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Overview of Achondroplasia Vs Pseudoachondropasia in Children

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Abstract

Chondrodysplasia and pseudochondrodysplasia are both forms of dwarfism, but their genetic origins differ significantly. Chondrodysplasia is caused by mutations in the FGFR3 gene, which regulates bone growth by restricting cartilage proliferation. This mutation leads to abnormal bone growth, primarily affecting long bones.

Pseudochondrodysplasia, on the other hand, stems from mutations in the COMP gene (chondromatrix oligomeric protein). This protein is crucial for the structure and function of cartilage. This mutation disrupts cartilage formation and causes abnormal bone growth, but unlike chondrodysplasia, it does not affect the FGFR3 pathway.

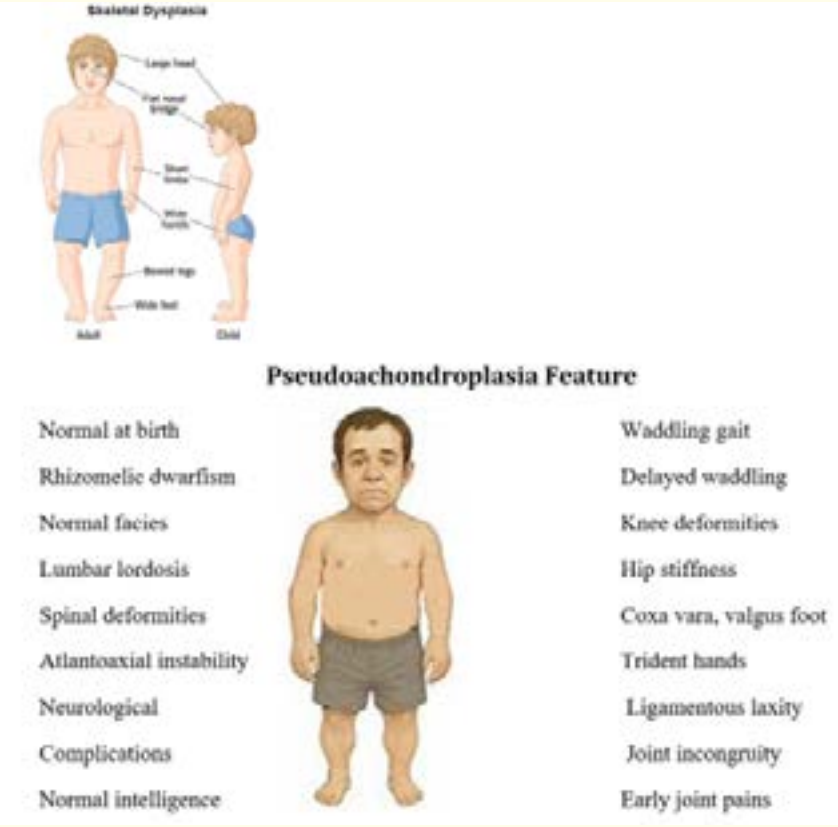
The inheritance patterns are also slightly different. Chondrodysplasia follows an autosomal dominant inheritance pattern, meaning that just one copy of the mutated gene can cause the disease. Pseudochondrodysplasia is also autosomal dominant but usually presents with different symptoms, and sometimes mild symptoms in carriers. Pseudochondrodysplasia is a genetic disorder of bone development characterized by short stature. Other characteristics include short limbs, a waddling gait, early-onset joint pain (degenerative arthritis), and limited range of motion in the elbows and hips. Intelligence, facial features, and head size are usually normal. Pseudochondrodysplasia is caused by genetic changes in the COMP gene. This condition is inherited in an autosomal dominant manner. Pseudochondrodysplasia is a genetic disorder of bone development characterized by short stature. Other characteristics include short limbs, a waddling gait, early-onset joint pain (degenerative arthritis), and limited range of motion in the elbows and hips. Intelligence, facial features, and head size are usually normal. Pseudochondrodysplasia is caused by genetic changes in the COMP gene. This condition is inherited in an autosomal dominant manner.

Keywords: *Achondroplasia; Pseudoachondropasia; Children; COMP Gene; Dwarfism; Genu Varum*

Introduction

Chondrodysplasia and pseudochondrodysplasia are both forms of dwarfism, but their genetic origins differ significantly. Chondrodysplasia is caused by mutations in the FGFR3 gene, which regulates bone growth by restricting cartilage proliferation. This mutation leads to abnormal bone growth, primarily affecting long bones.

Pseudochondrodysplasia, on the other hand, stems from mutations in the COMP (chondroma oligomeric matrix protein) gene. This protein is crucial for the structure and function of cartilage. This mutation disrupts cartilage formation and causes abnormal bone growth, but unlike chondrodysplasia, it does not affect the FGFR3 pathway.



Figure

The inheritance patterns are also slightly different. Chondrodysplasia follows an autosomal dominant pattern, meaning that only one copy of the mutated gene is needed to cause the disease. Pseudochondrodysplasia is also autosomal dominant but usually presents with different symptoms, and sometimes milder symptoms in carriers.

Pseudochondrodysplasia is a type of dwarfism caused by a gene mutation. This condition results in short stature, short limbs, bone abnormalities, loose joints, and joint pain. However, it does not affect facial features, head size, intelligence, or lifespan. Many people with this disorder eventually require joint replacement or other surgery.

Materials and Methods

Pseudochondrodysplasia is a genetic disorder of bone development. It is an autosomal dominant genetic disorder associated with mutations in the COMP gene located on chromosome 19. The disease is often not detected until children are 2 - 3 years old, as development initially appears normal. Pseudochondrodysplasia is usually first detected by stunted growth compared to peers, a waddling gait, or lower limb deformities.

Pseudochondrodysplasia (also known as PSACH, pseudochondrodysplasia, and pseudoachondroplasia of the spine and epiphyseal cartilage) is a form of osteochondrodysplasia that results in mild to severe short stature due to inhibition of bone growth, primarily in the limbs. While the terminology may be confusing, pseudochondrodysplasia should not be confused with osteochondrodysplasia, a clinically

and genetically distinct form of bone dysplasia. Pseudochondrodysplasia is caused by heterozygous mutations in the gene encoding the chondrooligomeric matrix protein (COMP). COMP gene mutations can also cause multifocal chondrodysplasia. Although there are radiographic and clinical similarities between pseudochondrodysplasia and multifocal chondrodysplasia, multifocal chondrodysplasia is less severe.

Pseudochondrodysplasia. Shoulder and humerus. Note the dysplasia of the proximal humeral head, the enlargement of the sphenoid region, and the irregularities and ossification lines of the sphenoid region. These changes are collectively known as “rickets-like changes”. Bilateral symmetrical lesions.

