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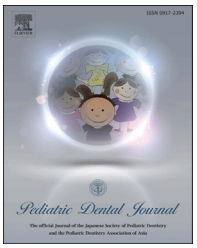

Invited Review Article

Cleidocranial dysplasia: Clinical overview and genetic considerations

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ABSTRACT

Cleidocranial dysplasia (CCD) is a congenital autosomal dominant syndrome characterised by dental and osseous dysplasia that leads to multiple dental and craniofacial anomalies. Two-thirds of CCD cases are associated with mutations of the runt-related transcription factor 2 (*RUNX2*) gene which codes for a transcription factor that is responsible for differentiation of osteoblasts and osteoclasts and skeletal development. Multiple mutations have been identified in the Runx2 gene, primarily clustered in the Runt domain. Other genes such as CCAAT/enhancer-binding protein beta (Cebpb) and T-box transcription factor TBX1 (Tbx1) are under investigation. There are multiple clinical and radiological signs of CCD, e.g. brachycephaly, frontal and parietal bossing, open sutures and fontanelles, delayed closure of fontanelles, kyphosis, narrow sloping shoulders, multiple wormian bones, and delayed mineralisation of the skull. Although the signs present themselves in varying degrees, certain signs such as supernumerary teeth, frontal bossing, hypoplastic maxilla, and prognathic mandible are characteristic. However, many of them may not appear before the growth spurt in all cases. Early identification of CCD, especially prenatal ultrasound diagnosis, has a better prognosis as early orthodontic intervention can be commenced. Apart from clinical and radiographic analysis, identification of a *RUNX2* mutation can serve as a diagnostic aid in families with a history of CCD. However, it is important to understand that only two-thirds of the people with CCD have *RUNX2* mutation, so genetic analysis will not be of use in people without the mutations.

Contents

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1. Background

Cleidocranial dysplasia (CCD) (MIM 119600), also known as cleidocranial dysostosis, is a rare hereditary skeletal disorder. In most cases, it is inherited as an autosomal dominant trait; but in some cases, the disorder appears sporadically. Clavicular defects have been reported as early as 1765, but Scheithauer was probably the first to describe the syndrome accurately [1]. Marie and Sainton in 1898 coined the term *dysostose cléido-crânienne héréditaire* (hereditary cleidocranial dysostosis) for this condition. One of the most colourful families, descendants of a Chinese named Arnold, was described by Jackson. He traced 356 members of this family, 70 of whom were affected with the so called "Arnold Head" that is now confirmed as CCD [2]. The worldwide prevalence of CCD is approximately 1/1,000,000 individuals [3].

2. Clinical and radiological considerations

2.1. *Clinical features*

CCD primarily affects the development of teeth and bones, particularly craniofacial bones. Signs and symptoms can vary widely in severity, even within the same family [4]. One characteristic is underdeveloped or absent clavicles, leading to narrow, sloping shoulders that can be brought unusually close together in front of the body and, in some cases, even made to meet in the middle of the body. Delayed fontanelle closure is also characteristic of this condition; the fontanelles may remain open even into the adulthood in some cases. Individuals with CCD may be 7.5–15 cm shorter than the other members of their family; they may have short tapering fingers and broad thumbs, short forearms, flat feet, knock knees, and scoliosis. Typical facial hallmarks include a wide, short skull (brachycephaly); a prominent forehead; wide-set eyes (hypertelorism); a flat nose; and a small upper jaw. Individuals with CCD may have decreased bone density (osteopenia) and may develop osteoporosis. Women with CCD often have a narrow pelvis, which increases the risk of requiring a caesarean section [5,6]. Dental abnormalities seen in CCD include delayed loss of primary teeth, delayed appearance of the secondary teeth, unusually shaped peg-like teeth, malocclusion, and supernumerary teeth [7]. In addition to skeletal and dental abnormalities, people with CCD may have hearing loss and be 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, as well as other orthopaedic problems such as pes planus, genua valga, and scoliosis; however, intelligence is unaffected.

2.2. *Radiological features*

Frontal bossing, hypoplastic maxilla, and prognathic mandible are characteristic of CCD. However, these signs may not appear before the growth spurt in all the cases. The radiograph of the skull would show multiple wormian bones, segmental calvarial thickening, unossified sutures, patent fontanelles, basilar invagination, hypoplasia of the maxilla, delayed mineralisation of the skull, delayed or an absence of calcification of the nasal bone, and hypoplasia of the paranasal, frontal and mastoid sinuses. Other abnormalities observed on radiographs include the following: (i) thorax: cone-shaped thorax, hypoplastic scapulae, clavicular hypoplasia/aplasia, and cervical or missing/supernumerary ribs; (ii) hip/pelvis: delayed ossification of the pubic bone, iliac wing hypoplasia, widened sacroiliac joints, and large femoral necks and epiphyses; (iii) spine: hemivertebrae, spondylolysis, spondylolisthesis, and spina bifida occulta; and (iv) limbs: short/absent fibula, short/absent radius, short middle phalanges and metacarpals, hypoplastic distal phalanges, accessory epiphyses, and long second metacarpals with cone-shaped epiphyses [8–11].

Golan et al. [12] assessed early craniofacial features and showed that only 14% exhibited frontal bossing, 35% had hypoplasia of their mid-face, and 57% had a prognathic mandible; also, 80% of the patients had an erupted second permanent molar, while the primary dentition was retained and all cases demonstrated widely spaced incisors. The nasal bones were present in only 64% of the cases, whereas wormian bone, a markedly rounded gonion angle, and a kyphotic sphenoid bone were present in all of the cases, as were supernumerary teeth and a parallel-sided ascending ramus. The changes suggest that the gene responsible is not only active during early development, as is implied by changes in the shape or number of bones, but is also important during foetal and postnatal growth.