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Clinical Manifestation and pathogenesis of Cleidocranial dysplasia

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Abstract:

Cleidocranial dysplasia is a condition that primarily affects development of the bones and teeth. Signs and symptoms of cleidocranial dysplasia can vary widely in severity, even within the same family.so this report will discuss the general, oral manifestation and pathogenesis.

Introduction:

Cleidocranial dysplasia (CCD) is an uncommon but well-known genetic skeletal condition. Several hundred affected persons are members of a large extended family The clinical manifestations are often innocuous, but hyperdontia and other developmental abnormalities of the teeth are a major feature and may require special dental management.[1]

Discussion:

Clinical presentation:

Individuals with cleidocranial dysplasia usually have underdeveloped or absent collarbones, also called clavicles ("cleido-" in the condition name refers to these bones). As a result, their shoulders are narrow and sloping, can be brought unusually close together in front of the body, and in some cases can be made to meet in the middle of the body. Delayed maturation of the skull (cranium) is also characteristic of this condition, including delayed closing of the growth lines where the bones of the skull meet (sutures) and larger than normal spaces (fontanelles) between the skull bones that are noticeable as "soft spots" on the heads of infants. The fontanelles normally close in early childhood, but they may remain open throughout life in people with this disorder. Some individuals with cleidocranial dysplasia have extra pieces of bone called Wormian bones within the sutures.

Affected individuals are often shorter than other members of their family at the same age. Many also have short, tapered fingers and broad thumbs; flat feet; bowed legs or knock knees; short shoulder blades (scapulae); and an abnormal curvature of the spine (scoliosis). Typical facial features include a wide, short skull (brachycephaly); a prominent forehead; wide-set eyes (hypertelorism); a flat nose; and a small upper jaw.

Individuals with cleidocranial dysplasia often have decreased bone density (osteopenia) and may develop osteoporosis, a condition that makes bones progressively more brittle and prone to fracture, at a relatively early age. Women with cleidocranial dysplasia have an increased risk of requiring a cesarean section when delivering a baby, due to a narrow pelvis preventing passage of the infant's head.

Dental abnormalities are very common in cleidocranial dysplasia and can include delayed loss of the primary (baby) teeth; delayed appearance of the secondary (adult) teeth; unusually shaped, peg-like teeth; misalignment of the teeth and jaws (malocclusion); and extra teeth, sometimes accompanied by cysts in the gums.

In addition to skeletal and dental abnormalities, people with cleidocranial dysplasia may have hearing loss and are prone to sinus and ear infections. Some young children with this condition are mildly delayed in the development of motor skills such as crawling and walking, but intelligence is unaffected.[2]

Pathogenesis:

The molecular defect in CCD is situated at the chromosomal locus of 6p21 and the causative gene in the South African family is located at this site. The determinant gene, *RUNX2* codes for a core-binding transcription factor protein (CBFA1), which is involved in the differentiation of osteoblasts and bone formation. *RUNX2* plays an important role in the

epithelial-mesenchymal interactions that control progressive tooth morphogenesis and histodifferentiation of the epithelial enamel organ.[2]

Experimental studies have revealed that mice lacking the *RUNX2* gene fail to develop bone and tooth structure, whereas mice with mutant *RUNX2* genes show arrested tooth development.[35] The most common site of *RUNX2* gene expression during odontogenesis is the papillary mesenchyme; levels are highest before the development of the tooth crown but taper after completion of crown formation.[36] In mice, the *RUNX2* gene is also expressed in the mesenchyme of the dental follicle and periodontal ligament before tooth eruption. A lack of both alleles of the *RUNX2* gene results in absence of osteoblastic differentiation, whereas haploinsufficiency of *RUNX2* in mice impairs the differentiation and recruitment of osteoclasts together with reduction in the capacity of periodontal ligament cells to induce active osteoclastic differentiation. These processes could, in part, account for delayed tooth eruption patterns in humans with CCD.

Bone is formed by 2 processes, namely, endochondral and intramembranous osteogenesis, both of which require the presence of the *RUNX2* protein. The formation and development of both the cranium and clavicles occur by intramembranous ossification. Although the clavicles are the first embryonic bones to ossify, the maturation process is slow. In mice, clavicular defects result from the disruption of intramembranous bone formation during embryogenesis. Low levels of functional *RUNX2* protein are implicated as the causative agent. Although this process begins during early embryonic development, the effects are evident in adult mice. The mouse model offers a reasonable explanation of the clavicle and cranial abnormalities occurring in CCD in humans. It also suggests that the levels of normal *RUNX2* proteins are critical for the successful intramembranous ossification during embryogenesis.[3,4]

Conclusion:

Cleidocranial dysostosis (CCD), also called cleidocranial dysplasia, is a birth defect that mostly affects the bones and teeth. The collarbones are typically either poorly developed or absent, which allows the shoulders to be brought close together. The front of the skull often does not close until later, and those affected are often shorter than average. Other symptoms may include a prominent forehead, wide set eyes, abnormal teeth, and a flat nose. Symptoms vary among people; however, intelligence is typically normal.

The condition is either inherited from a person's parents or occurs as a new mutation. It is inherited in an autosomal dominant manner. It is due to a defect in the RUNX2 gene which is involved in bone formation.

References:

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