GRADUATION PROJECT

Degree in Dentistry

ACHONDROPLASIA AND ORAL CAVITY

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ABSTRACT

Introduction: Achondroplasia is the most common skeletal dysplasia, caused by FGFR3 gene mutations that impair endochondral ossification. Affected individuals often exhibit skeletal anomalies, particularly craniofacial problems such as midface hypoplasia, mandibular prognathism, dental crowding, and skeletal malocclusion, which may impact chewing, breathing, aesthetics, and quality of life; **Objectives:** To update information on dental malocclusion in patients with achondroplasia using clinical and radiographic diagnostic methods, focusing on identifying distinct malocclusion patterns and evaluating the effectiveness of orthodontic and surgical treatments in both short and long-term outcomes; **Methods:** A systematic literature review was conducted using sources including the CRAI Dulce Chacón library, PubMed, CINAHL with full text, and MedLine complete. Full-text, English-language articles from the past 10 years addressing oral conditions and treatments in achondroplastic patients were selected; **Results:** Analysis of six studies and clinical cases showed that orthodontic and surgical treatments significantly improved malocclusions in achondroplastic patients. Bimaxillary orthognathic surgery yielded the most stable long-term outcomes, while orthodontic treatments alone showed higher relapse rates. Early diagnosis and personalized treatment planning were key to achieving functional, aesthetic, and lasting results; **Conclusions:** Class III malocclusion is highly prevalent in achondroplastic patients. CBCT imaging is critical for accurate diagnosis and treatment planning. While orthodontics is effective for mild cases, severe skeletal discrepancies require orthognathic surgery. A multidisciplinary approach enhances long-term outcomes and highlights the need for further research and individualized therapeutic protocols.

KEY WORDS

Achondroplasia, Oral affectation, Dental malocclusion, Surgical treatments, Orthodontic treatments.

RESUMEN

Introducción: La acondroplasia es la displasia esquelética más común, causada por mutaciones del gen FGFR3 que afectan la osificación endocondral. Los individuos afectados a menudo presentan anomalías esqueléticas, particularmente problemas craneofaciales como hipoplasia del tercio medio del rostro, prognatismo mandibular, apiñamiento dental y maloclusión esquelética, que pueden afectar la masticación, la respiración, la estética y la calidad de vida; **Objetivos:** Actualizar la información sobre la maloclusión dental en pacientes con acondroplasia utilizando métodos diagnósticos clínicos y radiográficos, enfocándose en la identificación de patrones distintos de maloclusión y evaluando la efectividad de los tratamientos ortodónticos y quirúrgicos tanto a corto como a largo plazo; **Métodos:** Se realizó una revisión sistemática de la literatura utilizando como fuentes la biblioteca CRAI Dulce Chacón, PubMed, CINAHL con texto completo y MedLine completa. Se seleccionaron artículos relevantes en inglés y en texto completo de los últimos 10 años que abordan condiciones orales y sus tratamientos en pacientes acondroplásicos; **Resultados:** El análisis de seis estudios y casos clínicos mostró que los tratamientos ortodónticos y quirúrgicos mejoraron significativamente las maloclusiones en pacientes acondroplásicos. La cirugía ortognática bimaxilar ofreció los resultados más estables a largo plazo, mientras que los tratamientos únicamente ortodónticos mostraron mayores tasas de recaída. El diagnóstico precoz y una planificación terapéutica personalizada fueron clave para lograr resultados funcionales, estéticos y duraderos; **Conclusiones:** La maloclusión de Clase III es altamente prevalente en pacientes con acondroplasia. La imagen CBCT es fundamental para un diagnóstico y planificación del tratamiento precisos. Mientras que la ortodoncia es eficaz en casos leves, las discrepancias esqueléticas graves requieren cirugía ortognática. Un enfoque multidisciplinario mejora los resultados a largo plazo y resalta la necesidad de más investigaciones y planes terapéuticos individualizados.

PALABRAS CLAVE

Acondroplasia, Afectación oral, Maloclusión dental, Tratamientos quirúrgicos, Tratamientos ortodónticos

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1. INTRODUCTION

1.1 Definition, background and epidemiology

The most prevalent form of skeletal dysplasia which cause a disproportionate short stature in the affected patient is a rare genetic disorder known as Achondroplasia (ACH) (1,2).

This disease is considered to be in the ranking as causing fatal outcomes for life, disabling growth and to produce developmental disorders in children due to the mutation of the fibroblast growth receptor 3 (FGFR3) gene. (3,4)

By several study performed it has been estimated that the estimated occurrence of this pathology worldwide should be from 0.4 to 0.6 per 10,000 newborns, these numbers can be translated into almost 250,000 people that are affected by this condition worldwide, actually the global incidence of Achondroplasia is around 4.6 cases over every 100.000 live births even it is expected to decrease in the following decade.(2,5,6)

The ACH is considered to be related to various multi-systemic comorbidities being some of them also related to the scull and the oral cavity.

The Achondroplasia as we defined before is a rare genetic condition and it is known to be the most common skeletal dysplasia which is characterized by a typical very short stature normally with an average height among adult patient varying between 131 cm (4 ft. 4 in) ± 6 cm (2 in) for males and 123 cm (4 ft) ± 6 cm (2 in) for females. (2,5,7)

The ACH is affecting both genders with a male to female ratio of affectation near 1 (0,80), meaning that the possibility of being affected is almost equal for males and females. (8)

1.2 Pathophysiology

Achondroplasia arises from autosomal dominant mutations that are considered to be fully penetrant with minimal variability in expression and it is the most common among all the other dwarfing dysplasia. Due to the dominant inheritance pattern, all the ones with achondroplasia have a 50% of possibility to each child if the partner is an average height individual, however almost 80% of the cases who present ACH are due to new spontaneous mutation. This mean that 80% of newborns with this condition are born to two unaffected parents. (9)

From this point of view, one is led to believe that the recurrence to unaffected parents should be the same than occurrence in the whole population, but studies have shown that this is not the case, in fact, there have been observed a great number of unexpected cases of recurrence among siblings. (9)

The scientist has been studying how ACH manifested itself paying close attention to all genetic factors.

Nowadays after several researches, there have been identified almost 461 different genetic skeletal disorders related to more than 430 different causative genes. (5)

Among all these genes and factors that play an essential role for the human axial and craniofacial skeletal development, those with greater importance are the Fibroblast growth factor and receptors known as FGFs and FGFRs. (5)

After several studies about the genetic abnormalities in patients with Achondroplasia in 1994 has been discovered that ACH is characterized by a mutation which appear at the level of the transmembrane domain of the fibroblast growth factor receptor 3 (FGFR3), which is located on the short arm of the chromosome 4 affecting chondrocytes and mature osteoblast. (6)

The FGFR3 it is represented by a characteristic empty cup shape placed on the cell surface mainly in chondrocytes surface that generate cartilaginous bone, even if it is also expressed for examples in calvarias sutures, testes and brain. (9)

The FGFR3 activation after birth affect the body of the affected person by enhancing the inhibition of chondrocytes proliferation and hypertrophy. (6,7,10)

The mutation affecting the FGFR3 gene has the ability to activate tyrosine protein kinase activity enhancing negative regulatory function, which purpose is to inhibit the proliferation and differentiation of the chondrocytes, doing, it affects negatively the correct formation of the trabecular bone and consequently the correct bone growth. (6)

In the same study performed in 1994 it has been shown that 95-98% of all the population affected by ACH present a G (guanine)-A (adenine) base exchange at position 1138 of cDNA in exon 10 of the fibroblast growth factor receptor gene (FGFR3), while the amino acid at position 380 exchange glycine to arginine. (6)

It has been discovered, in 1998 that FGFR3 mutations normally are used to occur during the spermatogenesis process, with a huge possibility of developing new mutation point and increasing the probability to occur as soon as the paternal age advance. (6)

cDNA	Nucleotide alteration	Protein	Percentage	allele frequencies
c. 1138G > A or c. 1138G > C	glycine to arginine	p.Gly380Arg	95.5% (446/467)	4.79e-6 or 6.85e-7
c.1031C > G	serine to cysteine	p.Ser344Cys	0.4% (2/467)	NA
c. 375G > T	glycine to cysteine	p.Gly375Cys	0.6% (3/467)	1.20e-6
c.833A > G	tyrosine to cysteine	p.Tyr278Cys	0.4% (2/467)	NA
c.831A > C	serine to cysteine	p.Ser279Cys	0.2% (1/467)	NA
c.970_971 ins TCTCCT	the insertion of Ser-Phe after position Leu324	p.L324delinsLSF	0.2% (1/467)	NA
c.1043C > G	serine to cysteine	p.Ser348Cys	0.4% (2/467)	NA
c.649A > T	serine to cysteine	p.Ser217Cys	1.3% (6/467)	NA
c.1180A > T	threonine to serine	p.Thr394Ser	0.9% (4/467)	NA

Table 1. Showing the probability of a mutation causing ACH in the patient to occur from the one with more probability to occur to the one with less probability. (6)

