What is acrodysostosis? (medical version)

Acrodysostosis is a rare genetic disorder characterized by skeletal malformations, growth delays, short stature, and distinctive facial features caused, in part, by underdeveloped (hypoplastic) of certain facial bones, particularly those in the middle portion of the face.

A characteristic symptom is abnormally small hands and feet with short, stubby fingers and toes that may affect all or some of the fingers and toes. Some affected children have varying degrees of intellectual disability; in other children intelligence is unaffected.

Some children experience resistance to certain hormones, which means that the tissues of the body do not respond to the hormone in question despite normal or high activity levels of the hormone.

Acrodysostosis may be caused by mutations in the PRKAR1A gene (type 1) or the PDE4D gene (type 2). These mutations usually occur sporadically without a positive family history; mutations in PDE4D can be inherited in an autosomal dominant manner.

It is likely that additional forms of acrodysostosis exist; caused by as-yet-unidentified gene mutations.

Signs & Symptoms

Although researchers have been able to establish a clear syndrome with characteristic or “core” symptoms, much about the disorder is not fully understood.

Several factors including the small number of identified cases, the lack of large clinical studies, and the possibility of other genes influencing the disorder prevent physicians from developing a complete picture of associated symptoms and prognosis.

Therefore, it is important to note that affected individuals may not have all of the symptoms discussed below. Parents should talk to their children’s physicians and medical team about their specific case, associated symptoms and overall prognosis.

Skeletal malformations that characterize acrodysostosis include abnormal short, malformed (dysplastic) bones in the hands and feet. These dysplastic bones cause the hands and feet to be abnormally small with short, stubby fingers and toes (severe brachydactyly). In some individuals, the shortness may affect only one or two fingers and/or toes. The big toes are often not affected, or can be abnormally large. Abnormalities of the hands and feet are detected early in childhood (congenital). Abnormal shortening of the long bones is also common and can result in short stature.

Additional skeletal malformations include spinal malformations such as abnormal curvature of the spine (e.g. scoliosis or kyphosis), and a risk of spinal stenosis, a condition marked by narrowing (stenosis) of the spaces within the spinal canal, spinal nerve root canals, or bones of the spinal column. Affected individuals may experience numbness or pain in the lower back and/or legs. The chondrodysplasia develops and becomes more noticeable over time.

Individuals with acrodysostosis often have distinctive facial features including underdevelopment of the upper jaw (maxillary hypoplasia) and underdevelopment of the nasal bone (nasal hypoplasia) so that the nose is abnormally small and the bridge of the

nose may be flattened or depressed. In some cases, the tip of the nose is rounded (bulbous) and the nostrils point upward giving the appearance of an upturned nose (anteverted nares). The lower jaw bone (mandible) may appear abnormally prominent. Additional features can include widely-spaced eyes (hypertelorism), an extra fold of skin on either side of the nose that may cover the inner corners of the eyes (epicanthal folds), failure of the upper and lower teeth to meet properly (malocclusion), and low-set ears.

Some affected individuals may exhibit mild to moderate intellectual disability and experience delays in acquiring skills that require both mental and motor coordination (psychomotor delays), learning disabilities, and delays in learning to walk and talk.

Growth before birth (antenatal growth) is usually severely affected and babies are born small for gestational age. Mild to moderate growth delays after birth may also occur and affected individuals are often below average height for their age (short stature). A great part of the height deficit is due to the lack of the pubertal growth spurt.

Some individuals develop resistance to multiple hormones such as parathyroid hormone and thyroid-stimulating hormone. Resistance means that although the hormones are present in normal -or even high- levels, the tissues of the body do not fully respond to their presence or effects. In most patients with hormone resistance, the rise of the circulating level of the hormone is sufficient to induce the expected effect of the hormone (for example, the rise in parathyroid hormone will allow the body to maintain a normal serum calcium level). Under certain conditions, individuals may develop symptoms similar to those seen in individuals with deficiency of these hormones.

Additional physical findings have been reported in individuals with acrodysostosis including repeated middle ear infections (otitis media), hearing loss, obesity, skin lesions that are flesh-colored, brown or black (pigmented nevi), blue eyes, and red or blond hair. Affected individuals may eventually develop arthritic changes in the hands which can lead to problems moving the hands with skill and coordination (manual dexterity). In some affected males the opening of the urethra is on the underside of the penis rather than the tip (hypospadias) and/or testes may fail to descend into the scrotum (cryptorchidism).

Certain metabolic and cardiovascular manifestations have also been reported in acrodysostosis including high blood pressure (hypertension). Some reports suggest that affected individuals are at an increased risk for narrowing of the blood vessels (vascular stenosis).

Individuals with acrodysostosis type 1 appear to be more likely to develop hormone resistance. Individuals with acrodysostosis type 2 are more likely to have intellectual disability and characteristic facial features. Some recent cases described in the medical literature suggest that hormone resistance is more common in individuals with acrodysostosis type 2 than previously believed.

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. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain.

In many cases, these gene mutations are believed to occur as a new (sporadic or de novo) mutations, which means that a gene mutation has occurred at the time of the formation of the egg or sperm for that child only, and no other family member will be affected. The disorder is usually not inherited from or “carried” by a healthy parent. However, dominant inheritance (where a trait is transmitted from either an affected mother or father to their child) has been documented in acrodysostosis type 2.

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy regardless of the gender of the resulting child.

Investigators have determined that the PRKAR1A gene is located on the long arm (q) of chromosome 17 (17q24.2) and that the PDE4D gene is located on the long arm of chromosome 5 (5q11.2-q12.1). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated “p” and a long arm designated “q”.

