluded until 2 years of chronological age. Body mass index (BMI) was recorded annually from 2 years of age until the end of the study period. Obesity was diagnosed if a participant had a BMI greater than 30.[13] Interventions for obesity including dietician referral, weight management clinic, or medication were recorded. Obesity was recorded as resolved if the BMI fell below 30 and was maintained until the end of the study period.

Statistical analysis

Data were collected and analysed in Microsoft Excel. Data were visually reviewed for normality and standard descriptive statistics were used. Where data were normally distributed, the mean and SD were reported; for non-normally distributed data, the median and interquartile range (IQR) were reported. The frequency of medical investigations, complications, and interventions, and the age at which these occurred were calculated. Where possible, the length of the intervention and rate of resolution of complications were also calculated. Changes in the frequency of investigations including MRI and polysomnography over time were evaluated.

RESULTS

Participants

From 116 possible participants identified, 108 met the inclusion criteria. Reasons for exclusion were comorbid bone disease (n = 2), moving interstate (n = 5), and loss to follow-up (n = 1). Participant characteristics are summarized in Table 1. Ninety-nine participants (91.7%) entered the study at birth. The other nine (8.3%) participants entered the study after birth (mean age = 2 years 4 months, SD = 1 year 8 months) because they had only just moved to New South Wales or the Australian Capital Territory or presented late to specialist services. The median age of exit from the study was 8 years 8 months (IQR = 8 years 9 months) with a median follow-up of 8 years 8 months (IQR = 8 years 9 months). Longitudinal data were recorded across the entire period from birth to 2 years in 92 participants (85.2%), ages 2 to 5 years in 78 participants (72.2%), ages 6 to 10 years in 49 participants (45.4%), ages 11 to 15 years in 18 participants (16.7%), and ages 16 to 18 years in six participants (5.6%).

Craniofacial investigations, complications, and interventions

Half of the participants had a head ultrasound and almost half had a head MRI (Table 2); 75 (69.4%) participants had a head circumference above the 90th centile for achondroplasia, at least once in the first year of life, at a median age of 4 months (IQR = 2 months). The head circumference measures of 78.7% of these participants dropped back below the 90th centile, 33% by the age of 1 year, 28% between the ages of 1 and 2 years, 17% between the ages of 2 and 12 years, and 22% remained above the 90th centile until the end of the study. Fifteen participants were diagnosed with hydrocephalus, with four undergoing ventriculoperitoneal shunt insertion. Of these four, two had complete resolution of their hydrocephalus and two had partial resolution. One participant was diagnosed with left lambdoid craniosynostosis with marked plagiocephaly at 4 months of age and underwent cranial vault reconstruction surgery for this at 16 months of age with partial resolution. Three participants developed subdural haematomas during the study period. One was acute, that is, 3 years post-shunt insertion in a school-age child, and was treated with neurosurgery. Two were incidental findings in asymptomatic infants under 6 weeks old undergoing screening MRI and no treatment was required.

Of those participants who underwent cervical spine MRI, head MRI, or head computerized tomography, 51 (81.0%) were diagnosed with foramen magnum stenosis. Thirteen (12%) participants underwent decompression surgery at a median age of 10 months (IQR = 1 year 7 months). Subsequently, 10 had full resolution of their stenosis, two partial resolution, and one did not have resolution, with further surgery planned.

Three participants (2.8%) underwent orthodontic intervention and one participant had maxillary advancement. Outcomes were not available.

Mortality rate in this cohort was 1 in 54 (2%). Both deaths were sudden and unexpected in children under the age of 18 months with severe craniocervical stenosis. We cannot elaborate further due to ethical constraints.