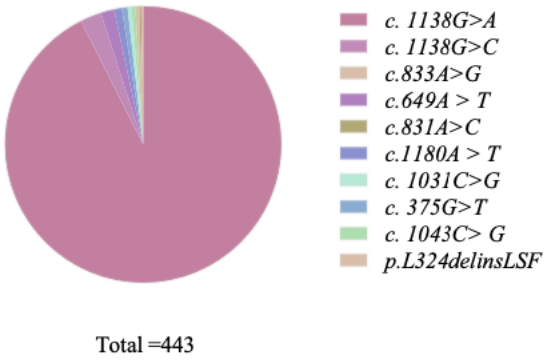

Figure 1. Graph showing the percentage of mutation happening in the different mutation site shown in the Table 1. (6)

1.3 Aetiology and risk factors

Achondroplasia is a recurrent Autosomal dominant disease that present a penetrance of 100% which is directly related to a pathogenic mutation Gly380Arg which affect the FGFR3 located in the 4p26.3 chromosome causing a variation in its codification in almost the 98% of the case in the patient affected by this pathology (11,12,13,14)

Through various studies performed over the heritability of the condition, it has been proved that the ACH condition in 80% of the cases is not related to a genetic pattern being both parents not affected by the disease, instead being directly related to a new mutation occurring in the spermatogenesis or during the oogenesis, being a mutation in the spermatogenesis the most likely to occur as soon as the paternal age advance.(6,14)

Only in about 20% of cases, achondroplasia is inherited from an affected parent due to the autosomal dominant inheritance. (13)

Focusing in the genetical pattern it can be affirmed that each child of an affected parent has a 50% chance of inheriting the mutation, while if both parents present the ACH condition each of the children follow this probability pattern: 25% chance of being of average height, 50% chance of inheriting Achondroplasia, while the last 25% chance for the child is to present a fatal condition called homozygous ACH, which consist in inheriting two copies of the gene mutation. (13)

Generally speaking, patients affected by ACH have a normal life span expectancy, however, it seemingly does occur that cardiovascular complications can happen in the middle age. Therefore, it is estimated that ACH patients have 10 years less to live than the ones who are not. (9)

1.4 Clinical manifestation

Almost all the ACH patients present some recurrent and specific physical clinical presentations of the condition:

- Small stature, even we can't consider this feature as a clear sign as soon as in infants mainly it's harder to recognize especially if they are very young. (9)
- Short limbs and rhizomelic disproportion, being this the most common feature and always present even if the severity of this feature can vary between every ACH patient. (9,11,15,16)
- Macrocephaly, means that the patient presents a larger head size compared to the normal people, maintaining this condition during their whole life. This condition in ACH patient present also a variable frontal and parietal prominence. (9)
- Midfacial retrusion is characterized by underdevelopment of the cartilaginous bones in the central facial region, leading to a flattened appearance of the midface. This condition also often presents with a low nasal bridge, a flattened nasal spine, and forward rotation of the nose. (9)
- Small chest: The chest is typically smaller than the average size of a patient not affected by ACH, while the ribs present an unusually flexibility. This condition causes a paradoxical movement during the inhalation, which is normally mistaken for retractions associated with respiratory distress. (9)
- Thoracolumbar kyphosis which is a spinal condition where there is an excessive, forward-rounded curvature in the area where thoracic and lumbar spine meet. This condition develops during infancy but is not present at the moment of the birth. (9)
- Lumbar hyper lordosis, a condition where the ACH patient present an exaggerated inward curve of the lumbar spine whit a more pronounced C-shape arch. This condition led to an

excessive forward tilt of the pelvis in a condition called “swayback” posture and begins when the child start walking. (9)

- Limited elbow extension (9)
- Short fingers and the possibility to present a specific hand configuration also known as trident configuration. (9)
- Hips and knees are presenting hypermobility. (9,17)
- Bowing of the legs mesial segment, it is the condition where the legs curve outward leaving space between the knees while the ankle is closer, even if this condition is not congenital, it can be developed during the childhood by ACH patients. (9)
- The majority of the ACH patients present a condition called hypotonia or easily described as reduced muscle tone, which leads the patient muscles to seems “floppy” or overly relaxed. (9)

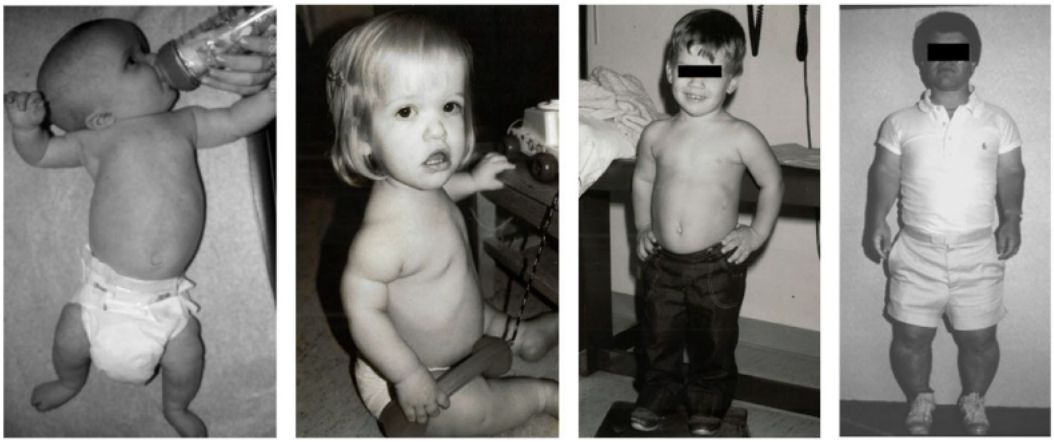

Figure 2. The picture shows the body phenotype in individuals of different ages, from left to right: infancy, early childhood, childhood and finally adulthood. (9)

Figure 3. The picture shows the variability of craniofacial characteristics of ACH patients. (9)

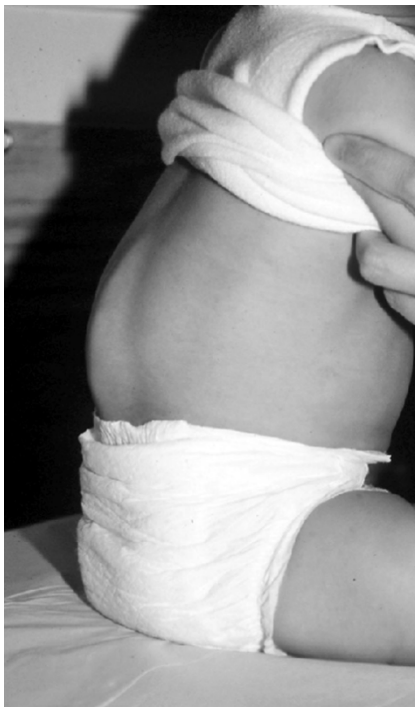

Figure 4. The picture shows the typical condition of flexible kyphosis that can be seen in infants and young children with ACH condition. (9)

1.4.1. Respiratory abnormalities.

It has been reported that in patient with Achondroplasia it is very common to face some breathing disorders especially during sleeping, as it could be among all the obstructive sleep apnoea (OSA) condition. Due to the small sample size of the studies performed till now it is difficult to do an estimation of how frequent OSA can occur in this kind of patients, however it is estimated that the prevalence of this respiratory condition has a range varying from 30% to 60% across all age groups and this prevalence make it clinically relevant. (9,14)

Obstructive sleep apnoea condition does not present any kind of life-threatening problem, even if in some cases can be the cause of long-term effects over the systemic health that must be mitigated if possible. (14)

One of the systemic problems that OSA can produce in ACH patients is related to growth hormone releasing that happen during night time while sleeping, which due to a disrupted sleep can negatively interfere with the growth of the patient. (9)

Obstructive sleep apnoea can produce serious effects at any age, particularly affecting the cardiovascular system producing low oxygen levels due to airway obstruction which lead to pulmonary hypertension progressing over time to cor pulmonale and systemic high blood pressure. (9,18)

The management of OSA can be divided in 3 different procedures, the first one performed on infants is the adenoidectomy because they do not present hypertrophy of the tonsils, the second

one is the tonsillectomy with adenoidectomy and the third one is the turbinectomy which can be performed at any age in case the turbinates are sufficiently big to perform this kind of surgery. (18)

1.4.2. Cardiovascular abnormalities.

Cardiovascular problems in patients with ACH are often due to complications from obstructive sleep apnoea (OSA) problems which can cause a prolonged oxygen desaturation possibly leading to pulmonary hypertension. If left untreated, this condition can progress to cor pulmonale, which is a form of heart failure affecting the right side of the heart due to chronic strain related to elevated pressure in the pulmonary arteries. Additionally, OSA and its associated intermittent hypoxia are believed to contribute to an increased risk of systemic hypertension. (9)

Another common cardiovascular abnormality to take into account in individuals with ACH is the Ventricular enlargement. This condition arises from basicranial hypoplasia caused by impaired endochondral ossification, which results in jugular vein stenosis and obstructed cerebrospinal fluid flow or due to high pressure in the dural venous sinus. Although true hydrocephalus (ventricular enlargement with neurological symptoms) is rare to find in achondroplasia patient even if, when it occurs it is a very severe complication. (14)

The best treatment in case the patients present a ventricular enlargement the best treatment option to perform is: VP shunt placement. (14)

1.4.3. Hearing abnormalities.

Due to an abnormal skull growth people with Achondroplasia, can face a very common condition in this kind of patient which is middle ear problem directly caused by poorly functioning Eustachian tubes or hearing loss due to jugular bulb dehiscence.