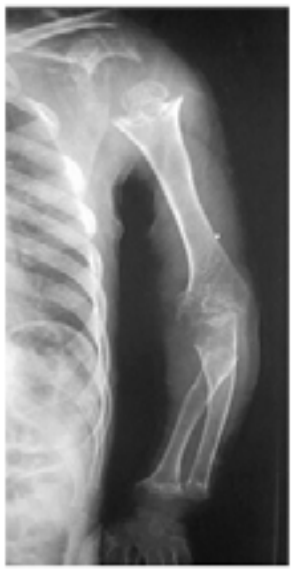


Figure 1: *Shoulder and humerus.*

Signs and symptoms

Short stature, disproportionate lower limb deformities, short fingers, and ligament laxity are distinctive features of pseudochondrodysplasia. The average height of adult males with this condition is approximately 120 cm, while that of adult females is typically around 116 cm. Patients are not born with pronounced short stature. Patients with pseudochondrodysplasia often present with gait abnormalities, lower limb deformities, or growth retardation, typically appearing around 2 - 3 years of age. Disproportionate short stature is characterized by shortening of the proximal limb segments (humerus and femur), also known as proximal limb shortening. Other clinical features include bowlegs/knees, short fingers, flexible flexion deformities of the hips and knees, excessive lordosis of the lumbar spine, boat-shaped feet, and widening of the long bone ends, particularly around the wrists, knees, and ankles. Patients with pseudochondrodysplasia have normal intelligence and craniofacial features (i.e. patients have normal heads) [1].

Achondroplasia

Achondroplasia is a genetic disorder characterized by dwarfism. It is the most common cause of dwarfism, affecting approximately 1 in 27,500 people. In individuals with this condition, the arms and legs are short, while the torso is usually of normal length. Affected individuals have an average adult height of 131 cm for males and 123 cm for females. Other features may include a large head with a protruding forehead (frontal projection) and underdevelopment of the midface (midfacial hypoplasia). Complications may include

sleep apnea or recurrent ear infections. Chondrodysplasia includes the extremely rare short limb dysplasia with severe associated immunodeficiency.

Chondrodysplasia is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene (located on chromosome 4) resulting in its protein being overactive. Chondrodysplasia is a condition characterized by impaired intrachondral bone growth (bone growth within the cartilage). It is inherited in an autosomal dominant manner, meaning that only one mutated copy of the gene is needed to cause the disease. Approximately 80% of cases occur in children whose parents are unaffected and result from a novel mutation (spontaneous mutation), often originating from a spontaneous change in spermatogenesis. The remainder are inherited from one affected parent. The risk of a novel mutation increases with the father's age. In families where both parents are affected, children inheriting both affected genes (with a 25% probability) often die before birth or in infancy due to respiratory distress. The disease is usually diagnosed based on clinical features but can be confirmed by genetic testing. Mutations in the FGFR3 gene also cause diseases related to chondrodysplasia, including hypochondriac and SADDAN (severe chondrodysplasia with growth retardation and acanthosis nigricans), a rare bone growth disorder characterized by abnormalities of the bones, brain, and skin leading to severe short limb dysplasia with severe combined immunosuppression.

Treatments include small molecule therapy with the natriuretic peptide C analog (vosoritide), approved to improve growth rate in children with chondrodysplasia based on results from phase 3 human clinical trials, although its long-term effects are unknown. Growth hormone therapy may also be used. Efforts must be made to treat or prevent complications such as obesity, hydrocephalus, obstructive sleep apnea, middle ear infections, or spinal stenosis. Support groups exist for people with this condition, such as Little People of America (LPA). There are also non-profit medical organizations that disseminate information about treatment and management options, including developing resources for patients.

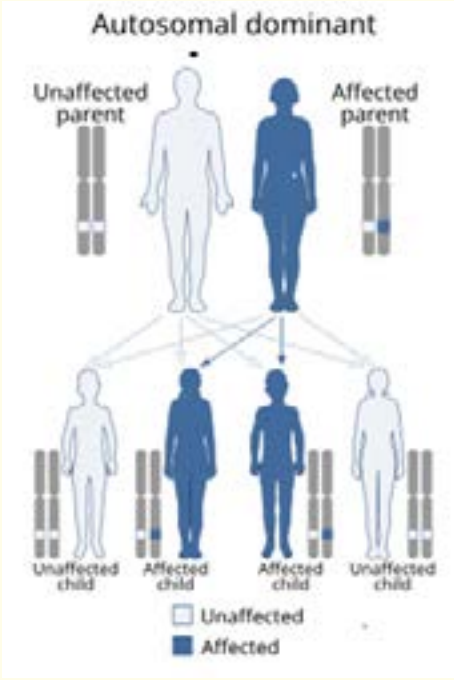


Figure 2: *Autosomal dominant.*

Signs and symptoms

- Disproportionate dwarfism.
- Short proximal limbs (called abduction of the proximal limbs).
- Short fingers and toes, with "trident hands" (short hands with thick fingers, and a gap between the middle and ring fingers - reminiscent of a trident on fetal ultrasound).
- Large head with a prominent forehead.
- Small mid-face with a flat nasal bridge.
- Kyphosis (convex curvature) or lordosis (concave curvature).
- Bowleg deformity (X-shaped legs) or knock knees (X-shaped legs).
- Frequent ear infections (due to Eustachian tube obstruction), sleep apnea (possibly central or obstructive), and hydrocephalus.

Result

Case illustration

A 7-year-old boy presented with complaints of short stature and an abnormal gait. According to his parents, the boy was normal until 3 years of age when he developed waddling gait, deformity of lower limbs, and retarded growth. The younger sibling was also normal since birth but had started developing waddling gait around 2 years of age.

Physical examination of the elder child revealed markedly reduced height measuring only 94 cm (< 3rd percentile for age). Both the upper and lower segment length was reduced, but the limbs were disproportionately shortened (Figure 3).

The upper segment measured 59 cm (mean for age is 65.4 cm), while the lower segment measured 35 cm (mean for age is 60 cm) [3]. The ratio of the length of the arm to forearm compartment was 0.62 and that of thigh to leg compartment was 0.69. In addition, there was limited elbow extension (up to 130° only), genu varum deformity (Figure 4), and exaggerated lumbar lordosis. Systemic examination and intelligence were normal.

The younger child was 83 cm tall (50th percentile of age is 84.10 cm) with a upper segment length of 50 cm (normal mean for age is 51.3 cm) and leg length of 33 cm (mean for age is 34 cm) [3] and an exaggerated lumbar lordosis. Systemic examination and intelligence were normal.

The parents were of normal height and intelligence. They, however, had a consanguineous marriage. There was no family history of dwarfism (Figure 5). A skeletal survey of both siblings was obtained.

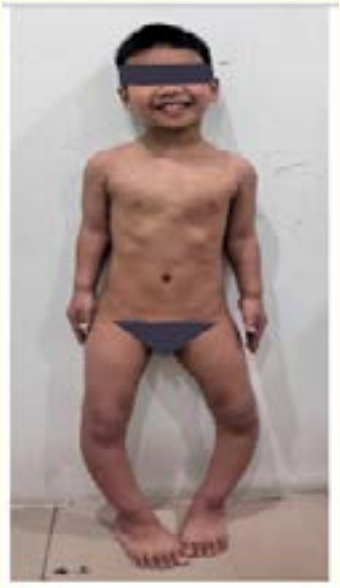
The radiograph of pelvis revealed broad and squared iliac wings, narrow sacrosciatic notches, and dysplastic acetabuli with horizontal roofs (Figure 6).

Metaphysis of all long bones were markedly flared and irregular with deformed, irregular, and fragmented epiphyses (Figure 7). The lumbosacral spine revealed thoracolumbar platyspondyly with normal interpedicular distance (Figure 8). Carpals were underdeveloped with short and broad metacarpals and phalanges (Figure 11). Skull radiographs, however, were normal (Figure 12). Both femora and humeri were disproportionately shortened with a characteristic medial beak at femoral neck (Figure 13).

