acrodysostosis
support and research

# Acrodysostosis: background, diagnosis and disease management

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## Abbreviations

- **17q24.2:** specific location on long arm of chromosome 17
- **25-OH:** 25-hydroxy
- **5q11.2-q12.1:** specific location on long arm of chromosome 5
- **ADHD:** attention deficit hyperactivity disorder
- **cAMP:** cyclic adenosine monophosphate
- **GH:** growth hormone
- **GI:** gastrointestinal
- **GPCR:** G protein-coupled receptor
- **Gsα:** alpha subunit of the Gs protein
- **HCPs:** healthcare professionals
- **iPPSD:** inactivating PTH/PTHrP signalling disorder
- ***PDE4D:*** phosphodiesterase 4D
- **PHP:** pseudohypoparathyroidism
- **PKA:** protein kinase A
- ***PRKAR1A:*** protein kinase cAMP-dependent type 1 regulatory subunit alpha
- **PTH:** parathyroid hormone
- **PTH-rp:** parathyroid hormone-related protein
- **rhGH:** recombinant human growth hormone
- **TSH:** thyroid-stimulating hormone

## Medical terms explained

- **2q37 microdeletion syndrome:** a genetic disorder caused by a deletion of genetic material, which can affect many body parts
- **5q12.1 haploinsufficiency syndrome:** an extremely rare disorder where structural chromosome abnormalities result in limited production of the *PDE4D* gene
- **Brachydactyly:** disproportionately short fingers and toes
- **Chiara malformation type 1:** a birth defect where the brain tissue extends into the spinal canal
- **Craniosynostosis:** a birth defect when the fibrous joints between the bones of a baby's skull close before the brain is fully developed
- **Dysplasia:** a disorder of the development of bone and cartilage
- **Dysostosis:** defective formation of bones
- **Exostosis:** formation of new bone on the surface of a bone
- **Genu valgum:** knee misalignment that turns your knees inward
- **Genu varum:** lateral bowing of the legs at the knee
- **Hydrocephalus:** excess fluid on the brain
- **Hypodontia:** developmental absence of one or more teeth
- **Hypoplasia:** underdevelopment of a tissue or bone
- **Kyphosis:** excessive forward curvature of the upper back
- **Maxillonasal hypoplasia:** underdeveloped upper jaw and nasal area
- **Pseudohypoparathyroidism:** a genetic disorder associated primarily with resistance to parathyroid hormone
- **Scoliosis:** ideways curvature of the spine
- **Spinal stenosis:** narrowing of spaces within the spine and compressing of the spinal cord

## Development of the leaflet

This leaflet was developed following a thorough review of the literature as well as consultation from individuals living with acrodysostosis and their families and carers. Additionally, healthcare professionals (HCPs) with experience in managing patients with acrodysostosis have also contributed to the information provided in this leaflet. Acrodysostosis is a rare genetic disease, and the research landscape is constantly evolving. As such, this leaflet aims to combine the findings of recent research, the knowledge of HCPs and the lived experience of those affected by acrodysostosis to provide the most relevant and up-to-date information to aid the diagnosis and management of individuals living with acrodysostosis.

## Background

Acrodysostosis is a group of rare genetic diseases of which the exact prevalence is currently unknown. The term acrodysostosis refers to a clinical description rather than a final diagnosis, which is made upon genetic confirmation. Acrodysostosis is a heterogenous group of skeletal dysplasia that is characterised by severe **brachydactyly**, **facial dysostosis** (leading to a broad face, widely spaced eyes, and maxillonasal hypoplasia) as well as **nasal hypoplasia**.[1]

Persons living with acrodysostosis also frequently experience a wide range of other symptoms. These include: being born small for gestational age and delayed growth into adulthood; craniosynostosis; cognitive impairment and behavioural issues; resistance to several hormones e.g., parathyroid hormone (PTH) and thyroid-stimulating hormone (TSH) (see **'Symptoms'** for further details).[1] Acrodysostosis belongs to a group of rare diseases that share symptoms due to the impairment of the PTH/PTH-related protein (PTHrp) signalling pathway, which regulates skeletal development, bone turnover and mineral ion homeostasis.[2] To date, at least two types of acrodysostosis have been identified (**Type 1** and **Type 2**). These differ in terms of their causative mutations and subsequent symptoms; however, the symptoms experienced from the two known mutations demonstrate substantial overlap (see **'Types of acrodysostosis'** for further details). It is important to note that in some patients presenting with the clinical characteristics of acrodysostosis, a genetic cause has not yet been identified and these patients may carry mutations in multiple genes that we are not yet aware of.