TABLE 1 Participant characteristics (n = 108)

Characteristic	*n* (%)
Country of birth	
Australia	99 (91.7)
Overseas	9 (8.3)
Preterm birth	
Yes	9 (8.3)
Parental status	
Neither parent with achondroplasia	90 (83.3)
Sex	
Male	58 (53.7)
Female	50 (46.3)
Reason for exit from study	
Deceased	2 (1.9)
Study end date	89 (82.4)
Commenced active treatment on pharmaceutical trial	9 (8.3)
Transitioned to adult services	4 (3.7)
Moved interstate or overseas	4 (3.7)
Diagnosis[a]	
Clinical diagnosis	108 (100)
Prenatal genetic diagnosis	16 (14.8)
Prenatal diagnosis of shortened bones on ultrasound	51 (47.2)
Radiological diagnosis	60 (55.6)
Postnatal genetic diagnosis	88 (81.5)

[a]Diagnosis method is more than 100% because most participants had more than one diagnosis.

Ear, nose, and throat investigations, complications, and interventions

Most participants had at least one polysomnography test (Table 2). The median number of polysomnography tests was 2 (IQR = 3). Forty-eight participants had non-invasive ventilation recommended and five used supplemental oxygen. The median age of ceasing non-invasive ventilation was 2 years 8 months (IQR = 3 years) and ceasing supplemental oxygen took place at 1 year 4 months (IQR = 9 months), resulting in a median non-invasive ventilation duration of 1 year 7 months (IQR = 2 years 6 months) and supplemental oxygen of 8 months (IQR = 7 months). Sleep apnoea monitors were recommended for seven participants (median age of initiation was 2 months [IQR = 1 month]). Two participants with sleep-disordered breathing had resolution without the use of continuous positive airway pressure. Information on cessation of apnoea monitors was not available.

The median number of episodes of tympanostomy tube insertion was 1 (IQR = 2.5) with tympanostomy tube treatment lasting for a median of 3 years 9 months (IQR = 4 years 1 month). During that time, the tubes may have extruded and been replaced several times. Forty-seven participants had removal of both tonsils and adenoids, of which 11 required repeat removal of their adenoids.

Hearing impairment was diagnosed in 66 participants (61.1%) at a median age of 2 years 1 month (IQR = 2 years 1 month).

Orthopaedic investigations, complications, and interventions

Around half of the participants had lower-limb X-rays performed and almost a quarter required lower-limb corrective surgery including corrective osteotomies and hemiepiphysiodesis (Table 2). Of those who had lower-limb surgical correction, 11 required a second related surgery and a further three had a third surgical procedure performed. All but two participants had full or partial resolution of their lower-limb orthopaedic complications. One patient had surgery recommended in young adulthood while the other had a minor residual malalignment requiring ongoing monitoring in adulthood.

The eight participants who had spinal bracing did so for a median of 2 years 10 months (IQR = 1 year 1 month). Five participants had full resolution of thoracolumbar kyphosis with bracing, two did not have resolution, and data were not recorded for one participant. No kyphectomies were performed.

Of a proportion of participants over the age of 8 years (n = 61) at the end of the study period, 10 (16.4%) had symptomatic spinal stenosis. Three participants underwent decompression for symptomatic spinal stenosis, one cervical, one thoracic, and one thoracolumbar. Two had documented resolution and one did not resolve, with further surgery planned.

Obesity

Of the participants who were over the age of 12 years by the end of the study period (n = 39), 10 were obese. Three of these 10 participants were referred to a dietician and none were referred to a weight management clinic or were prescribed medication. Only one participant had documented resolution by the end of the study period.

Respiratory complications

Sixteen participants (14.8%) were hospitalized at the Children's Hospital at Westmead at least once due to a respiratory infection. The median age of first admission was 1 year 6 months (IQR = 1 year 7 months), with a median length of stay of 6 days (IQR = 3.5). A further four children were admitted for a second time at a median age of 2 years 2 months (IQR = 1 year), with a median length of stay of 3 days (IQR = 3). Two children were admitted a third time before the age of 3 years.