In the child, the pelvic radiograph revealed squared iliac wings with dysplastic acetabuli and underdeveloped femoral epiphysis. The long bone shortening and severe metaphyseal changes seen in the elder sibling had not yet developed. The spine revealed mild

platyspondyly. Based on clinicoradiological features, a diagnosis of pseudoachondroplasia was made with classical features in elder child and early manifestations of this uncommon disorder in younger sibling.

Figure 3: *Both the upper and lower segment length was reduced.*



Figures 4: *Genu varum deformity.*

Figure 5: *There was no family history of dwarfism.*

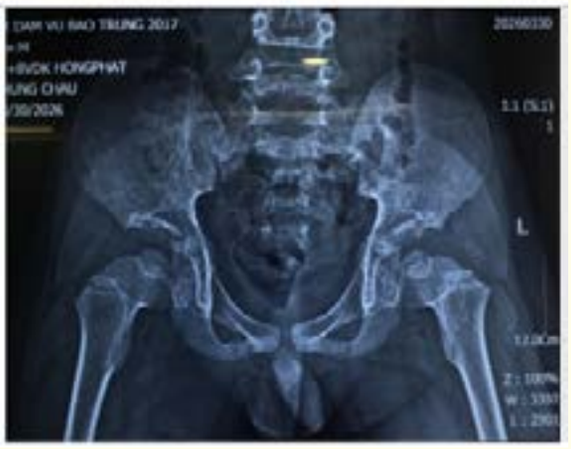


Figure 6: *The radiograph of pelvis revealed broad and squared iliac wings, narrow sacrosciatic notches, and dysplastic acetabuli with horizontal roofs characteristic medial beak at femoral neck.*

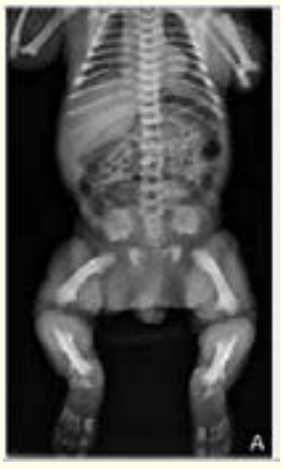


Figure 7: *Metaphysis of all long bones were markedly flared and irregular with deformed, irregular, and fragmented epiphyses.*

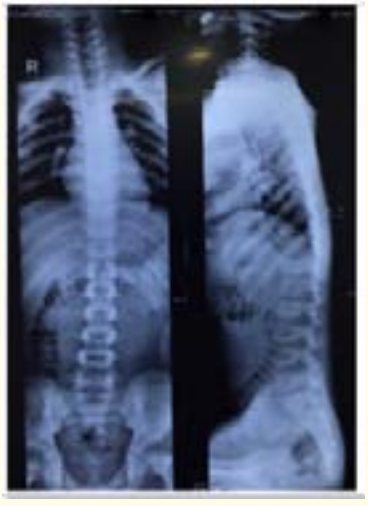


Figure 8: *The spine revealed mild platyspondyly.*

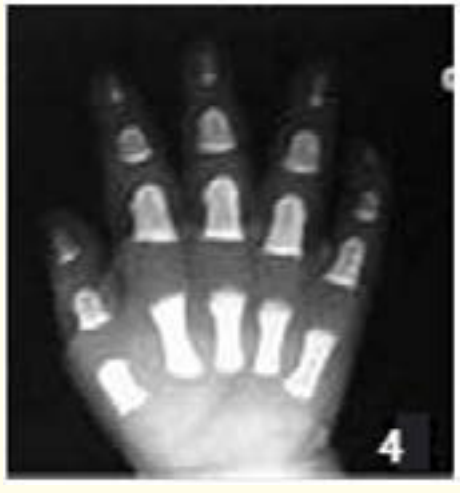


Figure 9: *Carpals were underdeveloped with short and broad metacarpals and phalanges.*

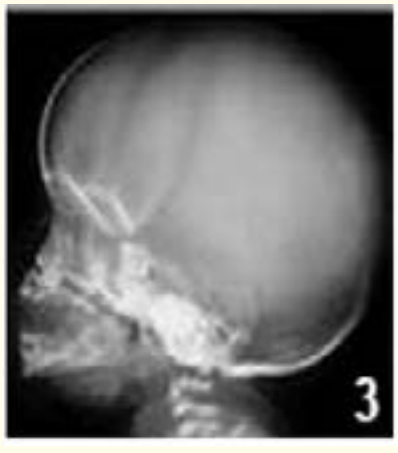


Figure 10: *Skull radiographs, however, were normal.*

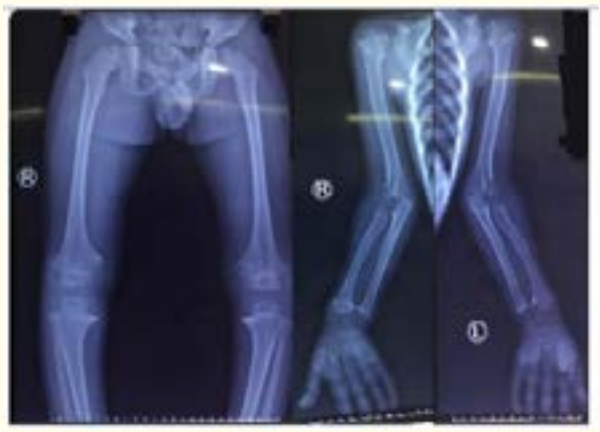


Figure 11: *Both femora and humeri were disproportionately shortened with a characteristic medial beak at femoral neck.*

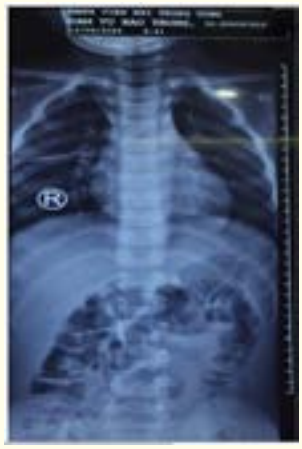


Figure 12: *Chest.*

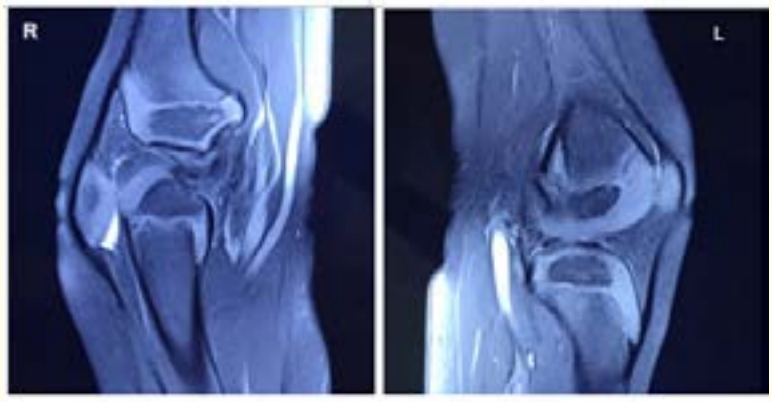


Figure 13: *Knee MRI.*

Understanding the genetic roots

Chondrodysplasia and pseudochondrodysplasia are both forms of dwarfism, but their genetic origins differ significantly. Chondrodysplasia is caused by mutations in the FGFR3 gene, which regulates bone growth by restricting cartilage proliferation. This mutation leads to abnormal bone growth, primarily affecting long bones.