The PRKAR1A and PDE4D genes both create (encode) proteins that play a key role in the cAMP signaling pathway. A signaling pathway is the series of chemical processes by which certain cell activities are controlled and managed. The cAMP signaling pathway is essential for the proper formation of bone (skeletogenesis) and for the action of many hormones including the parathyroid hormone and the thyroid stimulating hormone. Mutations in these genes modify the function of the specific protein product, which ultimately leads to the symptoms of acrodysostosis.

Affected Populations

Acrodysostosis affects males and females in equal numbers. The disorder is present at birth (congenital) but may not be apparent until years after birth. The exact incidence and prevalence of the disorder is unknown. Because many cases can go misdiagnosed or undiagnosed, determining the true frequency of acrodysostosis in the general population is difficult.

Related Disorders

Symptoms of the following disorders can be similar to those of acrodysostosis. Comparisons may be useful for a differential diagnosis.

Albright hereditary osteodystrophy (AHO) is a rare disorder characterized by short stature, an unusually round face, abnormally short fingers (brachydactyly), and/or the development of bony growths (osseous plaques) on the surface of the skin but not in the deep connective tissue. These growths may spread to the lower level of the skin as well (subcutaneous

ossification). Other symptoms may include mild intellectual disability and obesity. AHO may be isolated or associated with hormone resistance, such as parathyroid hormone resistance which manifests as abnormally low levels of calcium in the blood (hypocalcemia). Therefore, symptoms of pseudohypoparathyroidism include weakness, muscle cramps, excessive nervousness, headaches, and/or abnormal sensations such as tingling, burning, and numbness of the hands.

The association of AHO and hormone resistance is termed pseudohypoparathyroidism type 1A. AHO (sometimes called pseudopseudohypoparathyroidism or PPHP) and PHP1A are caused by loss of function mutations of the same gene (GNAS). GNAS encodes the alpha stimulatory subunit of the G-proteins that are needed to properly respond to parathyroid hormone and other hormones. Each condition can be inherited in an autosomal dominant manner. However, isolated AHO (PPHP) is inherited from fathers whereas PHP1A is inherited from mothers. (For more information on this disorder, choose “Albright” as your search term in the Rare Disease Database.)

5q12.1-haploinsufficiency syndrome is an extremely rare disorder that has only been described in several individuals. These individuals have structural chromosome abnormalities (e.g. deletions) that involve the PDE4D gene, resulting in half the normal production of the protein product of that gene (haploinsufficiency). The symptoms of these individuals were extremely similar to those seen in individuals with acrodysostosis type 2 including underdevelopment of certain facial bones, brachydactyly, and intellectual disability.

2q37 microdeletion syndrome is a rare disorder characterized by a broad range of signs and symptoms. Affected individuals often develop varying degrees of intellectual disability, abnormal short bones in the fingers and hands (brachymetaphalangy), short stature, obesity, and distinctive facial features. Additional symptoms include diminished muscle tone (hypotonia), joint abnormalities, abnormal sideways curvature of the spine (scoliosis), and autism spectrum disorder. Some affected individuals may have congenital heart disease, seizures, central nervous system abnormalities, hernias, gastrointestinal abnormalities, and kidney (renal) malformations. Parathyroid hormone resistance was described in few cases. 2q37 microdeletion syndrome is caused by a small loss of genetic material on the long arm (q) of chromosome 2. The specific gene(s) involved in this disorder are not known.

Diagnosis

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

Clinical Testing and Workup

Prenatal fetal ultrasonography, an exam in which reflected sound waves create an image of the developing fetus, may potentially reveal intrauterine growth retardation and short long bones that are compatible with the diagnosis of acrodysostosis. However, no specific antenatal signs have been isolated.

Some symptoms of acrodysostosis may be obvious at birth such as characteristic facial features and growth retardation. Traditional x-ray studies may reveal abnormally short bones in the hands and feet and premature fusion of the end portions (epiphyses) of certain bones

of the hands, feet, and elbows. The appearance of spots on the epiphyses (stippling) may also be detected by traditional x-ray.

In some cases, molecular genetic testing can confirm a diagnosis of acrodysostosis. Molecular genetic testing can detect mutations in one of the two specific genes known to cause the disorder, but is available only as a diagnostic service at specialized laboratories.

Standard Therapies

Treatment

The treatment of acrodysostosis is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, specialists who diagnose and treat skeletal abnormalities (orthopedists), specialists who diagnose and treat hormonal imbalance (pediatric endocrinologists), orthopedic surgeons, specialists who diagnose, prevent, and/or treat abnormalities of the teeth (orthodontists), neurologists, ophthalmologists, physical therapists, and other health care professionals may need to systematically and comprehensively plan an affected child's long-term treatment.

There are no standardized treatment protocols or guidelines for affected individuals. Due to the rarity of the disease, there are no treatment trials that have been tested on a large group of patients. Various treatments have been reported in the medical literature as part of single case reports or small series of patients. Treatment trials would be very helpful to determine the long-term safety and effectiveness of specific medications and treatments for individuals with acrodysostosis.

Specific therapies for the treatment of acrodysostosis are symptomatic and supportive. Surgery may be performed to correct specific abnormalities such as underdeveloped (hypoplastic) and/or abnormally prominent jaws (prognathism). In some cases, dental braces may be required to correct misaligned teeth (malocclusion). In addition, in some cases, physical therapy may also be required. Thyroid hormone supplementation and vitamin D supplements may contribute to improve growth and prevent obesity.

Early intervention is important to ensure that children with acrodysostosis reach their full potential. Special services that may be beneficial to affected children may include special remedial education, social support, and/or other medical, social, and/or vocational services.

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