Regarding all the patients facing audio abnormality, it has been shown that around 50-70% of the patients experience middle ear dysfunction, while only 38-60% of them face hearing loss.

Audio abnormalities are considered especially problematic in the very young age of the patient when hearing is fundamental for the speech and language development. (9)

Being hearing loss early detection fundamental for individuals with achondroplasia, especially at a young age, to reduce any kind of language development problem, hearing tests and tympanometry should start from birth until school age. Being medical treatments for these conditions almost always ineffective, the best treatment option should be pressure-equalizing tubes until the age of 7-8 years more or less. (9)

1.4.4. Metabolic abnormalities.

Metabolic processes are equally of significance as craniofacial disorders, specifically for patients with achondroplasia.

These children are likely to suffer from overweight as early as in the childhood, since they need a lower calorie intake and at the same time, their energy expenditure during the day is lower than a person without ACH, and exacerbate during adolescence. (9,19)

Some studies found out that this obesity, which is affecting the patients with ach it is not shown to be directly related with a diabetic profile, instead of low-level insulin production and glucose levels. (19)

Early intervention by establishing healthy diet habits, active and regular exercise, and consistent health monitoring improves life quality and prolongs lifespan. (19)

Another intervention which has been performed successfully in obese adult patient with ACH is the bariatric surgical procedure. (9)

This procedure does not guarantee any kind of results in the medium-long term, that is why is highly contraindicated due to the high risk it involves for the patients (19).

1.4.5. Neurological Abnormalities.

Given the functional skeletal alteration and development, individuals with achondroplasia frequently exhibit neurological anomalies. It is characteristic of typical achondroplasia to have a narrowed foramen magnum which can compress the brainstem and the upper parts of the spinal cord bringing about central apnoea and sudden infant death syndrome. (9)

Another issue of concern is hydrocephalus which results from impaired flow of cerebrospinal fluids due to jugular vein stenosis or high venous pressure. (14)

These disorders may exhibit signs and symptoms such as headaches, vomiting, increased irritability or in notable cases developmental retardation disorders. (9)

By causing nerve compression, spinal stenosis, may cause some pain, numbness and weakness in both lower limbs, motor impairment, intermittent claudication or even muscle control over the bladder and bowel. (14)

Hydrocephalus should be diagnosed early and managed with pertinent treatments such as surgical decompression or ventriculoperitoneal shunting. (9)

1.4.6. Psychosocial and psychological problems.

Quality of life in ACH patients can be viewed as both a physical and a psychosocial consequence of the disease. Many studies combine informations related to all skeletal dysplasia, so specific information about achondroplasia only is relatively limited. (9)

One of the most important complications to take into account in adult ACH patients is the chronic pain, with almost 2/3 of them having significant pain which affect their normal lifestyle. This pain often leads to incapacitation in normal physical functioning, by reducing walking endurance and also hampers independence in some activities of daily living, with 10-15% of the

patients needing assistance. Generally functional health in these patients start to show decline in the 4th and 5th decades of life due to lumbosacral spine problems. (9)

All these daily problems that ACH patients can face can also be added to psychosocial problems, including social inconvenience, working inconvenience and impaired self-esteem, associated with short stature which potentially impact their perceived competence and a possible suitability for some work occupation. (4)

In general, Achondroplasia and the others dysplasia are associated with increased depression, anxiety and reduced self-esteem. More specifically, ACH can be associated in adults with reduced income, education and employment success, with adverse implication for social, economic and also family life. (4,9)

1.4.7. Craniofacial abnormalities and dental malocclusion.

Due to midfacial hypoplasia, malocclusion is often present in people with achondroplasia. This combine hypoplastic maxillary elements in conjunction with quite pronounced mandible growth. (9)

This characteristic together with macroglossia can cause a malocclusion presenting most of the times a skeletal class III together with dental crowding, which in turn can cause delayed teeth eruption and other systemic condition such as sleep apnoea.(2,13,20)

Some studies have been conducted on dental malocclusion and craniofacial abnormalities in patients with ACH, one of these studies reports the results shown in the Table :

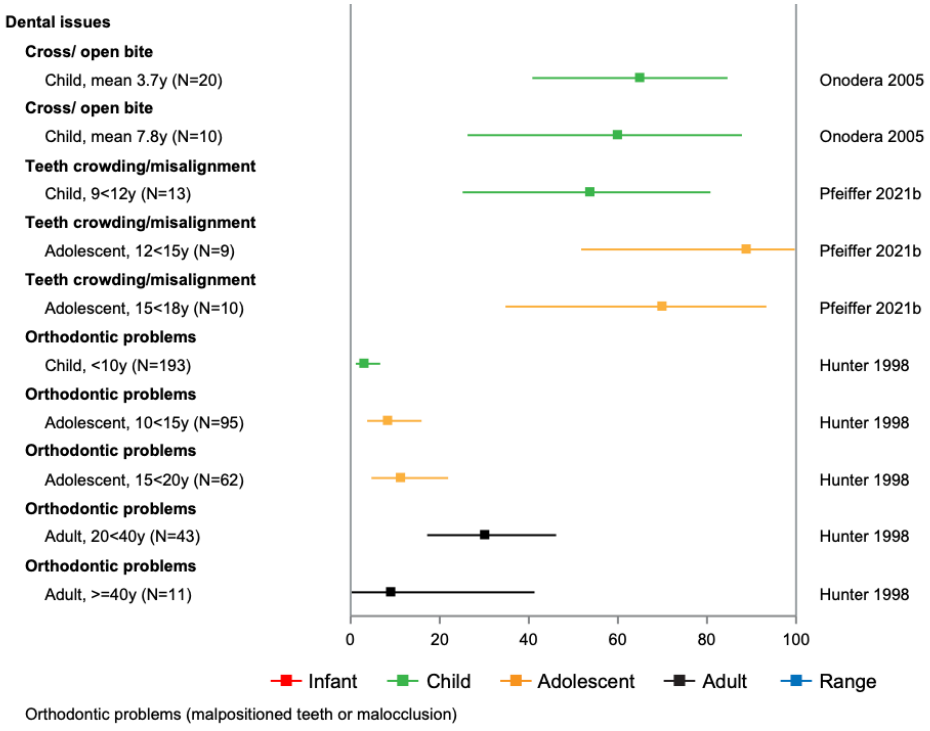

Table 2. Dental malocclusion problems at different ages. (2)

Table 2 shows the dental and orthodontics findings in patients with Achondroplasia at various age groups, the prevalence of the different types of malocclusions, and its related problems.

Crossbite and open bite are seen mainly in young children with an average age of 3.7 and 7.8 years.

Crowding and displacement of teeth are more marked in older children and in adolescents near to the puberty, between 12 and 18 years. Orthodontic problems, including malpositioned teeth and other malocclusions, continue throughout childhood into adulthood.

However, the prevalence and nature of orthodontic problems change with age, reaching a peak during adolescence and continuing into adulthood.

These findings point to the need for early and continued dental assessment and preventive dentistry as well as an early treatment to avoid future complication and a better general health. (2,13)

Depending on each patient and the severity condition present in every case the treatments we can take into consideration are: maxillary orthodontic expansion treatment and orthognathic surgical treatment which are the most common types of treatment performed in patients affected by ACH. (13)

1.5 Diagnostic findings

The diagnosis of Achondroplasia can be easily performed in the early infancy of the patient due to physical and radiological findings, although prenatal diagnosis lately has become more accurate and efficient. (5,9,12)

One could be almost certain that, even if no official clinical diagnostic criteria have been published, Achondroplasia normally presents with some clear clinical and radiologic characteristics that allow a highly confident diagnosis near the 100% of probability, even if there are some exceptions as, for instance, the cases of significantly premature newborns where the diagnosis can be extremely challenging. (9,10)

Normal findings in cases of patients with ACH

- Prenatal findings

  During the prenatal period there are certain studies which, with the help of some ultrasound technique during the pregnancy help one to confidently assume that the new patients will present shortness of the extremities at a mean age of 28.7 weeks (±3.6 SD).

  These ultrasound techniques have an 84.2% chance of ascertaining the diagnosis. (8)

- Early infancy

  During the early infancy period it is possible to diagnose ACH through different typical physical and radiological signs.