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Research findings

Research variants (with potential relevance to the described phenotype) are variants in genes with no or only partial experimental evidence for their involvement in human disease.

The data was analyzed focusing on variants affecting protein function (nonsense, frameshift, conserved splice site and missense with high pathogenicity predictions) in genes with supporting evidence on zygosity, segregation or functional importance of the gene. Available literature or experimental data on expression and/or animal models were considered. However, no such variants could be identified for the patient.

Secondary findings

If consent is provided, in line with ACMG recommendations (ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing; *Genetics in Medicine*, 2023; PMID: 37347242) we report secondary findings, i.e. relevant pathogenic and likely pathogenic variants in the recommended genes for the indicated phenotypes in this publication.

We did not detect any relevant variants in the genes for which secondary findings are reported.

Carriership findings

In this table we list sequence variants previously ascertained or evaluated and classified in CENTOGENE as “pathogenic” and “likely pathogenic”, in selected genes associated with recessive severe and early-onset Mendelian diseases. As only in-house classified variants are presented, it should not be considered a comprehensive list of variants in these genes and does not provide a complete list of potentially relevant genetic variants in the patient.

The complete gene list can be found at: www.centogene.com/carriership-findings (please contact CENTOGENE customer support if the gene list has been updated after this report was issued). Orthogonal validation was not performed for these variants. Therefore, if any variant is used for clinical management of the patient, confirmation by another method needs to be considered. Furthermore, the classification of these variants may change over time, however reclassification reports for these variants will not be issued. CENTOGENE is not liable for any missing variant in this list and/or any provided classification of the variants at a certain point of time. As the identified variants may indicate (additional) genetic risks or diagnoses in the patient and/or family and/or inform about reproductive risks, we recommend discussing these findings in the context of genetic counselling.

Pathophysiology

COMP is an extracellular calcium-binding protein directly involved in the migration and proliferation of chondrocytes. It is observed in high frequency in chondrocytes during bone and tendon development. In pseudochondrodysplasia, COMP is not secreted but instead accumulates in chondrocytes, eventually causing toxicity and killing them. Although some chondrocytes may survive, growth is significantly reduced, resulting in the characteristic short limbs and seemingly unaffected face and trunk in individuals with this disorder (OMIM 2008). Mutations in COMP lead to a different phenotypic spectrum, ranging from pseudochondrodysplasia (at the most extreme level) to pleomorphic epiphyseal chondrodysplasia or MED (a genetically similar, though milder, form of osteodysplasia) [2].

Studies by Hetch., *et al*. showed that type IX collagen, a type of collagen that is particularly active in the structure of cartilage, plays a crucial role in pseudochondrodysplasia. Researchers discovered that collagen type IX accumulates within the chondrocytes of pseudochondrodysplasia. This discovery suggests that the pathogenesis of pseudochondrodysplasia involves the interaction of mutated COMP gene products with specific chondrocomponents, such as collagen type IX, and that it is not simply a result of the impact of mutated molecules on COMP production and secretion (OMIM 2008).

Key clinical features: Differences

Both disorders share the characteristic short stature, but their clinical manifestations differ significantly upon closer examination.

Appearance

Chondrodysplasia has characteristic facial features: a prominent forehead (forehead protrusion), midfacial hypoplasia (underdeveloped midfacial region), and a flat nasal bridge. The limbs are disproportionately short, especially the arms and thighs (radicular shortening). Trunk size remains relatively normal.

Patients with pseudochondrodysplasia typically have symmetrical facial features without the characteristic changes in the forehead or nose seen in chondrodysplasia. Limb shortening also occurs, but tends to be more diffuse rather than radicular. The trunk may appear shorter than normal due to spinal involvement.

Growth pattern

In chondrodysplasia, physical growth retardation becomes apparent early in childhood with slow growth in length, primarily affecting the long bones. Height rarely exceeds 1.2 meters in adulthood without intervention.

Pseudochondrodysplasia manifests later in childhood; infants are usually of normal length at birth but develop short stature as growth slows in the early years. Unlike the consistent pattern of chondrodysplasia, the severity of pseudochondrodysplasia can vary considerably even within the same family.

Joint and mobility issues: Joint laxity is common in pseudochondrodysplasia, leading to early degenerative arthritis and joint pain due to abnormal cartilage function. This laxity can cause a limping gait and difficulty with movement over time.

Patients with chondrodysplasia may experience limited elbow extension and lumbar scoliosis, but generally have less joint laxity than those with pseudochondrodysplasia. However, spinal stenosis is a notable complication of chondrodysplasia due to abnormal vertebral growth.

Radiological differences: What imaging reveals

X-rays provide critical clues that help differentiate these two conditions.

Feature	Achondroplasia	Pseudoachondroplasia
Long bones	Shortened with flared metaphyses; characteristic "bullet-shaped" femur.	Shortened with irregular metaphyseal changes; more generalized shortening.
Spine	Short pedicles causing spinal stenosis; lumbar lordosis common.	Platyspondyly (flattened vertebrae) with irregular endplates.
Pelvis	Narrow sciatic notch; squared iliac wings.	Mildly irregular iliac wings; less pronounced pelvic changes.

Table 1

These differences in X-ray imaging help clinicians make an accurate diagnosis when clinical symptoms overlap.

Genetic counseling

Because both disorders are inherited in an autosomal dominant pattern, genetic counseling is important for affected families considering having children. Understanding the risk of recurrence will help in making effective family planning decisions.

Differences in lifespan and prognosis

Lifespan differs between the two disorders primarily based on complications rather than dwarfism itself.

Patients with chondrodysplasia typically have a near-normal life expectancy if properly managed; however, risks including sleep apnea, spinal cord compression, and obesity-related complications require lifelong monitoring.

The prognosis of pseudochondrodysplasia depends on the severity of joint degeneration. Early-onset osteoarthritis can severely impair mobility in middle age but usually does not directly affect life expectancy unless secondary complications arise from immobilization or surgical intervention.

A detailed comparison table: Achondroplasia vs pseudoachondroplasia features

Aspect	Achondroplasia	Pseudoachondroplasia
Genetic cause	FGFR3 gene mutation (gain-of-function).	COMP gene mutation (protein defect).
Limb shortening pattern	Rhizomelic (proximal limbs).	Mildly disproportionate/generalized shortening.
Craniofacial features	Prominent forehead and midface hypoplasia.	No distinctive facial abnormalities.
Skeletal radiology findings	Bowed long bones; spinal stenosis risk; Narrow pelvis sciatic notch.	Poorly formed epiphyses; Plethora of metaphyseal irregularities; Pretzel-shaped vertebrae; Mild pelvic involvement; Severe joint degeneration risk.
Joint involvement and pain levels	Mild joint laxity; limited elbow extension frequent; Spinal complications common.	Marked joint laxity leading to early arthritis and pain; Mobility challenges increase over time.