Overall, very little is known about acrodysostosis and persons living with this disease frequently encounter HCPs who have limited prior knowledge of acrodysostosis or its management. Having to explain the symptoms and disease diagnosis to HCPs and getting appropriate management can be very challenging for patients, carers and parents and adds to the burden placed on families with an affected member.

## Causes of acrodysostosis

Acrodysostosis can be caused by mutations in the protein kinase cAMP-dependent type 1 regulatory subunit alpha *(PRKAR1A)* gene (**Type 1** acrodysostosis) or in the phosphodiesterase 4D *(PDE4D)* gene (**Type 2** acrodysostosis).

In many cases, these mutations are sporadic, meaning that the mutations are not usually inherited. However, some cases of familial acrodysostosis (**Type 2**), with apparent autosomal dominant inheritance of a *PDE4D* mutation, have been documented.[3,4] Experts suspect that additional genes that contribute to the disease may exist; for example, in some cases no genetic defect is found after the analysis of *PRKAR1A* and *PDE4D*.

The genes *PRKAR1A* and *PDE4D* code for two proteins: the type 1 regulatory subunit of cyclic adenosine monophosphate (cAMP)-dependent protein kinase alpha and the cAMP-specific phosphodiesterase 4D, respectively. These two proteins play an important role in the G protein-coupled receptor (GPCR)-Gsα-cAMP-protein kinase A (PKA) signalling pathway.[3] The *PRKAR1A* gene is located on the long arm of chromosome 17 (17q24.2) and the *PDE4D* gene is located on the long arm of chromosome 5 (5q11.2-q12.1).[4]

The cAMP signalling pathway plays an important role in:

- The formation of bones
- The central nervous system
- The development of cognitive functions
- The correct functioning of multiple hormones

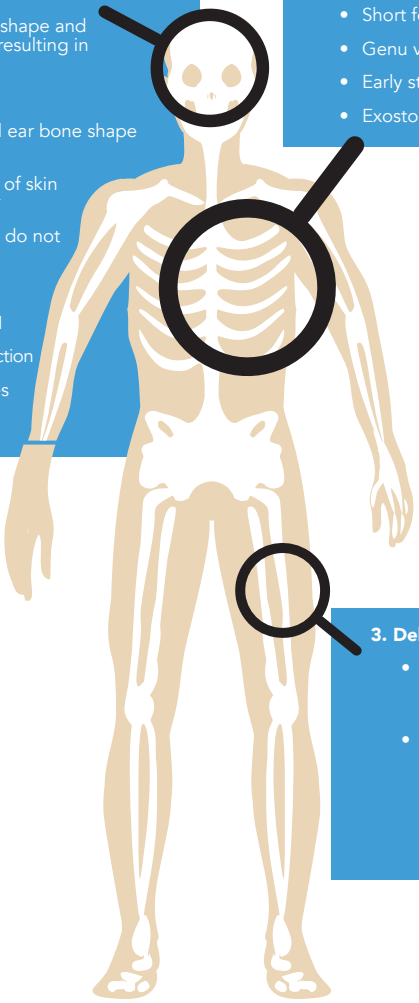
Therefore, a mutation of these genes leads to a disruption of these processes and contributes to the symptoms of acrodysostosis.[2] A genetic defect leading to the misfolding of proteins is different within each tissue, which explains the variety of the symptoms experienced by persons living with acrodysostosis.