From a clinical point of view the most important physical characteristics to pay attention are the rhizomelic limb shortening together with other physical markers such as shortened fingers, condition known as brachydactyly, which in the most of the cases is matched with a distinctive hand shape characteristic for this disease called “trident hands condition”. (5,9)

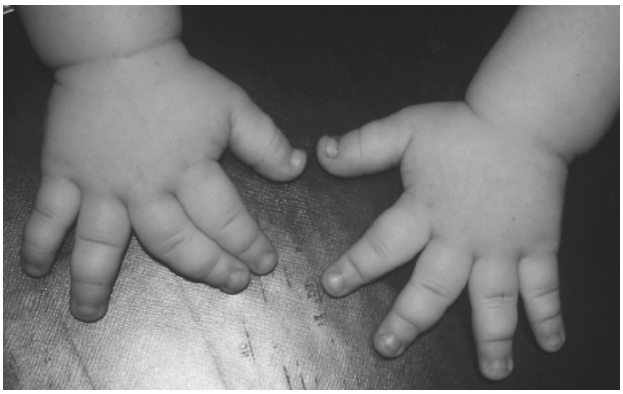

Figure 5. Show a patient hands with achondroplasia presenting brachydactyly and trident hand condition. (9)

Other physical condition that can help to diagnose the ACH can be: The Macrocephaly condition which can be find with some unique facial features such as prominent forehead or flattened nasal bridge or other typical characteristics but harder to recognize such as limited elbow movement, hyper mobile joints, bowed legs or narrow chest cavity (5)

Radiologically a patient with ACH shows several key features such as the shortening of the long bones of the whole body especially arms and legs, presenting a more marked flaring of the metaphysis of these bones. (5)

In the legs the femoral necks are shortened presenting two different typical condition, the first one affect the proximal part of the femur appearing more radiolucent in the x-ray, while the distal end of the femur present a Chevron-like shape. (5)

The fibula bones are proportionally longer than the tibias.

Other details that can be find analysing the patients with ACH are:

A short and broad appearance of the pelvis presenting at the same time the acetabulae oriented in a horizontal way and squared-off iliac wings, while in the spine the vertebrae present shortened pedicles, and the spaces between each vertebra in the lower spine become narrower in the caudal direction. (5)

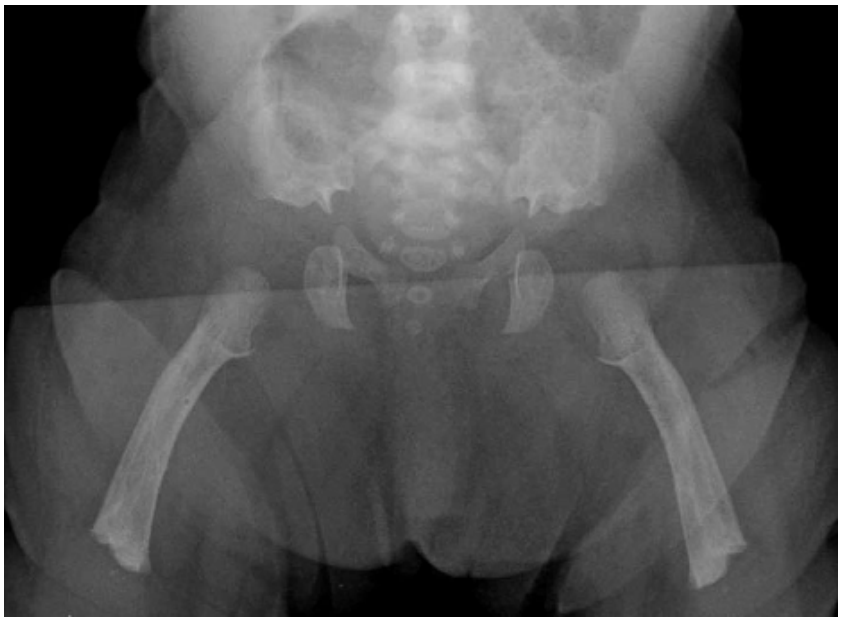

Figure 6. Anteroposterior radiograph showing the pelvis with the acetabule oriented in a horizontal way and squared-off iliac wings, femoral necks shortened with the proximal part more radiolucent and the distal part showing a chevron-like shape. (9)

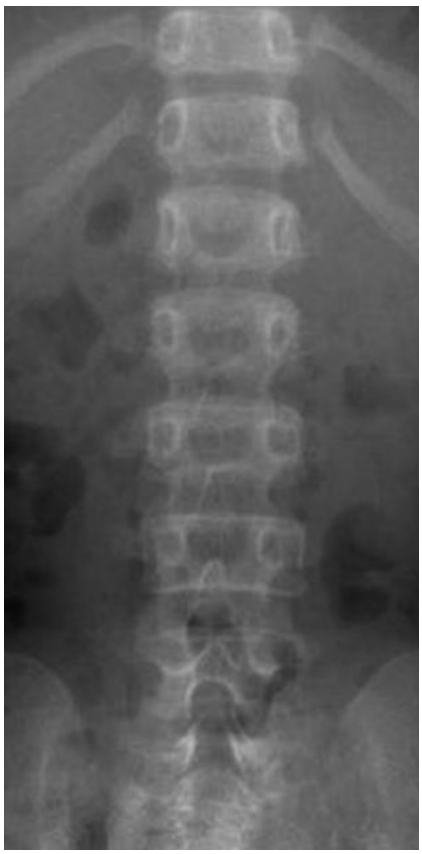

Figure 7. Can be observed the narrowing of the space between each vertebra in the lower spine (14).

To detect and diagnose ACH can be also used the molecular confirmation through the PCR even if this method is not generally needed as soon as normally the typical anatomical findings are enough to have a almost sure diagnosis near to the 100%. (5,9,10)

In fact, in all the studies performed over molecular tests, the results obtained present a 99% of mutation 1138G > A and only a 1 % presenting the 1138 G > C mutation. (9)

A. Symptoms 1. Short stature with marked shortening of the extremities due to rhizomelia (Short stature of −3 SD below average, shortening of extremities with an arm span/body height of < 0.96) 2. A characteristic facial configuration (relatively large cranium, protruding forehead, a flattened nasal bridge, central facial hypoplasia, and relative protrusion of the mandible): head circumference >1 SD above average 3. Trident hand (widening of the space between the middle and ring fingers when the fingers are splayed)
B. Findings on plain X-ray examination 1. Limbs (frontal view): Tubular bones are thick and short; metaphysis of long bones having a large width, irregular with a cup-shaped deformity (cupping); shortening of the femoral neck; belt-like translucency of proximal part of femur; characteristic reverse V shape on the distal femur epiphysis; fibula is longer than the tibia (fibula length/ tibia length) > 1.1; determination is difficult during infancy because ossification is not yet progressed. 2. Spinal column (frontal view, lateral view): Progressive decrease in the interpedicular distance in the lumbar spine (interpedicular distance ratio of L4/L1 < 1.0) (not prominent during infancy); concavity to the posterior lumbar vertebral body. 3. Pelvis (frontal view): Narrowing of the sciatic notch; iliac wing hypoplasia with a rectangular or round shape; the acetabular roof is flat, and the cavity of the lesser pelvis resembles a champagne glass. 4. Cranium (frontal view, lateral view): Basicranial shortening, facial bone hypoplasia 5. Hand (frontal view): Trident hand, and tubular bones are thick and short.
C. Differential diagnosis The following disorders are included in the differential diagnosis: Skeletal dysplasia, such as hypochondroplasia, metatropic dysplasia, and pseudoachondroplasia. When the differential diagnosis is difficult based on clinical symptoms and X-ray findings, a genetic diagnosis should be performed.
D. Genetic testing G380R mutation is observed on the fibroblast growth factor receptor 3 (*FGFR3*) gene.
<Diagnostic category> Definite: Satisfies all 3 items from A and 5 items from B, and excludes differential diagnosis diseases identified in C. Or, satisfies D for Probable or Possible. Probable: Satisfies at least 2 items from A and at least 3 items from B, and excludes differential diagnosis diseases identified in C. Possible: Satisfies at least 2 items from A and at least 2 items from B, and excludes differential diagnosis diseases identified in C.

Table 3. Table describing the diagnostic criteria used for detecting Achondroplasia. (14)

1.6 Management of Achondroplastic patients

When we talk about management of ACH patients it can be divided into different section taking as a reference the age of the affected person.

The Management of ACH can be divided in:

1.6.1 Management of the condition in infants:

The patient should be reevaluated by a multidisciplinary team every 2-4 months in the first year of life and 3-6 month during their infant period, in this revaluation they are subjected to MRI to be sure there are not observed any developmental delays which can help to evaluate the foramen magnum stenosis and cervicomedullary compression condition among other things. (9,13)

Every time the patients are going to be revaluated it is mandatory to perform a detailed evaluation for cervicomedullary compression, hearing evaluation, neurological evaluation and an evaluation of the growth of the whole body to avoid any severe consequence for the baby. (13)

1.6.2 Management of the condition in childhood:

It is important to evaluate the patient and being able to identify when the patient present some abnormal development so the right support can be provided to the affected child.

The most important thing to be checked during their childhood of the patients are: Hearing, speech and language delay, obstructive sleep apnoea (OSA), careful monitoring of the spine to avoid the progression of kyphosis, Genum varum condition and healthy lifestyle together with physical activity being monitored by a physiotherapist. (13)

1.6.3 Management of the condition in adolescence:

One of the most important things to evaluate in adolescence patient with ACH as well as in adult patient is: Identify and analyse every type of activity limitation such as daily activity due to their short stature or some other condition, such as obesity which is affecting most of the ACH patients, through regular follow up visits. (9,13)

During the adolescence ACH patient can also face physical activity problems that is why it is advisable to be followed by a physiotherapist.