TABLE 2 Medical investigations, complications, and interventions (n = 108)

Investigation, complication, or intervention	*n* (%)	Median age and IQR (years:months) at initial investigation, complication, or intervention	Complication as the proportion of those who underwent relevant investigation, *n* (%)
Craniofacial investigations			
Head ultrasound	54 (50)	0:2 (0:4)	N/A
Cervical spine MRI	51 (47.2)	1:1 (3:5)	N/A
Head MRI	45 (42)	0:8 (2:10)	N/A
Head CT	17 (16)	1:0 (2:7)	N/A
Craniofacial complications			
Craniocervical stenosis	52 (48)	1.0 (2:8)	51 (81.0) (head CT, head MRI, or cervical spine MRI)
Hydrocephalus	15 (13.9)	0:1 (2:6)	14 (17.1) (head ultrasound, head CT, or head MRI)
Subdural haematomas	3 (2.8)	0:1 (0:1)	2 (2.4) (head ultrasound, head CT, or head MRI)
Craniosynostosis	1 (0.9)	0:4 (0)	1 (6.0) (head CT)
Ear, nose, and throat investigations			
Polysomnography	99 (91.7)	0:8 (1:4)	N/A
Ear, nose, and throat complications			
Hearing impairment	66 (61.1)	2:1 (2:1)	66 (66.0) (hearing test)
Sleep-disordered breathing	44 (40.7)	0:8 (1:4)	44 (44.4) (polysomnography)
Ear, nose, and throat interventions			
Adenoidectomy	61 (56.5)	2:6 (2:8)	N/A
Repeat adenoidectomy	11 (10.2)	N/A	N/A
Insertion of tympanostomy tube (grommet)	55 (50.9)	2:8 (2:2)	N/A
Non-invasive ventilation	48 (44.4)	1.0 (2:6)	N/A
Tonsillectomy	47 (43.5)	2:9 (2:4)	N/A
Supplemental oxygen	5 (4.6)	1:7 (2:6)	N/A
Orthopaedic investigations			
Lower-limb X-ray	47 (43.5)	6:8 (6:7)	N/A
Whole-spine X-ray	31 (28.7)	1:6 (1:4)	N/A
Orthopaedic complications			
Clinically significant lower-limb malalignment	46 (42.6)	6:2 (6:0)	46 (97.9) (lower-limb X-ray)
Clinically significant thoracolumbar kyphosis	24 (22.2)	1:6 (1:4)	24 (77.0) (whole-spine X-ray)
Symptomatic spinal stenosis	10 (9.3)	12:3 (2:9)	10 (100.0) (whole-spine MRI)
Orthopaedic interventions			
Lower-limb orthopaedic surgery	25 (23.1)	8:7 (3:7)	N/A
Spinal bracing	8 (7.4)	2:9 (3:8)	N/A
Spinal decompression surgery	3 (2.7)	13:0 (2:10)	N/A

Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; N/A, not applicable.

Changes in investigations over time

There was an increase in the percentage of participants having at least one cervical spine MRI and at least one polysomnography test over time (Figure 1). Forty-eight (44.4%) participants had both.

Investigations, complications, and interventions by age

Figure 2 shows the median age at which investigations, complications, and initial interventions occurred. Most investigations and complications occurred before the age of 4 years,

with orthopaedic complications and obesity occurring in later childhood and adolescence.

DISCUSSION

Our study reports contemporary data on medical complications in Australian children with achondroplasia. In contrast to previous Australian studies, all participants had a confirmed diagnosis of achondroplasia.[14] We had a mean follow-up of almost 9 years and report on the time after the AAP Committee on Genetics first published guidelines on Health Supervision for Children with Achondroplasia.[15] Our study provides comprehensive, continuous, retrospective data. This is valuable because emerging pharmaceutical treatments limit future opportunities for recording the natural history of medical complications in unmodified achondroplasia, particularly in children.

Our study reflects changes in practice for investigating medical complications in achondroplasia,[3-5] particularly rates of cervical spine MRI and polysomnography that increased over the study period (Figure 1).