Growth pattern and onset	Noticeable from infancy; consistent height deficit; Adult height ~4 feet.	Normal length at birth; growth slows during childhood; Variable adult height depending on severity.
Life expectancy and prognosis	Near-normal lifespan with management; Watch for neurological issues.	Variable based on joint health; Mobility impairment common but lifespan usually unaffected directly.

Table 2

Physical characteristics of achondroplasia

Physical characteristics of chondrodysplasia

Chondrodysplasia causes disproportionate short stature. Specifically, the limbs (arms and legs) are smaller in proportion to the torso. In the arms and legs, the upper segment is shorter, known as rhizomelia. The average height of an adult with chondrodysplasia is 138 cm (52 inches) in men and 147 cm (49 inches) in women. Individuals with chondrodysplasia have average intelligence and can live very fulfilling and productive lives.

Face and skull:

- Head circumference may be larger than normal.
- The forehead tends to be prominent. The medical term for this is frontal bossing.
- The nasal bridge tends to be concave.
- The midface is underdeveloped, known as midface hypoplasia or midface retrusion.
- The foramen magnum, the opening at the base of the skull where the spinal cord passes through, is smaller than normal.

Trunk, chest, and spine:

- Lumbar kyphosis (LKY) is a condition where the lower back bulges. Most infants with chondrodysplasia have this symptom, and it is a typical sign. LKY is thought to be due to a larger head size and low muscle tone in pre-walking infants. This condition improves without treatment in 90% of children with chondrodysplasia after they gain good trunk control and begin to walk.
- After children learn to walk well, those with chondrodysplasia will develop excessive lordosis, also known as arching of the back.
- The spinal canal is smaller than normal in people with chondrodysplasia.

Arms and legs:

- Loose joints are a typical feature.
- Although most joints are loose, the elbows often cannot be fully extended due to bone differences. This rarely causes symptoms or loss of function.
- In infancy and early childhood, there is an extra gap between the third and fourth fingers. This condition is sometimes called trident hand, and is often not very apparent in later childhood.
- The fingers are short and wide.

X-ray features:

- The long bones are relatively wide and shorter than normal.
- In infants, the upper part of the femur has a peculiar shape.
- The fibula tends to be longer than the tibia in the lower leg.

- The distance between the vertebral pedicles decreases rather than increases in the lumbar spine as it moves from the head to the pelvis.
- The pelvis is short and wide with wide, non-flaring iliac wings.

How is achondroplasia diagnosed?

For parents of normal stature, chondrodysplasia is sometimes suspected when a third-trimester prenatal ultrasound shows short limbs and a larger-than-normal head size. Diagnosis can be confirmed by genetic testing via prenatal amniocentesis, or by postnatal genetic testing or X-rays.

For those with a family history of chondrodysplasia, chorionic villus sampling (CVS) is another option that can be performed earlier in pregnancy to look for genetic alterations associated with chondrodysplasia. Genetic testing can also be performed before pregnancy, as part of *in-vitro* fertilization (IVF).

Most infants with chondrodysplasia are of average length and weight at birth. Up to 15% of children with chondrodysplasia are undetected at birth. In infants, toddlers, older children, or adults, diagnosis of chondrodysplasia may be based on clinical examination and X-rays. An FGFR3 genetic test can also be performed for confirmation.

Medical problems associated with achondroplasia

Foramen magnum stenosis

Essentially, all children with chondrodysplasia have a smaller-than-normal foramen magnum. The foramen magnum is the opening through which the spinal cord exits the head and descends into the spine.

For most children, this doesn't cause any problems. However, about 15 - 20% of children with chondrodysplasia have a foramen magnum that is too small for the spinal cord, leading to spinal cord compression. When the spinal cord is compressed, it can lead to differences in neurological examination, muscle weakness, slower-than-expected gross motor skills, and/or central sleep apnea. This requires surgical correction by a neurosurgeon because it can cause complications, and even be life-threatening in rare cases. This is usually a problem in infants, not in older children/adults.

Hydrocephalus

A larger head size is common in chondrodysplasia, but it is not a problem unless there is increased pressure due to fluid in the skull. One sign of this is increased pressure leading to faster-than-expected head size growth. Head circumference growth charts for chondrodysplasia are available. If you notice sudden head growth, or a fontanelle (soft spot) that is harder than normal, you should refer to a neurosurgeon for further evaluation. This condition can be treated with a ventriculoperitoneal shunt (a tube that drains excess fluid from the brain into the abdominal cavity). This is usually a problem in infants, not in older children/adults [3,5].

Sleep apnea or sleep respiratory disorders

Sleep respiratory disorders (apnea) are common in chondrodysplasia. In a large group, up to 38% of children with chondrodysplasia experience severe apnea [4]. There are two types of apnea, and these will be discussed separately:

- **Obstructive apnea:** Caused by an obstruction of airflow into and out of the lungs with proper respiratory dynamics. This is the most common type of sleep apnea in people with chondrodysplasia due to midfacial recession and decreased pharyngeal muscle tone, along with a "smaller" airway. This can lead to chronic snoring and disrupted sleep with prolonged periods of apnea. Symptoms of obstructive sleep apnea may include fatigue, irritability, and daytime sleepiness. Treatment for obstructive sleep apnea may include weight loss, tonsillectomy/nasopharyngectomy, continuous positive airway pressure (CPAP) or bipolar positive airway pressure (BiPAP) at night with a nasal mask to keep the airway open.

- **Central sleep apnea:** Occurs when the respiratory centers in the brain fail to control breathing during sleep. In the brainstem, the respiratory centers are located near the foramen magnum. Therefore, if the foramen magnum is too small and compresses the spinal cord, it can lead to central sleep apnea.

Care for achondroplasia at every age

At Boston Children's Hospital, we care for infants, children, adolescents, and young adults with chondrodysplasia at our multidisciplinary Bone and Joint Health Center. We employ a team-based care approach, bringing together specialists in endocrinology, genetics, orthopedics, neonatology, adolescent medicine, neurosurgery, clinical bone density, otolaryngology, sleep medicine, and other specialties to ensure each child with chondrodysplasia receives a personalized treatment plan that considers all aspects of their health.

We support families from prenatal counseling through adulthood, ensuring coordinated care and follow-up based on the latest research and clinical guidelines on chondrodysplasia.

Prenatal counseling

Through Boston Children's Hospital's Center for Fetal Care and Surgery, we provide prenatal counseling and detailed information on the diagnosis and prognosis of chondrodysplasia, helping families make informed decisions. We address diagnostic studies, potential outcomes, and family planning options, ensuring families are well-prepared for childbirth and ongoing care.

Infants to 2 years old

We recommend routine checkups every 2 to 3 months, focusing on early detection of potential complications such as foramen stenosis or hydrocephalus, both of which require close monitoring. During these visits, doctors will check the child's development using special growth charts designed specifically for infants and children with chondrodysplasia. They will also assess potential issues such as:

- Narrowing at the base of the skull (foramen stenosis).
- Fluid buildup in the brain (hydrocephalus).
- Ear problems.
- Sleep breathing difficulties.
- Leg position.
- Spinal health.

From 2 to 12 years old

As children get older, the frequency of checkups can gradually decrease. Typically, these are semi-annual check-ups to continue monitoring growth and development, and to ensure timely intervention when needed. At this stage, our care focuses on monitoring orthopedic issues, hearing problems, sleep apnea, and psychosocial and academic success.

