What is acrodysostosis?

Acrodysostosis is a rare genetic disease characterized by skeletal malformations, growth delays, short stature and distinctive facial features. A characteristic symptom is unusually small hands and feet with short, stubby fingers and toes.

Some children and young people diagnosed with the disease have varying degrees of intellectual disability. Another characteristic of the disease is a resistance to certain hormones that occur naturally in the body.

Acrodysostosis is believed to be caused by mutations in the PRKAR1A gene (type 1) or the PDE4D gene (type 2), although this is not known for certain. These mutations usually occur sporadically and are not passed down through families.

It is likely that additional forms of acrodysostosis exist.

Signs and symptoms

Although certain characteristic and symptoms are known to be indicators of acrodysostosis, there's a lot about the disease that is not yet fully understood. It's important to note that affected individuals may not have all of the symptoms listed below.

1. Skeletal malformations

The hands and feet of a person with acrodysostosis will appear small, with short, stubby fingers and toes. Shortening of the long bones is also common and can result in short stature. This is caused by unusual bone formation, known as dysplasia. These symptoms can often be detected early in childhood.

Another symptom could be an abnormal curvature of the spine and a risk of spinal stenosis. This may cause numbness or pain in the lower back and/or legs.

2. Distinctive facial features

A child or young person with acrodysostosis may have all or some of the following distinctive facial features:

- an underdeveloped upper jaw and nasal bone, with an unusually small nose and the bridge of the nose appearing flattened
- a rounded nose tip with nostrils pointing upward, giving the appearance of an upturned nose
- a very prominent lower jaw bone
- widely-spaced eyes
- an extra fold of skin on either side of the nose that may cover the inner corners of the eyes
- the upper and lower teeth not meeting completely
- low-set ears.

These symptoms tend to affect those with acrodysostosis type 2.

3. Intellectual disability

Some children and young people may exhibit mild to moderate intellectual disability, but this is not a universal symptom. In young children there can be delays in acquiring mental and motor skills, such as learning to walk or talk. This symptom tends to affect those with acrodysostosis type 2.

4. Delayed growth

Growth before birth is usually severely affected and babies can be born unusually small. This growth delay can continue after birth, affecting the child or young person's height for their age and limiting growth spurts during puberty.

5. Hormonal resistance

Some individuals develop resistance to multiple hormones such as the parathyroid hormone and thyroid-stimulating hormone. The hormones are still present in normal to high levels in the body of someone with acrodysostosis, but the tissues of the body do not fully respond to their presence or effects. This symptom tends to affect those with acrodysostosis type 1.

The following symptoms have also been reported in some people living with acrodysostosis: repeated middle ear infections; hearing loss; obesity; skin lesions that are flesh-coloured, brown or black; blue eyes, and red or blond hair; arthritic changes in the hands and problems moving the hands with skill and coordination; in males, the opening of the urethra is on the underside of the penis rather than the tip and/or testes may fail to descend into the scrotum; high blood pressure; and an increased risk of a narrowing of the blood vessels.

Causes

Acrodysostosis is caused by a mutation in either the PRKAR1A gene or the PDE4D gene.

Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, or absent. This can affect many organ systems of the body, including the brain.

The gene mutations that cause acrodysostosis are believed to occur sporadically in the egg or sperm before conception. This means that parents who give birth to a child with acrodysostosis are very unlikely to give birth to another child who is similarly affected.

The disease is not usually inherited; however, some inheritance has been documented in acrodysostosis type 2.

Who is affected?

Acrodysostosis affects males and females in equal numbers. The disease is present at birth but may not be apparent until years later.

Because many cases can go undiagnosed or wrongly attributed to a different condition, determining the true frequency of acrodysostosis in the general population is difficult.

Diagnosis

A diagnosis of acrodysostosis relies on identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation, and a variety of specialized tests including X-rays.

Some symptoms, such as the characteristic facial features and unusually limited growth may be obvious at birth. An X-ray might reveal shorter bones in the hands and feet or the appearance of spots on the rounded end of a long bone.

A foetal ultrasound may potentially reveal underdeveloped growth and short long bones. However, no specific antenatal signs have been identified.

In some cases, molecular genetic testing can confirm a diagnosis of acrodysostosis, but this is only available at specialised laboratories.

Standard Therapies

Early intervention is important to ensure that children and young people with acrodysostosis reach their full potential and live life to the full.

The treatment of acrodysostosis currently involves addressing the specific symptoms that occur in each individual. Treatment may require the coordinated efforts of a team of specialists, including:

- paediatricians
- physical therapists
- orthopaedics (specialising in skeletal abnormalities)
- paediatric endocrinologists (specialising in hormonal imbalances)
- orthodontists (specialising in abnormalities of the teeth)
- neurologists (specialising in the nervous system)
- ophthalmologists (specialising in diseases of the eye)

Surgery may be performed to correct specific abnormalities such as an underdeveloped jaw. In some cases, dental braces may be required to treat misaligned teeth. Physical therapy may also be beneficial. Thyroid hormone supplementation and vitamin D supplements may contribute to improved growth and to prevent obesity. Special services that may be beneficial to affected children may include special remedial education; social support; and other medical, social, and vocational services.

The future of treatment for acrodysostosis

There is currently no typical approach to treatment. Due to the rarity of the disease there are no treatment trials that have been tested and proven to be effective on a large group of patients, although some treatments have been reported on an individual basis.

Treatment trials could be very helpful to determine the long-term safety and effectiveness of specific medications and treatments for people living with acrodysostosis.

Information derived from the National Organization of Rare Diseases (NORD).