**1. Distinctive facial and cranial features**

- Broad face
- Widely spaced eyes
- Maxillonasal hypoplasia (underdeveloped upper jaw)
- Abnormal positioning of facial bones, leading to:
  - Nasal hypoplasia (underdeveloped or small nasal bone, flattened nasal bridge)
  - Related respiratory problems (e.g. aspiration, sleep apnoea requiring a continuous positive airway pressure [CPAP] machine or supplemental oxygen)
  - Frequent ear infections, which can lead to eustachian tube dysfunction and subsequent hearing loss
  - A change in the bone shape and internal ear structure, resulting in hearing difficulties
- Prominent lower jawbone
- Low-set ears and abnormal ear bone shape and structure[4]
- Epicanthal folds (extra fold of skin on either side of the nose)[4]
- The upper and lower teeth do not meet correctly[4]
- Craniosynostosis
- Chiara malformation type 1
- Hypodontia and tooth impaction
- Hydrocephalus and seizures

**2. Skeletal malformations**

- Brachydactyly (short fingers and toes - usually affects all fingers and toes; sometimes the thumbs and big toes appear less affected)
- Spinal malformations (scoliosis, kyphosis and stenosis)
- Advanced bone age (and associated difficulties including arthritis and joint pain)
- Pain associated with skeletal malformations (including arthritis, bone fusion and discrepancies in leg length, exacerbated by lack of available supportive shoes)
- Narrowed lumbar canal
- Short femoral necks
- Genu valgum/genu varum
- Early stiffness
- Exostosis

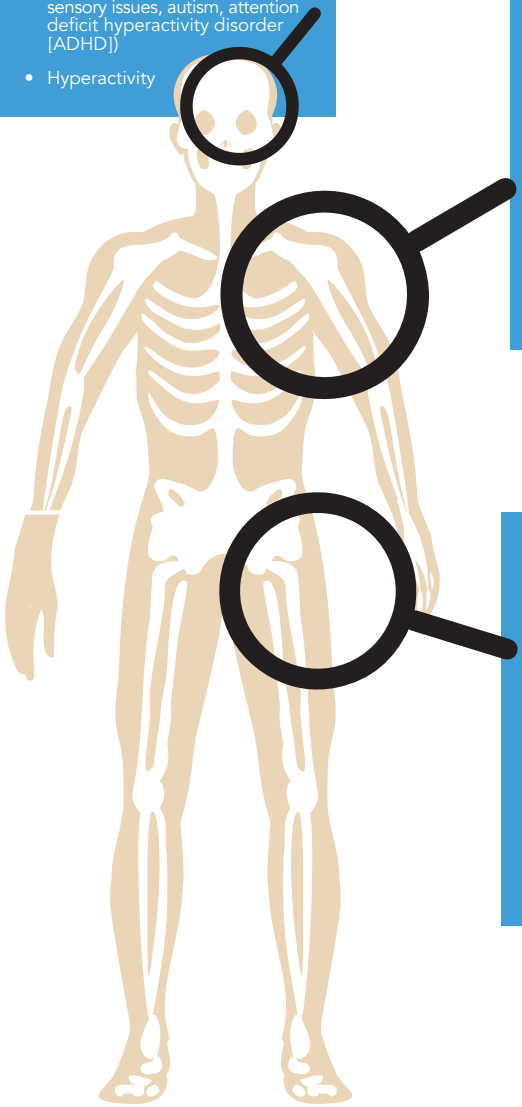


**3. Delayed growth**

- Born small for gestational age (antenatal growth is often impaired)
- Delayed growth can continue after birth and almost all persons affected by acrodysostosis are significantly shorter than expected for their age

**4. Intellectual and motor development**

- Cognitive impairment, developmental and learning delay; the severity of which differs amongst individuals with acrodysostosis, even within the same mutation group
- Delayed speech development, potentially related to facial dysostosis. In some cases delayed speech can be mistaken for developmental delay
- Depression, extreme anxiety and behavioural problems (e.g. sensory issues, autism, attention deficit hyperactivity disorder [ADHD])
- Hyperactivity



**5. Hormonal resistance**

- Resistance to hormones that act via the PKA signalling pathway, especially PTH and TSH
  - o Elevated TSH with normal or low thyroxine levels, is more prevalent in persons with acrodysostosis Type 1 (mutation in *PRKAR1A*)
- Growth hormone resistance (more prevalent in persons with acrodysostosis due to mutations in *PRKAR1A*)
- Some menstruating persons living with acrodysostosis may experience associated difficulties, including:
  - o Menorrhagia (excessive and prolonged menstrual bleeding)
  - o Dysmenorrhea (painful menstrual periods caused by uterine contractions)
  - o Amenorrhea (absence of menstruation)
- Obesity
- Easily fatigued

**6. Other key features (non-exhaustive)**

- High pain tolerance with atypical presentation (persons affected by acrodysostosis may appear happy and alert, while being severely unwell, e.g. with broken bones or pneumonia)
- Kidney problems (e.g. kidney reflux and kidney disease)
- Gastroenterology issues such as chronic constipation, intestinal inflammation and other structural and functional abnormalities of the gastrointestinal (GI) tract

## Symptoms

The symptoms, and their severity, experienced by persons living with acrodysostosis differs largely between individuals, even between those with the same genetic mutation. This can make it difficult for HCPs, including specialists, to correctly identify acrodysostosis as the systemic cause behind the symptoms. In turn, this can contribute to the delay in effective early management, as well as the potential for misdiagnosis, which can have detrimental consequences.