Adolescents and young adults

Continued monitoring during adolescence and adulthood supports the transition to adult care with ongoing risk assessment and management. This helps detect new problems that may arise as your child grows older. One problem they may experience is spinal stenosis, which is when the spinal canal narrows and causes pain or numbness. We also check for issues such as chronic pain, weight problems, sleep apnea, and hearing loss. Early detection of these problems can prevent serious issues and help those with chondrodysplasia maintain better health.

Related musculoskeletal problems

Genu varum (Bowlegs)

Bowlegs (genu varum) are far more common than knock knees (genu valgus) in chondrodysplasia [3,5]. Both require monitoring as the child grows older because the curvature of the legs can worsen. Bowlegs can lead to symptoms around the knee such as pain that restricts mobility and instability. Components of bowlegs include inward curvature both above (femur) and below (tibia) the knee, as well as above the ankle (tibia). While some speculate that overgrowth of the fibula may lead to bowlegs, this relationship is unclear. There is often internal tibial torsion associated with bowlegs, resulting in the foot turning inward.

While bowlegs can be treated with osteotomy (bone resection surgery) and leg straightening, recent good results have been seen with gradual correction. Before bone maturation, temporary fixation of one side of the growth plate allows for correction of the angle of leg flexion. This can be achieved using a small plate or screw, which is removed when the correction is complete. Orthopedic splinting is ineffective in treatment, as it cannot create consistent correction to the knee affecting growth.

Symptomatic knee osteoarthritis is not a common problem in adults with chondrodysplasia and this may be good news for parents. Current recommendations are that surgery should only be considered when there are bothersome symptoms (pain or instability), or if there is severe, progressive deformity.

Spinal stenosis

Spinal stenosis in the lumbar spine is relatively common in adults with chondrodysplasia, although it can occur at any age [3,5]. The spinal canal is narrow, but the spinal cord is of normal size, so there is less space for the spinal cord in the spine of someone with chondrodysplasia. In some individuals, this narrowing of the spinal canal leads to compression of the nerves. Symptoms include activity-related leg pain relieved by squatting, numbness, tingling, or numbness in the feet (paresthesia), leg weakness, or, rarely, impaired bladder or bowel control (urinary incontinence). X-rays, CT scans, and MRIs of the lumbar spine can be used to diagnose and manage this problem. We believe that obesity significantly increases the risk of developing this problem.

Fixed thoracic-lumbar kyphosis (Fixed kyphosis)

As mentioned above, infants with chondrodysplasia often develop thoracic-lumbar kyphosis (TLK) [3,5]. In most cases, by the time the child begins to walk, the TLK resolves spontaneously without treatment. However, in some children, the TLK becomes fixed or permanent. Prolonged sitting without support can contribute to fixed kyphosis. Typically, when a child lies prone, the thoracolumbar region flattens out, indicating that the kyphosis (thigh back) is correctable. When the kyphosis is not correctable, there is growing concern that it will require treatment. The use of braces has mixed evidence in treating this problem, and if severe enough, surgery may be necessary to straighten the spine and relieve stress on the spinal cord and nerves.

Other health issues and achondroplasia

Obesity

Obesity is a common problem in children and adults of all heights, but especially with bone dysplasias such as chondrodysplasia [3,5]. A weight-for-height chart specifically for individuals with chondrodysplasia is a helpful guide to weight management. Attention to weight issues in childhood (after age 2) is crucial, as we believe obesity significantly increases the risk of spinal problems in adults with chondrodysplasia. Equally important to dietary management is attention to appropriate physical activity and exercise.

Speech and hearing

Midfacial recession in chondrodysplasia can lead to problems in the ear, nose, and throat [3,5].

The Eustachian tube is the passage between the middle ear and the upper part of the throat. In chondrodysplasia, the anatomical structure of this tube is different, and fluid cannot drain from the middle ear effectively. In the long term, this can lead to conductive hearing loss. Regular hearing tests are necessary. Ear infections are easily treated, and the use of middle ear drainage is common.

Midfacial hypoplasia can also lead to crowded teeth and may require palatal expanders and orthodontics.

Pregnancy

Women with chondrodysplasia often require a cesarean section due to the reduced size and shape of the pelvis.

Discussion

What to watch for with achondroplasia

Children with chondrodysplasia will develop head control, sitting, crawling, and walking at a later age than their peers, which is normal. Due to differences in body proportions, using a growth chart for a typical child to assess a child with chondrodysplasia is inappropriate. There are specialized growth charts for children with chondrodysplasia, and it is important to use these charts [3].

We believe that physiotherapy should be reserved for individuals with genuine gross motor developmental delay based on expectations for a child with chondrodysplasia, after common causes have been ruled out. If a child has gross motor developmental delay at infancy, we recommend first evaluating for severe foramen ovale, so that the problem can be treated instead of just the symptoms. Exercises/positions designed for a typical child to catch up with a normal schedule may increase the risk of spinal cord compression associated with foramen ovale stenosis and/or increase the likelihood of fixed TLK.

Extreme care should be taken in positioning and handling infants to minimize sudden movements of the head and neck due to the smaller foramen ovale. As the child grows older, activities that may pose a risk of neck injury, such as contact sports, diving, gymnastics, tumbling, and trampoline play, should be avoided.

Motor developmental delay, reduced endurance, sleep apnea, or any neurological symptoms should be examined by a specialist.

To avoid fixed TLK, proper back support should be provided for all infants, including reclining seats, and "hammock"-style backrests should not be used until the child is able to sit independently. Soft-back swings, parasol strollers, and bouncers should also be avoided. Backpacks and chest carriers should not be used until the child has full head and body control.

Proper installation of a rear-facing car seat with neck support is a crucial safety measure when traveling by car. The car seat should be kept rear-facing until the child weighs at least 9 kg or reaches the state's prescribed weight, whichever is higher.

Head size should be carefully monitored at least every three to six months during the first few years of life. We believe parents should become familiar with palpating the anterior fontanelle, also known as the soft spot on the top of a baby's head, about once a week. The fontanelle should be soft and flat. If the fontanelle becomes hard (like a tabletop) or bulges when the child is healthy and at rest, immediate medical attention is necessary as this could be a sign of increased pressure on the brain in infants.

Delayed speech may be a sign of conductive hearing loss, so hearing assessment is necessary in addition to seeking speech therapy. Ears should also be checked after each ear infection to ensure fluid has been drained.

Sleep disturbances such as chronic snoring and/or long periods of silence during sleep may be a sign of obstructive sleep apnea or central sleep apnea due to spinal cord compression and should be brought to the attention of an experienced physician. There is a risk of obstructive sleep apnea in both children and adults.

In general, we also recommend talking about chondrodysplasia - both with your child and others - as a difference rather than a problem. Your attitude can help your child develop good self-esteem. Treat children by age, not size, and encourage others to do the same. At the same time, find ways to accommodate. For example, buy a light switch extension and a step stool so your child can turn lights on and off and reach the sink independently. Encourage your child's school to make adjustments/supports to maximize your child's independence in an age-appropriate way. Join groups like Little People of America. Getting to know other people with chondrodysplasia and other forms of dwarfism can help your child feel connected.