The patients with symptoms of spinal stenosis should be referred to a spinal specialist with experience with patients affected by ACH. (13,21)

1.6.4 Management of the condition in adulthood:

In adult patient with ACH, it really important to perform regular follow up visits to avoid any complications, even if at this stage the doctors focus to treat the symptoms more than evaluating the progression of the severity of the ACH condition (13)

The doctors mainly focus on monitoring back pain, symptomatic spinal stenosis, blood pressure, hearing loss, psychosocial conditions and obstructive sleep apnoea (OSA). (13)

The treatment of Achondroplasia aims to interact with FGFR3 by reducing its excessive activation, reducing in this way its function and consequentially stimulate a linear bone growth.

Now there are many studies try to find the best treatment for ACH condition.

Current efforts to find effective treatments for Achondroplasia have taken divergent leads on innovative pathways that focus on FGFR3 overactivity:

- One of the possible strategies used by the scientist is by applying FGFR selective small molecules TKI (tyrosine kinase inhibitors) to reduce the overactivity of FGF3. (12)

- Another promising strategy employs monoclonal antibodies that block ligand binding to the receptor that sequester the FGFs and thereby prevent any kind of receptor activation even if monoclonal antibodies have not been tested in vivo in ACH cases. (12)

There are also other kind of treatments which aim to act on the defects in chondrocyte proliferation and differentiation:

- One of the possible strategies is the intermittent injection of PTH 1-34 (Teriparatide), which have been used successfully in animal models of ACH to improve skeletal development. The clinical use of this treatment, is currently limited to short-term use in human beings due to a need for further trials on its long-term safety for ACH. (12)

Other emerging strategies also involve repurposing existing drugs such as:

- Antihistamines, for motion sickness, such as meclizine, have demonstrated an increase in chondrocyte activity and bone growth in mouse; however, the impact was limited with respect to structure size of the foramen magnum. (12)
- Statins, on the other hand, are widely used because have shown early promise in restoring normal chondrocyte function, leading to a improved bone growth (12)

However, there are still concern about their potentially harmful effects on the development of cartilage which still need further research. (12)

Nowadays we have some promising treatment, the most promising is BMN-111 which is a stabilized form of C-type natriuretic peptide (CNP), which controls bone growth through its receptors. This has shown encouraging results in preclinical studies and is currently considered the leading candidate to improve the growth complications in patients with ACH. (12)

The most used treatment nowadays is the use of GH (growth hormone) in patients starting at their 3 years old till their 17 for the boys and 15 for the girls. (14)

1.7 Justification of the work

Achondroplasia as described in the past paragraphs can cause craniofacial development and oral health problem such as midface hypoplasia, mandibular prognathism and last but not least important dental malocclusion.

Due to all this condition affecting ACH patients the oral health challenges faced by these individuals go beyond a mere aesthetics problem, in fact, these characteristics affectation cause various functional issues such as chewing or speech problems or even some temporomandibular joint disorder.

All these problems caused by ACH condition have been shown to significantly impact the quality of life of the affected patients.

A bibliographic review of this condition and more specifically ACH problems affecting the oral cavity is useful to fill the gaps in all the different oral studies performed in ACH patients helping the dentists to adopt a well-defined and a standardized approach to the diagnosis and treatment of Achondroplastic patients suffering oral problems and craniofacial developmental disorders.

2. OBJECTIVE

Update dental malocclusion in patients with achondroplasia using both clinical and radiographic diagnostic methods, with a focus on identifying distinct malocclusion patterns: assessing the efficacy of both orthodontic and surgical interventions, examining their impact on dental alignment and chewing function over a short and long term.

3. MATERIAL AND METHODS

3.1 Type of study

This study is a systematic review performed with the use of the following database: CINAHL with full text, MedLine complete, PubMed.

All the article used in this study were written in the English language, dated within the last 10 years (published after 2014). Excepted for the following articles: Oral findings in a typical case of achondroplasia. Celenk P. et al. in 2003 (22), Correction of anterior open bite in a case of achondroplasia. Karpagam S. et al. in 2005 (23), Survey of the present status of sleep-disordered breathing in children with achondroplasia. Kieko Onodera et al. in 2005 (24), and Medical complications of achondroplasia: a multicentre patient review. Hunter AGW et al. in 1998 (25).

The PICO research question used was: In patients with Achondroplasia condition (P), by looking dental malocclusion (I); which are the best treatment option (C), when comparing orthodontic and surgical interventions over a short and a long-term treatment (O)?

The research equations used in the CINAHL with full text database were “Achondroplasia” AND “Clinical manifestation” OR “General manifestation”; “Achondroplasia” AND “Oral Manifestation”; “Achondroplasia” AND “Dental treatment”; “Achondroplasia” AND “Dental problems” OR “Dental malocclusion”

The research equations used in the MedLine complete database were “Achondroplasia” OR “Dwarfism” AND “Oro dental effects”; “Achondroplasia” AND “Dental alteration” OR “Oral manifestations”; “Dental treatment” AND “Achondroplasia”

The research equations used in the PubMed database were “Achondroplasia” OR “Dwarfism” AND “Oral findings”; “Achondroplasia” AND “Dental Manifestations” OR “Oral affectation”; “Dental treatment” AND “Achondroplasia”; “Anterior open bite” AND “Achondroplasia”.

4. RESULTS:

A total of 1093 articles were obtained primarily using the scientific databases PubMed, Dental and Oral Science Sources, and CINAHL with full text. After removing 149 duplicate articles, and 87 more for other reasons, a further 804 records were excluded. In total, 53 articles were assessed for eligibility, with 47 being removed for reasons such as having insufficient data, lack of relevance based on the title and being based on other congenital syndromes. The final number of studies included in the review was 6 , all of which were published in English.

Among the studies and cases reports considered in this systematic review, one was carried out in France (7), one in USA and Spain (21), one in Turkey (22), one in India (23), one in Japan (24) and one only USA (Delaware) (25). There is no age range taken into consideration and they are including both male and female genders.

The studies were mostly cross sectional or case studies reports. Although there weren´t many with large samples, we included in this study some cases report. Four of the articles used for the results were published outside the 10 years limit in the exclusion criteria: Celenk P. et al. in 2003 (22), Karpagam S. et al. in 2005 (23), Kieko Onodera et al. in 2005 (24), and Hunter AGW et al. in 1998 (25).

However, these studies were included in the review because of their relevance.

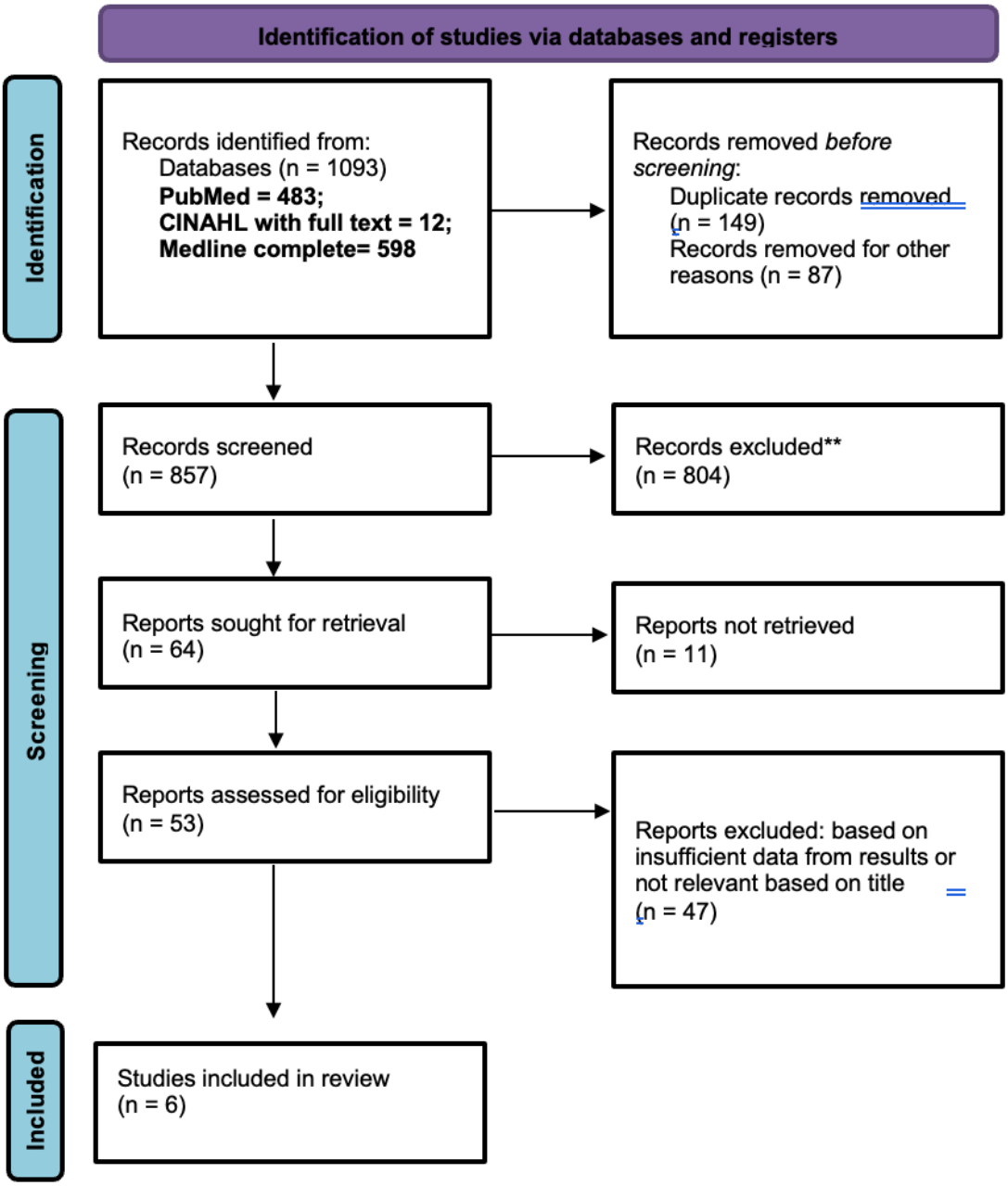

Figure 8. PRISMA flow diagram showing the articles selection process and the included studies.