The rate of preterm birth (8.3%) was similar to the 2017 data, showing that 8.7% of all Australian infants are born preterm.[16] This is in contrast to a recent study in the USA, which found higher rates of preterm birth (12.7%) than the US population preterm birth rate of 9.8%.[17]

There was a gradual change in the use of head MRI investigations over the study period, with participants only having head MRI in response to clinical symptoms in the early 2000s transitioning to almost all children having screening MRIs by the end of the study period. Forty-eight per cent of participants were diagnosed with craniocervical stenosis. However, when taken as a proportion of participants who had a head MRI, the percentage was 84.3%. This suggests craniocervical stenosis is probably underestimated in our cohort. Forty-four per cent of our cohort had both cervical MRI and polysomnography. This is considered complete screening for craniocervical stenosis according to the 2020 AAP guidelines.[5] This compares favourably with recently published data showing that only 14% of a large cohort in the USA had both investigations.[18]

We found that most participants who had a head circumference above the condition-specific 95th centile[13] did so at a median age of 4 months (IQR = 2 months). Rapid increases in head circumference are concerning because they may indicate the need for neurosurgical intervention.[9] The fact that this threshold is commonly reached so early supports the AAP guidelines recommendation for early clinical evaluation, MRI, and polysomnography.[5] Careful clinical evaluation must be included in the first 12 months of life.

Individuals with achondroplasia are likely to be more vulnerable to subdural haemorrhages due to intracranial venous hypertension, a result of jugular foraminal stenosis and enlargement of subarachnoid spaces putting the bridging veins at increased risk of rupture.[7] Although the phenomenon of subdural haemorrhages after minimal trauma has been reported,[7] we are not aware of rates previously published for comparison.

The use of BMI to define obesity in achondroplasia is problematic due to the reliance on height in the measurement.[19] Additional anthropometric measurements including waist circumference and skin fold thickness have been recommended; however, these measures were not routinely collected and were not available for the participants in this study. Despite the limitations of the BMI measure, we chose to use this as an indicator to evaluate the prevalence of obesity, interventions, and outcomes in our clinic. Obesity is thought to aggravate lumbar lordosis and consequently spinal stenosis,[19] but a link between obesity and symptomatic spinal stenosis has yet to be demonstrated.[19] We found that 3 of 10 participants with symptomatic spinal stenosis were obese; a larger cohort is needed for formal analysis.

In our cohort, 16 (14.8%) participants had at least one admission for acute respiratory symptoms. The rate of admission for typically developing children with bronchiolitis in the UK is 0.86%[20] and the Dutch 0 to 17 years population rate of admission with any acute respiratory infection is 1.8%.[21] We hypothesize that the high rate of hospital admissions in our study may be due to children with achondroplasia having anatomically narrow airways,

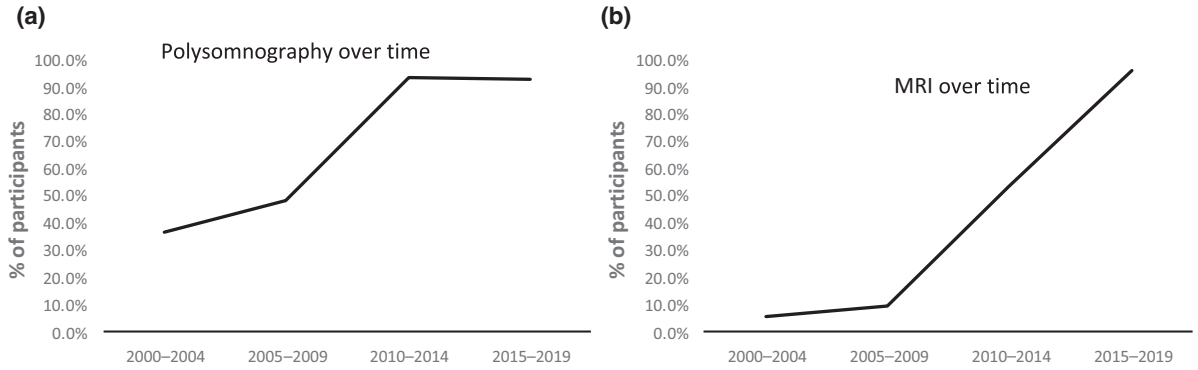

FIGURE 1 (a) Percentage of participants with polysomnography over time. (b) Percentage of participants with cervical spine magnetic resonance imaging (MRI) over time. Cohort 2000 to 2004: $n = 19$; cohort 2005 to 2009: $n = 31$; cohort 2010 to 2014: $n = 30$; cohort 2015 to 2019: $n = 28$