The following list presents the key symptoms experienced by individuals living with acrodysostosis; it is important to note that this list is not exhaustive:

Those affected by acrodysostosis have reported symptoms relevant to a wide range of medical specialities. Therefore, physicians should treat persons affected by acrodysostosis on an individual basis and in active collaboration with other medical specialties. To provide the best medical care to affected persons, physicians should listen to each affected individual and try and understand their specific symptoms.

## Types of acrodysostosis

There are a large range of symptoms experienced by persons with acrodysostosis. However, the disease can be split into two broad types based on the genetic mutation present: *PRKAR1A* or *PDE4D* mutations (**Type 1** and **Type 2** acrodysostosis, respectively).

Although the main skeletal characteristics are similar and many symptoms are seen in both types of acrodysostosis (due to *PRKAR1A* mutations and *PDE4D* mutations), there are some key differences in the characteristics of the two known types. For example, individuals with acrodysostosis due to *PRKAR1A* mutations are more likely to develop hormone resistance, whilst individuals with acrodysostosis due to *PDE4D* mutations are more likely to have neurocognitive impairment and characteristic facial features.[4]

The characteristic symptoms of acrodysostosis due to each type of mutation are presented in Table 1. However, the overlap between the types of acrodysostosis mean that these characteristic symptoms are not confined to the respective types of acrodysostosis; individuals with acrodysostosis due to *PRKAR1A* mutations can present with characteristic symptoms of acrodysostosis due to *PDE4D* mutations, and vice versa. Additional forms of acrodysostosis are also likely to exist due to mutations in other genes but they have not been characterised yet.

**Table 1:** Characteristic symptoms of acrodysostosis due to *PRKAR1A* mutations and due to *PDE4D* mutations

| Characteristic symptom | Acrodysostosis due to mutations in *PRKAR1A* gene (Type 1) | Acrodysostosis due to mutations in *PDE4D* gene (Type 2) |
|---|---|---|
| **Growth** | • Born small for gestational age<br>• Adult short stature<br>• Often shorter than persons with acrodysostosis **Type 2** | • Born small for gestational age (less severe)<br>• Adult short stature |
| **Obesity** | √ | √ |
| **PTH resistance**[1] | √[a] (~100%) | √[a] (~30%) |
| **TSH resistance**[1] | √[b] (~100%) | √[b] (~15%) |
| **Neurological symptoms** | Unknown | Neurocognitive impairment is frequent |
| **Brachydactyly** | √ | √ |
| **Advanced bone age** | √ | √ |

**Abbreviations:** *PDE4D*: phosphodiesterase 4D; *PRKAR1A*: regulatory subunit alpha; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone.

**Footnotes:** The above data were derived from a literature search by Mantovani et al. (2018)[1]. [a]PTH resistance present in 100% and 29% of persons with **Type 1** and **Type 2** acrodysostosis, respectively. [b]TSH resistance present in ~100% and 16% of persons with **Type 1** and **Type 2** acrodysostosis, respectively.

**Source:** Mantovani et al 2018[1]

# Diagnosis

**How is acrodysostosis diagnosed?**

Diagnosis should be based on clinical, radiological and biochemical characteristics. As the clinical features vary greatly between individuals affected by acrodysostosis, intensive clinical evaluation and different specialised tests, including X-rays, should be carried out to identify different characteristics.