Table 4. Dental issues incidence at all ages in patients with Achondroplasia.

	TYPES OF STUDY	SAMPLE SIZE (n)	AFFECTED PATIENTS	INCIDENCE PERCENTAGE	AGE OF THE PATIENTS	TYPE OF DENTAL ISSUE
Onodera 2005 (24)	Comparative study	20	17	70%	3.7 y/o average	Cross bite / Open bite
		10	6	60%	7.8 y/o average	Cross bite / Open bite
Pfeiffer 2021 (21)	Qualitative research study	13	7	54%	9 <12 y/o (child)	Teeth crowding / Misalignment
		9	8	89%	12<15 y/o (adolescent)	Teeth crowding / Misalignment
		10	7	70%	15<18 y/o (adolescent)	Teeth crowding / Misalignment
Hunter 1998 (25)	Restrospective cross-sectional study	193	6	3%	<10 y/o (child)	Malocclusion / Orthodontic problem
		95	8	8.5%	10<15 y/o (adolescent)	Malocclusion / Orthodontic problem
		62	7	11.3%	15<20 y/o (adolescent)	Malocclusion / Orthodontic problem
		43	13	30.3%	20<40 y/o (adolescent)	Malocclusion / Orthodontic problem
		11	1	9%	>/= 40 y/o (adolescent)	Malocclusion / Orthodontic problem

AUTHORS	TYPE OF STUDY	SAMPLE SIZE (n)	AFFECTED PATIENTS	INCIDENCE PERCENTAGE	AGE OF PATIENTS	TYPE OF DENTAL ISSUE
Onodera 2005 (24)	Comparative study	30	20	66%	6 y/o average	Cross bite/ Open bite
Pfeiffer 2021 (21)	Qualitative research study	32	22	68.8%	9<18 y/o	Teeth crowding / Misalignment
Hunter 1998 (25)	Restrospective cross-sectional study	404	35	8.7%	All ages	Malocclusion / Orthodontic problem

Table 5. Dental issues incidence in patient with achondroplasia, comparison of 3 different studies and age group

PATIENT	AGE	SEX	ORAL MANIFESTATION	TREATMENT PERFORMED	START OF THE TREATMENT (AGE)	RESULTS		
						MOLAR CLASS ACHIVED	DENTAL ALLIGMENT ACHIVED	OCCLUSAL RELATIONSHIP
Patient 1 (7)	12	Female	-Class III molar relation -Midface hypoplasia -Concave facial soft tissue profile -Vertical chin excess -Dental malocclusion	-Orthodontics procedure (transverse maxillary expansion) -Orthognathic surgery (placement of a palatal circuit breaker) -Bimaxillary orthognathic surgery (Le Fort I advancement osteotomy) -Bilateral sagittal split osteotomy -Reduction genioplasty -Orthodontic treatment	15(ortho tto) 17 (bimaxillary surgery)	Class I achieved	Good alignment	---
Patient 2 (7)	16	Male	-Class III molar relation -Anterior open bite -Dentoskeletal dysmorphias	-Orthodontics treatment -Bimaxillary orthognathic surgery (Le Fort I advanced osteotomy and bilateral sagittal split osteotomy)	12 (ortho tto) 17 (surgery)	Class I achieved	Good alignment	Correction of the open bite
Patient 3 (7)	11	Male	-Class III skeletal and dental relation -Edge to edge incisors relation -Narrow maxilla -Dental malocclusion	-Orthodontic treatment by anchorage plates	11	Class III	Bad alignment	---

Patient 4 (22)	16	Male	-Crowded teeth -Class III skeletal and dental relation -Posterior open bite -Cross bite -Narrow maxilla	-orthodontic treatment with Hyrax (palatal expansion to correct cross bite) -Orthodontic treatment with brackets (for alignment)	16 (hyrax tto) 17(brackets)	Class I	Good alignment	Correction of the open bite and cross bite
Patient 5 (23)	14	Female	-Maxillary retrognathism -Vertical excess -Anterior open bite with crowded lower incisors and protruded upper incisors -Class III skeletal and dental relation -Missing 22	-Presurgical orthodontic procedure -Modified anterior maxillary osteotomy (for vertical and sagittal augmentation at the same time) -Postsurgical orthodontic intervention		Class I	Good alignment	Correction of the anterior open bite

Table 6. The table shows the oral manifestations presented in 5 different patients with ACH, the treatments performed in each case and the results achieved.

5. DISCUSSION

5.1. Prevalence and Patterns of Dental Malocclusion in Achondroplasia

The study of all the data carried out following the analysis of various articles regarding patients affected by achondroplasia shows a high prevalence of malocclusions or different dental pathologies depending on the group and age of the considered subjects.

The most frequent dental malocclusions in patients with achondroplasia fall into different categories; in general, they can be divided into skeletal or dental malocclusions.

In the first case, the most frequent is maxillary retrognathism, while in the second one, it is dental crowding.

Going deeper into the conducted study, in Table 4, we can notice three dental problems to be considered that have a high incidence in achondroplastic patients.

- Crossbite and Open Bite: The study by Onodera carried out in 2005 (24), highlighted a significant incidence of crossbite and open bite in younger patients, with an overall incidence rate of 66% in patients with an average age of about 6 years. This suggests that skeletal discrepancies due to midface hypoplasia manifest early in the development of patients and with a high incidence rate, given that more than 50% of patients affected by achondroplasia present this characteristic.
- Dental Crowding and Misalignment: In the study carried out by Pfeiffer in 2021 (21), a high prevalence of dental crowding and misalignment in adolescents was demonstrated, with incidences that can reach 89% in the age group between 12 and 15 years. This data correlates with continuous mandibular growth that exceeds maxillary development, further exacerbating Class III malocclusion and leading to dental crowding in most of studied cases.
- Malocclusion and Orthodontic Problems: The study conducted by Hunter in 1998 (25) showed and analyzed a relatively lower incidence of these conditions across all ages, about 8.7% in total. This is probably due to the fact that the study he conducted was carried out with a larger sample of studied patients and also included patients with milder dental and skeletal characteristics of the studied condition. However, the trend indicates an increase in the severity of malocclusion with age, reaching a peak of 30.3% in adults aged 20 to 40 years, reflecting the cumulative effect of untreated skeletal discrepancies over time.

These patterns underline the necessity of early diagnosis and timely interventions, as the prevalence and severity of malocclusions increase with age and, moreover, are easier to prevent and treat when patients are still in the developmental age.

5.2. Clinical and Radiographic Diagnostic Approaches

To identify the complex malocclusion patterns related to patients affected by achondroplasia, the use of both clinical and radiographic diagnostic methods proved to be very useful and precise, as they were utilized in all cases to determine the best treatment methods for the patients in Table 6 by performing a cephalometric study.

Clinical diagnostic methods are more subjective and less precise than radiographic ones. Even though clinical examinations give us a more or less correct idea of the characteristics present in patients with achondroplasia, it is advisable to accompany them with radiographic examinations, which are essential to accurately assess craniofacial structures without ambiguity.

- Clinical Examinations: By clinical examinations, we mean all detailed intraoral and extraoral evaluations performed by dentists, which serve to effectively identify the most common characteristics present in patients affected by achondroplasia, including midface retrusion, Class III molar relation, and anterior open bite. Besides the aforementioned characteristics, we can also focus on other less frequent ones, which may be relevant when planning an appropriate treatment plan for these patients, such as posterior crossbite and macroglossia.
- Radiographic Analysis: Cephalometric imaging and CBCT (Cone Beam Computed Tomography) are considered the most important tests for achondroplastic patients to obtain the most accurate and error-free assessment of the patient's craniofacial structures. Nowadays, dentists use these types of tests to analyse the possible presence of specific characteristics of the craniofacial structures, such as maxillary hypoplasia and mandibular prognathism.
- These radiographic imaging modalities have facilitated a more accurate and precise diagnosis of the skeletal discrepancies contributing to the malocclusions that affect achondroplastic patients.

The combined use of these clinical and radiographic evaluations has ensured a complete diagnostic approach, allowing for a more accurate categorization of all types of malocclusions that may be present and increasingly guiding dentists toward more targeted and effective treatment plans.

5.3. Efficacy of Orthodontic and Surgical Interventions

As we could verify in Table 6 in patients affected by achondroplasia, and therefore presenting the classic craniofacial and dental characteristics, there are different types of possible interventions depending on the characteristics found in each patient.

The different types of interventions that were used and showed a fairly high success rate include both orthodontic and surgical interventions, which can be used individually or together depending on the type of malocclusion the patient presents and its severity.