Treatment

There is currently no known cure for chondrodysplasia, although the cause of the mutation in the growth factor receptor has been identified. While used by people without chondrodysplasia to aid growth, human growth hormone does not benefit those with chondrodysplasia, as the disease involves a different hormonal pathway. Typically, the best results appear in the first and second year of treatment [6]. After the second year of growth hormone treatment, beneficial bone growth diminishes [6], so this therapy is not an effective long-term treatment [6]. As of December 2020, treatment of chondrodysplasia with human growth hormone was only approved in Japan [7].

The small molecule vosoritide is used to improve growth rate in children with chondrodysplasia, although its long-term effects are unknown. Vosoritide inhibits the activity of FGFR3 [8]. This medication has been gradually made available in various countries starting in 2021.

Limb lengthening increases the length of the legs and arms of people with chondrodysplasia [9], but there is currently no medical consensus on this approach. The age of surgery can vary from childhood to adulthood [10].

Research has also shown that referring parents of children with chondrodysplasia to support and advocacy groups at the time of diagnosis can improve outcomes [10]. Several patient advocacy groups exist to support people with chondrodysplasia and their families [11]. Resources are available to support patients and their caregivers with information they can distribute to their doctors, who may not be familiar with the specific medical requirements in managing chondrodysplasia. Best practice guidelines for physicians are also available to guide physicians in managing spinal disorders [12], foramen stenosis [5], craniofacial complications [13], pregnancy [14] and the pre- and post-operative needs [15] of individuals with chondrodysplasia. Homozygous chondrodysplasia is always considered terminal even with aggressive treatment.

Treatment of chondrodysplasia

Infants should be closely monitored throughout the first two years of life, and then once or twice a year to check for complications.

Treatment options for chondrodysplasia include:

- Decompression and fusion surgery are potential therapies for spinal stenosis. Limb straightening surgery may be used to treat lower limb misalignment.
- If the foramen or spine is severely narrowed, the surgeon may need to remove bone and ligaments to create more space for the brain and spinal structures.
- The structural integrity of the neck or spine is not affected by these surgeries, and patients usually recover completely. Because children are still growing, they may need more decompression surgery. Decompression surgery is most beneficial when performed early because compression problems can become permanent after months or years if left untreated.
- Individuals with chondrodysplasia and hydrocephalus may need a ventriculoperitoneal shunt.
- A pediatric neurosurgeon will place a long, thin tube under the skin to remove cerebrospinal fluid (CSF) that has accumulated in the ventricles of the brain.

- One end of the tube is inserted into the ventricle and the other into the abdomen.
- The CSF is drained from the end at a controlled rate so that it can be quickly and safely absorbed into the bloodstream.

Early detection and treatment of chondrodysplasia can help minimize or prevent some of the problems associated with this type of dwarfism. In late 2023, the FDA approved a prescription drug called vosoritide (Voxzogo) to treat chondrodysplasia in children of all ages who are still growing. Vosoritide works by binding to a faulty receptor encoded by the FGFR3 gene, thereby allowing bone to grow. This drug can only be used in children with an "open growth plate," meaning their bones have not fully developed.

The treatment of pseudoachondroplasia?

The following treatments for pseudoachondroplasia could be considered depending on the concurrent orthopedic conditions in the person:

- Fusion of the posterior spine for kyphosis and scoliosis.
- Cervical fusion with a halo placement for instability.
- Hip subluxation treated with pelvic osteotomies.
- Osteotomies of the lower extremities are performed to treat malformed lower legs.
- Complete knee and hip replacements.

Treatment approaches and management strategies

Neither condition has a cure yet, but treatments focus on symptom management and improving quality of life.

Surgical interventions

In achondroplasia, decompressive surgery may be necessary for spinal stenosis or hydrocephalus complications. Limb-lengthening procedures have been explored but carry significant risks.

Pseudoachondroplasia patients often require orthopedic surgeries to address joint deformities or early arthritis symptoms-such as osteotomies or joint replacements-to maintain mobility.

The importance of accurate diagnosis: implications for families and caregivers

Misdiagnosing achondroplasia as pseudoachondroplasia or vice versa can lead to inappropriate treatment plans that fail to address specific needs effectively. Genetic testing combined with detailed clinical evaluation ensures precision diagnosis which guides targeted therapies-especially important given differences in orthopedic complications between these conditions.

Families benefit from understanding prognosis differences too: achondroplastic individuals might need monitoring focused on neurological risks while pseudoachondoplastic patients require ongoing care addressing joint health proactively to delay arthritis progression.

Healthcare providers must emphasize multidisciplinary approaches involving genetics specialists, orthopedic surgeons, physiotherapists, and counselors for comprehensive care tailored specifically according to whether it's achondroplasia vs pseudoachondroplasia under discussion.

Medical problems associated with achondroplasia

Foramen magnum stenosis

Depending on the accompanying orthopedic conditions, the following treatments may be considered for pseudochondrodysplasia:

- Posterior spinal fusion for kyphosis and scoliosis.
- Cervical spondylofusion with head fixation (halo) for spinal instability.
- Hip dislocation treated with iliopsoas surgery.
- Lower extremity osteotomy performed to treat tibial deformities.
- Total knee and hip replacement.

Treatment methods and management strategies

Currently, there is no cure for either condition, but treatments focus on symptom management and improving quality of life.

Surgical interventions

In pseudochondrodysplasia, decompression surgery may be necessary for complications such as spinal stenosis or hydrocephalus. Limb lengthening procedures have been studied but carry significant risks.

Patients with pseudochondrodysplasia often require orthopedic surgery to address joint deformities or early arthritic symptoms-such as osteotomy or joint replacement-to maintain mobility.

The importance of accurate diagnosis: Impact on family and caregivers

Misdiagnosing chondrodysplasia as pseudochondrodysplasia, or vice versa, can lead to inappropriate treatment plans that fail to effectively address specific needs. Genetic testing combined with a detailed clinical assessment ensures accurate diagnosis, thereby guiding targeted therapies-particularly important given the differences in orthopedic complications between the two conditions.

Families also benefit from understanding the prognostic differences: individuals with chondrodysplasia may require focused monitoring for neurological risks, while patients with pseudochondrodysplasia require ongoing, proactive joint health management to slow arthritic progression.

Healthcare providers should emphasize multidisciplinary approaches, including geneticists, orthopedic surgeons, physiotherapists, and counselors, to obtain holistic care, specifically tailored depending on whether it is chondrodysplasia or pseudochondrodysplasia.

Medical issues related to chondrodysplasia

Occipital foramen necrosis

Essentially, all children with chondrodysplasia have a smaller-than-normal foramen ovale. The foramen ovale is the opening through which the spinal cord exits the head to descend the spine.

For most children, this does not cause any problems. However, about 15 - 20% of children with chondrodysplasia have this opening too small for the spinal cord, leading to spinal cord compression [4]. When the spinal cord is compressed, it can lead to differences in neurological examination, muscle weakness, slower-than-expected gross motor skills, and/or central sleep apnea. This requires corrective surgery by a neurosurgeon because it can cause complications, and even be life-threatening in rare cases. This is usually a problem in infants, not in older children/adults.