Inactivating PTH/PTHrP signalling disorder (iPPSD) is the term for the group of rare diseases that acrodysostosis belongs to, which is defined by the impairment of the PTH/PTHrp signalling pathway. There is a list of major and minor criteria to aid classification within this group.[2]

**Major criteria:**

- PTH resistance
  - PTH resistance should be suspected when there is increased level of PTH in the absence of vitamin D deficiency and renal insufficiency, even when there is no apparent hypocalcaemia
- Ectopic ossifications
  - Superficial, subcutaneous nodules, defined as ectopic bone formation in the adipose or dermal tissue
- Brachydactyly

**Minor criteria:**

- TSH resistance
- Other hormone resistances
- Motor and cognitive retardation or impairment
- Intrauterine and postnatal growth retardation
- Obesity/overweight
- Flat nasal bridge and/or maxilla hypoplasia and/or round face

For the diagnosis of iPPSD, the presence of one of the major criteria is mandatory. Due to brachydactyly being less specific, it should be combined with at least one major or two minor criteria to trigger the diagnosis of iPPSD. Radiographs are used to identify features such as short and broad metacarpals and phalanges (finger bones), premature fusion of cone-shaped epiphyses (end of the long bones), advanced bone age. These abnormalities can present as early as birth or soon after.

Additionally, bone dysplasia might have a prenatal onset and could potentially be observed using prenatal foetal ultrasonography, which can support diagnosis. This is most commonly observed when acrodysostosis is caused by *PRKAR1A* mutations (**Type 1**).[1]

Once the diagnosis is made based on clinical and biochemical criteria, the diagnosis should be confirmed by genetic analysis. The correct diagnosis is crucial as it allows persons affected by acrodysostosis to start appropriate management of symptoms as soon as possible, while their families can be guided to support groups and family counselling, if needed.

**Difficulties associated with diagnosis**

The clinical presentation and severity of the disease differs among individuals and even among persons affected by acrodysostosis who have the same mutation. Thus, the diagnosis of acrodysostosis is often delayed. Early intervention, for example with speech and language therapy and feeding support, may help ameliorate and prevent more severe subsequent problems such as an inability to speak (some affected persons remain nonverbal) or pneumonia (e.g. from aspirated food).

Early genetic testing (facilitated by the charity 'Acrodysostosis Support and Research') may be beneficial to avoid delays in diagnosis but identification of acrodysostosis, even with the help of genetic testing, can remain difficult.

Individuals living with acrodysostosis can present with similar clinical and biochemical features to some other diseases, which can make the diagnosis of acrodysostosis challenging, especially if the symptoms are mild and overlap with other diseases. Clinical and biochemical characteristics of the disease have significant overlap to those of pseudohypoparathyroidism (PHP).[1]

Clinical and biochemical characteristics of acrodysostosis also resemble 2q37 microdeletion syndrome. Individuals living with 2q37 microdeletion syndrome often develop similar skeletal changes to those living with acrodysostosis, including abnormal short bones in the fingers and hands, short stature, and in some cases, PTH resistance.[5]

Acrodysostosis also shares similar genetic causes with other diseases, such as 5q12.1 haploinsufficiency syndrome. The genetic cause of 5q12.1 haploinsufficiency syndrome involves structural abnormalities in the same gene as that of **Type 2** acrodysostosis, *PDE4D*, and individuals living with 5q12.1 haploinsufficiency syndrome also display similar clinical characteristics to those living with acrodysostosis, including underdevelopment of particular facial bones, brachydactyly, and intellectual disability.[5]

## Management

There is currently no cure or standardised treatment guidelines for acrodysostosis, so its management focuses on interventions for the symptoms experienced by the individual. As a result, the management for different persons affected by acrodysostosis will be very different as they can present with a variety of symptoms. Clinical trials would be helpful to determine the effectiveness and safety of the management for the disease. However, to date, no clinical trials for acrodysostosis management have been conducted.