FIGURE 2 (a) Age at which the initial investigation occurred. (b) Age at which the diagnosis of complication occurred. (c) Age at which the intervention occurred. Top of the upper whisker: largest data element less than or equal to 1.5 times the interquartile range (IQR); top of the box: IQR (75th centile); line through the box: median; bottom of the box: IQR (25th centile); bottom of the lower whisker: smallest data element greater than 1.5 times the IQR; markers: mean; solid dots: outliers

a small chest due to rib shortening, and lack of respiratory reserve.

Limitations

This study has several limitations. A key limitation was the relatively smaller amount of data available as the age of participants increased. We collected data across the entire period from birth to 2 years in 85.2% of participants; however, this proportion decreased with increasing age. Data were not available for children between the ages of 12 and 18 years because they did not reach adolescence before the end of the study period, entered a drug trial ($n = 4$), moved interstate ($n = 2$), or transitioned to adult services ($n = 4$). No participant was lost to follow-up. Consequently, complication rates in later childhood and adolescence are less accurate than for younger children. Data for obesity and symptomatic spinal stenosis may be underestimated because this is the time when these complications are most likely to occur.

Participants had polysomnography tests at several centres and these were inconsistently reported, resulting in possible underestimation of sleep-disordered breathing. The approximate length of treatment with tympanostomy tubes was

measured using the dates of first and last insertion; however, tympanostomy tubes could have been in situ longer, until they extruded.

Tympanostomy tube insertion at other centres was not well documented, so the total number of episodes may be underestimated. There was a high rate of hearing impairment; however, there was poor documentation of the outcomes of hearing interventions. This was partly due to hearing tests being conducted at many different centres, with a lack of centralized record keeping.

Advice on delayed seating to prevent thoracolumbar kyphosis was given throughout the study period. However, there were no data on adherence to this and the impact this may have had on the development of thoracolumbar kyphosis.

This research focused on medical complications in achondroplasia and did not address the developmental, psychological, cultural, and social factors that contribute to 'complex developmental disability'.[22] We recognize that these factors may have influenced the investigation, diagnosis, and treatment of medical complications; however, the evaluation of this influence was beyond the scope of this work and could be an area for future consideration.

Recommendations

The severity of thoracolumbar kyphosis on X-ray was not uniformly documented. In future, a consistent scoring system would help with the evaluation of severity and outcomes of treatment.[23]

Documented interventions for obesity were low (33.3%) and only one participant had resolution of obesity. In future, more targeted intervention for obesity and evaluation of outcomes would be valuable.

The reasons for cessation of non-invasive ventilation were not consistently reported, particularly adherence or difficulties with mask fitting due to face shape. A better understanding of the factors affecting adherence would be helpful to guide future strategies to improve this.

Hearing should be tested annually[5] and we suggest a centralized approach to recording test results and outcomes of interventions. This will ensure that ongoing intervention including ear, nose, and throat consultations and hearing aids are provided in a timely manner.

Future studies are needed to explore the relationship between both head circumference and the need for foramen magnum decompression and body weight and orthopaedic complications.

We report contemporary rates of medical complications in an Australian population of children with achondroplasia. This information will guide clinicians with their expectant management of achondroplasia and provide context to families about the likelihood and timing of complications. With the emergence of pharmaceutical therapies in achondroplasia, this information is especially timely, providing data on the natural history of unmodified achondroplasia.

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DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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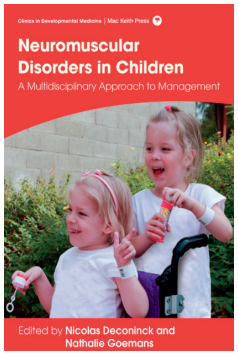

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