Orthodontic Interventions

Orthodontic treatments showed variable effectiveness depending on the type and severity of the malocclusion. In the cases studied in Table 6, the orthodontic considered interventions were the following:

- Transverse Maxillary Expansion and Hyrax Appliances: These types of orthodontic appliances, aimed at transverse maxillary expansion, proved to be very effective in managing transverse discrepancies caused by maxillary hypoplasia, leading to successful treatment by achieving a Class I molar relationship and good dental alignment in patients 1 and 4, who, before starting orthodontic treatment, presented crossbites and narrow maxillae.
- Fixed Orthodontic Appliances (Brackets): This type of orthodontic treatment in the studied patients has shown great effectiveness, especially in cases of patients with crowded teeth, leading them to achieve good dental alignment, as observed in the cases of patients 4 and 5, who resolved this problem. However, it should be noted that in cases of severe skeletal Class III malocclusion, such as in the case of patient 3, this specific orthodontic treatment and, more generally, orthodontics alone were not sufficient to resolve the problem, thus highlighting some limitations in non-surgical treatment approaches.

5.4 Surgical Interventions

Surgical interventions, as observed in Table 6, provided more effective definitive corrections in all cases, especially in those cases presenting severe skeletal discrepancies.

In the cases studied in this research, different types of surgical interventions aimed at correcting craniofacial and skeletal malocclusion problems were present, such as:

- Bimaxillary Orthognathic Surgery: This type of surgical intervention, which involves making cuts in the bone to separate the maxilla or mandible to reduce protrusion or retrusion of the maxilla or mandible, is mainly used in patients with Class III skeletal malocclusion and midface hypoplasia, such as patients 1, 2, and 5 studied in Table 6. In the just considered cases, at the end of the surgical treatment, a Class I molar relation was obtained, accompanied by significant aesthetic and functional improvements, thanks to specific types of surgical procedures, such as Le Fort I advancement osteotomy

and bilateral sagittal split osteotomy, which effectively repositioned the maxilla and mandible.

- Reduction Genioplasty and Maxillary Osteotomy: This type of surgical intervention consists of reducing excess mandibular bone. It is a procedure which is performed when there is a need to correct vertical chin excess and maxillary retrognathism, thus giving the face a more harmonious and linear appearance while also contributing to the improvement of the patient's functional occlusion.

5.5 Short-Term and Long-Term Results

5.5.1 Short-Term

Immediate post-treatment results showed significant improvements in almost all cases, especially in dental alignment, also improving occlusal relationships in most cases, with an increase in masticatory efficiency and the overall aesthetics of the patient's face and its proportions.

5.5.2 Long-Term

Patients who underwent the aforementioned surgical interventions improved and maintained functional improvements and occlusal relationships over time, transforming a Class III molar relationship into a Class I molar relationship in all cases, showing minimal relapse in a minority of cases, as in almost all examined cases, the results obtained were maintained over time. In contrast to surgical treatments, treatments that exclusively used orthodontic procedures showed a worst final result and a higher and more concerning risk of relapse, especially in cases with more severe and pronounced skeletal discrepancies.

The results highlighted by the analysis of the considered and studied cases have emphasized the importance of detailed, precise, and, above all, personalized planning of treatments to be carried out in each specific case, taking into particular consideration the patient's age, dental alignment, and the severity of the skeletal dysmorphias present.

6. CONCLUSIONS

1) This study shows that the dental or skeletal malocclusions most affecting patients with achondroplasia are Crossbite and Open Bite, Dental Crowding and Misalignment, Malocclusion, and Orthodontic Problems, with skeletal or dental Class III being the most prevalent among all.
2) The combined use of different types of clinical and radiographic diagnostic methods significantly improves diagnostic accuracy. For this reason, we can affirm that technologies such as Cone Beam Computed Tomography (CBCT) specifically provide dentists with essential information, allowing a more precise evaluation of skeletal and dental discrepancies present in the studied patient. Moreover, CBCT proves to be an essential tool in early anomaly identification, helping to plan targeted therapeutic plans, ensuring a more specific, effective, and personalized treatment plan for each treated case.
3) Orthodontic treatments, as analysed, are very useful in cases where the issue is related to dental alignment or moderate skeletal malocclusion, whereas surgical interventions, being more invasive, are indispensable when it is necessary to correct severe skeletal discrepancies, such as midface hypoplasia or severe mandibular prognathism.
4) In cases of severe skeletal discrepancies, orthognathic surgeries, such as Le Fort I advancement osteotomy and bilateral sagittal osteotomy, are essential as they provide long-term functional and aesthetic corrections. These procedures have been shown not only to improve occlusal relationships and dental alignment but also to positively affect facial aesthetics and masticatory function, ultimately enhancing the patient's quality of life in a positive and effective manner.
5) It was observed that some patients treated with orthodontic therapies had a higher recurrence rate of malocclusions compared to surgical therapies, highlighting the need for a long-term follow-up period accompanied by the use of post-treatment retainers.
6) In light of these results, to obtain more reliable outcomes and help dentists create increasingly effective treatment plans with fewer uncertainties, it would be essential to continue studying achondroplasia and its effects at the oral level through further longitudinal studies. These studies would aim to monitor the evolution of malocclusions and evaluate the long-term effectiveness of different treatment types, as there are currently few studies on post-treatment achondroplastic patients.
7) The multidisciplinary approach confirms itself as the most effective strategy for addressing the diagnostic and therapeutic challenges presented by patients affected by this genetic condition, achondroplasia, significantly improving their quality of life, oral

and facial aesthetics, and the psychological well-being of patients at the end of the treatment plan as well.

7. SUSTAINABILITY

Sustainability in the various surgical and orthodontic treatments that can be performed on achondroplastic patients who present with midface hypoplasia, mandibular prognathism, dental crowding, skeletal or dental malocclusion is an essential factor in ensuring long-term effectiveness, reducing environmental impact, and at the same time optimizing healthcare resources. Orthognathic surgeries, distraction osteogenesis, and customized orthodontic treatments are frequently required and necessary to improve oral function, aesthetics, and overall quality of life. The treatments currently performed on patients requiring these types of interventions are increasingly developing in a more sustainable direction, including the integration of digital technologies such as 3D scanning and printing to reduce reliance on disposable materials and minimize medical waste. The use of biocompatible and durable materials in implants and fixation devices contributes to long-term success, reducing the need for additional surgical interventions. Energy-efficient sterilization techniques, minimally invasive procedures, and telemedicine consultations further enhance sustainability by reducing carbon emissions and increasing accessibility to care and treatment efficiency. Moreover, interdisciplinary treatment planning, including early intervention with functional orthodontic appliances, can help reduce the severity of skeletal discrepancies, potentially decreasing the need for invasive surgical procedures in adulthood. By adopting these sustainable strategies, healthcare professionals can optimize patient care while simultaneously promoting environmental responsibility and resource efficiency in the field of oral and maxillofacial treatments for patients affected by achondroplasia.

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9. ANNEXES

Figure 1. Graph showing the percentage of mutation happening in the different mutation site shown in the Table 1. (6)

Figure 2. The picture shows the body phenotype in individuals of different ages, from left to right: infancy, early childhood, childhood and finally adulthood. (9)

Figure 3. The picture shows the variability of crasniofacial characteristics of ACH patients. (9)

Figure 4. The picture shows the typical condition of flexible kyphosis that can be seen in infants and young children with ACH condition. (9)

Figure 5. Show a patient hands with achondroplasia presenting brachydactyly and trident hand condition. (9)

Figure 6. Anteroposterior radiograph showing the pelvis with the acetabule oriented in a horizontal way and squared-off iliac wings, femoral necks shortened with the proximal part more radiolucent and the distal part showing a chevron-like shape. (9)

Figure 7. Can be observed the narrowing of the space between each vertebrae in the lower spine (14)

Figure 8. Prisma flow diagram showing the articles selection process and the included studies.

Table 1. Showing the probability of a mutation causing ACH in the patient to occur from the one with more probability to occur to the one with less probability. (6)

Table 2. Dental malocclusion problems at different ages. (2)

Table 3. Table describing the diagnostic criteria used for detecting Achondroplasia. (14)

Table 4. Dental issues incidence at all ages in patients with Achondroplasia.

Table 5**.** Dental issues incidence in patient with achondroplasia, comparison of 3 different studies and age group

Table 6. The table shows the oral manifestations presented in 5 different patients with ACH, the treatments performed in each case and the results achieved.

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REVIEW Open Access

Review of published 467 achondroplasia patients: clinical and mutational spectrum

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Abstract

Aim Achondroplasia is the most common of the skeletal dysplasias that cause fatal and disabling growth and developmental disorders in children, and is caused by a mutation in the fibroblast growth factor receptor, type 3 gene(*FGFR3*). This study aims to analyse the clinical characteristics and gene mutations of ACH to accurately determine whether a patient has ACH and to raise public awareness of the disease.

Methods The database of Pubmed, Cochrane Library, Wanfang and CNKI were searched with terms of "Achondroplasias" or "Skeleton-Skin-Brain Syndrome" or "Skeleton Skin Brain Syndrome" or "ACH" and "Receptor, Fibroblast Growth Factor, Type 3" or "*FGFR3*".