Hydrocephalus

A larger head size is common in chondrodysplasia, but it is not a problem unless there is increased pressure due to fluid in the skull. One sign of this is increased pressure leading to faster-than-expected head growth. Head circumference growth charts for chondrodysplasia are available. If you notice a sudden increase in head growth, or the soft fontanelle (fontanelle) feels harder than normal, you should be referred to a neurosurgeon for further evaluation. This condition can be treated with ventriculoperitoneal shunt (a tube that drains excess fluid from the brain into the abdominal cavity). This is usually a problem in infants, not in older children/adults [5].

Sleep apnea or sleep respiratory disorder

Sleep respiratory disorder (apnea) is very common in chondrodysplasia. In a large group, up to 38% of children with chondrodysplasia have severe apnea [6]. There are two types of apnea, and these will be discussed separately:

- **Obstructive apnea:** Caused by an obstruction of airflow into and out of the lungs with proper respiratory dynamics. This is the most common type of apnea in chondrodysplasia due to midfacial retraction and decreased pharyngeal muscle tone, and the fact that they have "smaller tubes" for air to pass through. This can lead to chronic snoring and disrupted sleep with prolonged periods of apnea. Symptoms of obstructive apnea may include fatigue, irritability, and daytime sleepiness. Treatment for obstructive sleep apnea may include weight loss, tonsillectomy/nasopharyngectomy, continuous positive airway pressure (CPAP) or bipolar positive airway pressure (BiPAP) at night using a nasal mask to keep the airways open.
- **Central sleep apnea:** Occurs when the respiratory centers in the brain fail to control breathing during sleep. In the brainstem, the respiratory centers are located near the foramen magnum. Therefore, if the foramen magnum is too small and compresses the spinal cord, it can lead to central sleep apnea.

Related musculoskeletal problems

Genu varum (Bowlegs)

Bowlegs (genu varum) are far more common than knock knees (genu valgus) in chondrodysplasia [5]. Both require monitoring as the child grows older because the curvature of the legs can worsen. Bowlegs can lead to symptoms around the knee such as pain, limited mobility, and instability. Components of bowlegs include inward curvature of both the upper (femur) and lower (tibia) knee, as well as above the ankle (tibia). While some speculate that overgrowth of the fibula may lead to bowlegs, this relationship is unclear. There is often inward twisting of the tibia associated with bowlegs, resulting in the foot turning inward.

While bowlegs can be treated with osteotomy (bone cutting surgery) and leg straightening, recent studies have shown good results with gradual correction. Before bone maturation, temporary fixation of one side of the growth plate allows for adjustment of the angle of flexion of the leg. This can be achieved using a small plate or screw, which is removed when the adjustment is complete. Orthopedic splinting is ineffective in treatment, as it cannot create consistent adjustment to the knee affecting growth.

Symptomatic knee osteoarthritis is not a common problem in adults with chondrodysplasia and this may be good news for parents. Current recommendations are that surgery should only be considered when there are bothersome symptoms (pain or instability), or if there is severe, progressive deformity.

Spinal stenosis

Spinal stenosis in the lumbar spine is relatively common in adults with chondrodysplasia, although it can occur at any age [5]. The spinal canal is narrow, but the spinal cord is of normal size, so there is less space for the spinal cord in the spine of someone with chondrodysplasia. In some individuals, this narrowing of the spinal canal leads to compression of the nerves. Symptoms include activity-related leg pain relieved by squatting, numbness, tingling, or paralysis in the feet (paresthesia), leg weakness, or, rarely, impaired bladder or bowel control (urinary incontinence). X-rays, CT scans, and MRIs of the lumbar spine can be used to diagnose and manage this problem. We believe that obesity significantly increases the risk of developing this problem.

Fixed thoracic-lumbar kyphosis (Fixed kyphosis)

As mentioned above, infants with chondrodysplasia often develop thoracic-lumbar kyphosis (TLK) [5]. In most cases, by the time the child begins to walk, the TLK resolves spontaneously without treatment. However, in some children, the TLK will become fixed or permanent. Prolonged sitting without support can contribute to fixed kyphosis. Typically, when a child lies prone, the thoracolumbar

region flattens out, indicating that the kyphosis (thigh back) is correctable. When the kyphosis is not correctable, there is growing concern that it will require treatment. The use of braces has mixed evidence in treating this problem, and if severe enough, surgery may be necessary to straighten the spine and relieve stress on the spinal cord and nerves.

Complications

Children

Achondroplasia in children

Children with chondrodysplasia often have lower muscle tone; therefore, they are often delayed in walking and motor skill development. Children also often have bowlegs, scoliosis, lordosis, arthritis, joint flexibility problems, breathing difficulties, ear infections, and crowded teeth [16]. These problems can be treated with surgery, splinting, or physical therapy [17].

Hydrocephalus is a serious complication associated with chondrodysplasia in children. This occurs when cerebrospinal fluid cannot flow into and out of the skull due to spinal stenosis [18]. This fluid buildup is associated with a large head, vomiting, lethargy, headache, and irritability [19]. Surgical drainage is often performed to treat this condition, but endoscopic third ventriculostomy may also be performed.

Adults

Adults with chondrodysplasia often experience obesity and sleep apnea. Adults also frequently experience numbness or tingling in the legs due to nerve compression.

Some studies have found that adults with chondrodysplasia may also experience psychosocial complications, often related to short stature [20].

Pregnancy in women with chondrodysplasia is considered to be at higher risk. Women with chondrodysplasia often give birth via cesarean section to prevent complications that can occur during vaginal delivery [21]. Intelligence and life expectancy are generally near normal, although cranial-cervical joint compression increases the risk of death in infants [22].

The most subtle but important differences: Chondrodysplasia vs. pseudochondrodysplasia:

Although both are dwarfism as a common feature of the disease group, chondrodysplasia vs. pseudochondrodysplasia represents two distinct genetic entities with distinct clinical course:

- **Gene mutations**: The FGFR3 gene vs. the COMP gene creates fundamentally different molecular pathways affecting cartilage/bone development.
- **Bone manifestations**: Radicular short limbs with craniofacial malformations are characteristic of chondrodysplasia, while generalized short limbs with severe joint laxity are characteristic of pseudochondrodysplasia.
- **Treatment focus**: Management of neurological complications predominates in the care of chondrodysplasia, while early intervention to prevent progression of arthritis is the treatment priority for pseudochondrodysplasia.
- **Life expectancy**: Generally favorable for both when properly managed, but heavily influenced by secondary complications specific to each disease.
- **Differential diagnosis**: X-ray imaging combined with genetic testing remains the gold standard for differentiation, ensuring accurate identification, which is essential for optimal outcomes.

These details form the basis for understanding the significant differences between these two forms of dwarfism despite their superficial similarities-an important understanding for clinicians, families, and patients facing these complex conditions.

Conclusion

Comparing chondrodysplasia and pseudochondrodysplasia reveals more than just differences in height or appearance-it highlights the different genetic causes that influence bone development through distinct biological mechanisms, leading to unique clinical challenges. Recognizing these differences improves diagnostic accuracy, and tailoring management strategies to the specific needs of each condition significantly enhances patient quality of life.

Both conditions require lifelong monitoring but differ fundamentally in terms of bone lesion patterns, associated complications such as neurological problems versus early arthritis risk, and subtle nuances in overall prognosis. Being equipped with knowledge of the differences between chondrodysplasia and pseudochondrodysplasia allows both families and healthcare providers to approach care in an informed manner-transforming complexity into step-by-step clarity.

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