**Table 2:** Common symptoms of acrodysostosis and the recommended management

| Symptoms | Recommended management |
|---|---|
| **PTH resistance** | Persons affected by acrodysostosis with hypocalcaemia, or considerable elevated levels of PTH (>2x the upper limit of normal levels) in the absence of hypocalcaemia, should be treated with active vitamin D metabolites or analogues, with oral calcium supplementation in most cases[1,6]<br><br>Measure PTH, 25-hydroxy (25-OH) vitamin D, calcium and phosphate regularly (e.g. in children every 3–6 months and at least every year in adults, except in individuals with acrodysostosis caused by a mutation in *PDE4D* gene [**Type 2**] where regular monitoring might not be required). Measuring should occur more frequently in symptomatic individuals, acute phases of growth, pregnancy and breastfeeding, and acute illness, as dosing requirements for vitamin D metabolites or analogues might change[6]<br><br>The aim should be to maintain the serum level of phosphorus and calcium, whilst avoiding hypercalciuria, as well as lowering PTH to within mid-normal to 2x the upper limit of normal levels, as permitted by the plasma and urinary calcium levels. Regardless of the level of serum calcium, treatment with vitamin D metabolites or analogues should be considered when PTH levels reach more then 2x the upper limit of normal[6]<br><br>Regular dental reviews every 6–12 months are recommended, at least during childhood[6]<br><br>Patients and their families should be taught to recognise the clinical signs of hypocalcaemia and hypercalcaemia[6] |
| **TSH resistance** | Treatment, doses, and target plasma level concentrations of TSH and thyroxine should be as those used in other forms of hypothyroidism[1]<br><br>Monitor TSH levels every 6 months in affected persons who are younger than 5 years and once a year in older children and adults[1] |

| Symptoms | Recommended management |
|---|---|
| **Growth hormone deficiency** | Careful and regular monitoring of growth, skeletal maturation, using radiography, and growth hormone (GH) secretion is advised in all affected children, starting from around the age of 3–6[6]<br><br>Persons affected by acrodysostosis with GH deficiency may be treated with recombinant human growth hormone (rhGH)[1] |
| **Alterations to gonadal function** | Perform tanner staging of sexual maturation at regular intervals to monitor pubertal development[1] |
| **Bone conditions/ orthopaedic issues** | Clinical and radiological examination of the hands and feet is important from early childhood onwards to establish the diagnosis of brachydactyly[6]<br><br>Persons affected by acrodysostosis with brachydactyly should receive an evaluation of their fine motor skills and be given any appropriate orthopaedic devices that they require[1]<br><br>Some persons affected by acrodysostosis with orthopaedic conditions, such as scoliosis, lumbar lordosis, kyphosis, spinal stenosis, may require multidisciplinary evaluation and orthopaedic corrective surgery[6] |
| **Cognitive impairment** | Individuals affected by acrodysostosis, should be referred to a neuropsychologist for neurocognitive and/or behavioural assessment at diagnosis, preschool age or when signs of cognitive impairment are displayed[6] |
| **Obesity** | Patients, parents and families should be provided with psychological support and educational programs, as early as possible, even in the presence of a normal BMI as a preventative strategy[6]<br><br>All patients should be screened for restless sleep, snoring, inattentiveness and daytime somnolence[6] |

**Abbreviations:** BMI: body mass index; GH: growth hormone; PTH: parathyroid hormone; rhGH: recombinant human growth hormone; TSH: thyroid-stimulating hormone

**Source:** Mantovani et al 2020[6], Mantovani et al 2018[1]

Surgery may be suggested to correct specific skeletal malformations, including underdeveloped or abnormally prominent jaws.[4,6] In addition, early intervention for obesity, in the form of diet plans and regulated eating, may be beneficial. Regular hearing tests should be performed, particularly in children with acrodysostosis who are in crucial phases of speech development and HCPs should evaluate whether feeding poses a risk for aspiration due to anatomical abnormalities. Craniosynostosis should also be screened for on the head circumference growth chart.

All persons affected by acrodysostosis including carers and any siblings may benefit from mental health support; early guidance towards support groups and mental health support is encouraged. Furthermore, communication between specialities to provide coordinated care for individuals living with acrodysostosis will help to alleviate some of the burden associated with managing the disease.

**Professionals involved in patient care**

The diagnosis and management of acrodysostosis requires the effort of a multidisciplinary team of specialists due to the variety of symptoms. Each individual will need the support of specialists to different degrees. The many HCPs involved in the care of patients with acrodysostosis are often scattered across a variety of healthcare centres and hospitals. The need for this wider care team to keep open channels of communication and to provide coordinated care is essential. HCPs frequently involved in the care of persons affected by acrodysostosis are (non-exhaustively):

- Audiology
- Behavioural therapist
- Cardiology
- Complex care
- Continence team
- Craniofacial
- Dentist
- Dermatology
- Developmental medicine
- ENT/Otolaryngology
- Endocrinology
- Gastroenterology
- Genetics
- Growth program
- Music therapist
- Nephrology
- Neurology/Neurosurgery
- Nutrition
- Occupational therapist
- Orthopaedics
- Ophthalmology/Neuro-Ophthalmology
- Paediatrician/Primary care doctor
- Physical therapist
- Pulmonology
- Sleep therapist
- Speech, language and feeding therapist
- Urology
- Vision therapist