Results Finally, four hundred and sixty-seven patients with different *FGFR3* mutations were enrolled. Of the 138 patients with available gender information, 55(55/138, 40%) were female and 83(83/138, 60%) were male. Among the patients with available family history, 47(47/385, 12%) had a family history and 338(338/385, 88%) patients were sporadic. The age of the patients ranged from newborn babies to 36 years old. The mean age of their fathers was 37 ± 7 years (range 31–53 years). Patients came from 12 countries and 2 continents, with the majority being Asian (383/432, 89%), followed by European (49/432, 11%). Short stature with shortened arms and legs was found in 112(112/112) patients, the abnormalities of macrocephaly in 94(94/112) patients, frontal bossing in 89(89/112) patients, genu valgum in 64(64/112) patients and trident hand were found in 51(51/112) patients. The most common mutation was *p.Gly380Arg* of the *FGFR3* gene, which contained two different base changes, *c.1138G > A* and *c.1138G > C*. Ten rare pathogenic mutations were found, including *c.831A > C*, *c.1031C > G*, *c.1043C > G*, *c.375G > T*, *c.1133A > G*, *c.1130T > G*, *c.833A > G*, *c.649A > T*, *c.1180A > T* and *c.970_971insTCTCCT*.

Conclusion ACH was caused by *FGFR3* gene mutation, and *c.1138G > A* was the most common mutation type. This study demonstrates the feasibility of molecular genetic testing for the early detection of ACH in adolescents with short stature, trident hand, frontal bossing, macrocephaly and genu valgum.

Keywords Achondroplasia, *FGFR3*, Molecular study

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REVIEW Open Access

Achondroplasia: a comprehensive clinical review

Richard M. Pauli

Abstract

Achondroplasia is the most common of the skeletal dysplasias that result in marked short stature (dwarfism). Although its clinical and radiologic phenotype has been described for more than 50 years, there is still a great deal to be learned about the medical issues that arise secondary to this diagnosis, the manner in which these are best diagnosed and addressed, and whether preventive strategies can ameliorate the problems that can compromise the health and well being of affected individuals. This review provides both an updated discussion of the care needs of those with achondroplasia and an exploration of the limits of evidence that is available regarding care recommendations, controversies that are currently present, and the many areas of ignorance that remain.

Keywords: Achondroplasia, FGFR3, Skeletal dysplasia, Natural history, Care guidelines

Introduction

Explicit guidelines for care of individuals with achondroplasia are available. Such guidelines were first developed by the American Academy of Pediatrics in 1995 and revised in 2005 [1]. These are now again somewhat out of date. Other care guidelines (for example see [2–4]) and clinically oriented reviews (such as [5–7]) are also available. However, none of these explores in detail the bases for recommendations and the uncertainties that exist. Therefore, this review is intended as both an updated discussion of care needs in achondroplasia and a platform for exploration of the evidence for recommendations, current controversies and areas of current ignorance (which are many).

As is the case for virtually all uncommon or rare genetic disorders, the level of evidence for care recommendations in achondroplasia is generally low. No controlled or blinded studies of any sort are available. Very few prospective investigations have been published (such as [8, 9] and a few others). Most care suggestions are based on retrospective series of varying size, or anecdotal information that lacks any rigorous confirmation. Both retrospective studies of large populations and selective prospective studies are much needed. Nonetheless, something has to be recommended for the care of affected individuals. Not surprisingly, lack of rigorous studies also results in considerable variation in the recommendations that are made. Unfortunately, this is not terribly different from much of current medical care. Some of these uncertainties will yield to studies of larger populations, as have been initiated recently [10].

History

The achondroplasia phenotype has been recognized for thousands of years, as evidenced in the artifacts of many different cultures [11], and remains the most readily recognizable of the dwarfing disorders. The term seems to have been first used in the nineteenth century, and, while the main features were described shortly thereafter [6], it often was used as a generic descriptor of all short-limb dwarfing disorders (in contrast to the short-trunk or Morquio type) for the first half of the twentieth century. Detailed and specific radiologic and clinical features were carefully delineated by Langer et al. [12]. It remains the best characterized and most studied of the hundreds of dwarfing skeletal dysplasias. It is sufficiently common that many pediatricians and family practitioners will help care for one or more individuals in their practices.

Appropriate distinction between this and other short-limb dwarfing disorders was, and remains,

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Special Report

Clinical Practice Guidelines for Achondroplasia*

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Abstract. Achondroplasia (ACH) is a skeletal dysplasia that presents with limb shortening, short stature, and characteristic facial configuration. ACH is caused by mutations of the *FGFR3* gene, leading to constantly activated FGFR3 and activation of its downstream intracellular signaling pathway. This results in the suppression of chondrocyte differentiation and proliferation, which in turn impairs endochondral ossification and causes short-limb short stature. ACH also causes characteristic clinical symptoms, including foramen magnum narrowing, ventricular enlargement, sleep apnea, upper airway stenosis, otitis media, a narrow thorax, spinal canal stenosis, spinal kyphosis, and deformities of the lower extremities. Although outside Japan, papers on health supervision are available, they are based on reports and questionnaire survey results. Considering the scarcity of high levels of evidence and clinical guidelines for patients with ACH, clinical practical guidelines have been developed to assist both healthcare professionals and patients in making appropriate decisions in specific clinical situations. Eleven clinical questions were established and a systematic literature search was conducted using PubMed/MEDLINE. Evidence-based recommendations were developed, and the guidelines describe the recommendations related to the clinical management of ACH. We anticipate that these clinical practice guidelines for ACH will be useful for healthcare professionals and patients alike.

Key words: achondroplasia, systematic review, guideline

*The Japanese version of these guidelines were published on the website of the JSPE (http://jspe.umin.jp/medical/files/guide20190111.pdf) on January 11, 2019.

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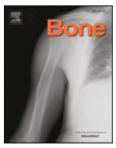

Review Article

Comprehensive literature review on the prevalence of comorbid conditions in patients with achondroplasia

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ABSTRACT

Background: Achondroplasia (ACH) is a rare, genetic condition and is the most common skeletal dysplasia resulting in disproportionate short stature and numerous multi-systemic comorbidities. As we enter an era of new treatment options which may impact comorbidities, it is important to understand the background rates of these events to aid evaluation of potential treatment effects. Thus, the aim of this literature review was to provide a comprehensive quantification of prevalence estimates of comorbidities in achondroplasia by age for use as a compiled reference to assist in quantifying the risk/benefit of new treatment options and informing timely management of ACH.

Methods: PubMed and Embase databases were searched, complemented by manual bibliography searching, for peer-reviewed articles published between 1975 and 2021, guided by PRISMA principles. Number of patients and the prevalence of specific comorbidities by age were extracted. We calculated exact 95 %-confidence limits for the proportion of affected patients (prevalence) and data were presented visually using forest plots. An a priori decision was made not to utilise meta-analytic techniques to pool estimates as we intended to understand the variability in comorbidities by displaying each estimate separately.

Results: The literature search identified 206 articles of which 73 were eligible for inclusion. The majority of studies (n = 34) had been conducted in the USA or in Europe (n = 20). Study designs were mostly retrospective chart reviews (n = 33) or small cohort studies (n = 19). The availability of literature on particular conditions varied but trended towards a focus on assessment and prevention of severe conditions, such as respiratory conditions in children (21 studies), neurological manifestations (16 studies) and upper spine compression (15 studies). There was substantial heterogeneity in study design, type of clinical setting, populations and use of definitions in reporting comorbidities which need to be considered when interpreting study results. Despite the variability of the studies, comorbidity patterns by age were recognizable. In infants, a high prevalence (>20 %) was found for kyphosis, a range of neurological manifestations and sleep apnea. There was also an excess mortality in infancy (4–7.8/100 person-years). Conditions identified in infancy continued to prevail in childhood. Genu varum was highly prevalent from the age children started to walk (9–75 %). Other conditions started to emerge in children; those with a high prevalence (>20 %) were hearing loss and pain. In adolescence, neurological manifestations in the arm, neck or leg were reported (~15 %), consistent with symptomatic spinal stenosis or spinal compression. Fewer studies were available in older populations, especially in adults; however limited data suggest that pain and cardiovascular conditions, particularly excess weight and obesity, became more prevalent into adulthood. Mortality rates increased again in older age-groups.

Conclusion: This review provides a reference base of current knowledge of the type and frequency of comorbidities in ACH. This not only allows future contextualisation of new treatment options but supports clinical decision-making on the timely medical management and intervention of ACH. This review also reflects the

Abbreviations: ACH, achondroplasia; AHI, apnea-hyponea index; BMD, bone mineral density; BMI, body mass index; CAD, coronary artery disease; CC, craniocervical; CCC, craniocervical compression; CHD, coronary heart disease; CI, confidence interval; CMC, cervicomedullary compression; CT, computer tomography; d, day(s); FM, foramen magnum; FMS, foramen magnum stenosis; LPA, Little People of America; m, month(s); MI, myocardial infarction; MRI, magnetic resonance imaging; nr, specific age not reported; OSA, obstructive sleep apnea; PSG, polysomnogram; SpS, spinal stenosis; TLK, thoracolumbar kyphosis; USC, upper spine compression; w, week(s); y, year(s); 1yFU, follow-up after 1 year.

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