## How acrodysostosis impacts affected persons and their families

Persons affected by acrodysostosis experience difficulties in their daily lives from fine motor skills, interconnected with personal care and hygiene to restricted mobility, pain, extreme anxiety, speech barriers, sensory issues and autism. In particular, the latter four make it very challenging to endure medical examinations, tests or invasive procedures. Frequent medical procedures and surgeries pose a constant strain on family life, education, careers and finances, for both persons living with acrodysostosis and their parents.

Persons affected by acrodysostosis with learning and speech difficulties may find it particularly challenging to ensure that their HCPs understand acrodysostosis and its related symptoms, placing a bigger burden on parents and caregivers. Furthermore, developmental delays in speech and language can be particularly distressing for the parents of individuals living with acrodysostosis.

Individuals living with acrodysostosis often have a high pain threshold, so do not show pain easily and they often have a reduced perception of danger, if any. This can be a source of worry for parents and in some cases requires constant supervision and care, even in adulthood. The lack of pain expression results in individuals with acrodysostosis often presenting as well and very happy children, but this can be a barrier to receiving medical attention and care.

## Advice from clinicians that work with persons affected by acrodysostosis

The personal experience of clinicians who have worked closely with individuals with acrodysostosis and their subsequent recommendations have been documented below. These should be taken into consideration alongside the rest of the document to ensure quality care for persons affected by acrodysostosis.

Clinicians emphasise the significance of craniosynostosis in individuals with acrodysostosis. These should be screened for in young children and MRIs provided for older children as required, together with examining the fundus oculi (concave interior of the eye).

Blood pressure and glucose levels should be regularly monitored and followed up with as necessary, as well as GH deficiency caused by GHRH resistance.

Physical activity should be encouraged to prevent weight gain and diet plans actively monitored. In particular, calcium and vitamin D intake should be followed to control PTH levels and optimise bone mineralisation and growth.

At adolescence, individuals with acrodysostosis should be explained the nature of the disease, including its transmission, genetics, and the transition to adulthood. A specific follow up should be organised at the time of expected menarche to check for genital malformations, namely the seminal vesicles in males and uterine in females, as well as abnormal menarche.

In terms of the management of acrodysostosis, the need for multidisciplinary and coordinated care should be emphasised at the beginning of care, with one HCP or team taking the role of coordinator, if possible.

## Useful sources of information

**Links to websites providing information on acrodysostosis:**

- www.acrodysostosis.org
- https://rarediseases.info.nih.gov/diseases/5724/acrodysostosis

**Social media groups to support individuals living with acrodysostosis and their families:**

- Facebook
  - Acrodysostosis Support Group
  - Acrodysostosis Support and Research
- Instagram
  - @acrodysostosis
- LinkedIn
  - Acrodysostosis Support and Research

**Acrodysostosis Support and Research contact details**

- Nina Knight
  - info@acrodysostosis.com
  - nina@acrosysostosis.org
  - +44 (0)7949 883 817

**Research papers related to the management of acrodysostosis:**


- Michot C, Le Goff C, Blair E, et al. Expanding the phenotypic spectrum of variants in *PDE4D/PRKAR1A*: from acrodysostosis to acroscyphodysplasia. Eur J Hum Genet 2018;26:1611-1622.
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**1.** Mantovani G, Bastepe M, Monk D, et al. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. Nat Rev Endocrinol 2018;14:476-500.

**2.** Thiele S, Mantovani G, Barlier A, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network. Eur J Endocrinol 2016;175:P1-p17.

**3.** Silve C, Le-Stunff C, Motte E, et al. Acrodysostosis syndromes. Bonekey Rep 2012;1:225.

**4.** Acrodysostosis. Volume 2021. NORD National Organisation for Rare Disoders, 2014.

**5.** Acrodysostosis Support and Research. Disorders related to Acrodysostosis.

**6.** Mantovani G, Bastepe M, Monk D, et al. Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: An Updated Practical Tool for Physicians and Patients. Horm Res Paediatr 2020;93:182-196.