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## Case Report

# Cleidocranial dysplasia with hypermobile Ehlers-Danlos syndrome: A case report <sup>☆,☆☆</sup>

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## ABSTRACT

Cleidocranial dysplasia (CCD) is a rare genetic skeletal syndrome. The most common features are open fontanelles, hypertelorism, mid-face retrusion, hypoplasia, or aplasia of the clavicles leading to excessive shoulder mobility, dental abnormalities such as supernumerary, and impacted teeth. This case report describes a 31-year-old male with CCD with several unusual symptoms like generalized joint hypermobility, skin laxity, and smooth skin, which leads to set a diagnosis of hypermobile Ehlers-Danlos syndrome (hEDS). To our knowledge, this is the first case report in the literature that describes a patient with these 2 distinct syndromes CCD and hEDS.

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## Introduction

Cleidocranial dysplasia (CCD) is a rare genetic skeletal dysplasia with a global prevalence of 1: 1,000,000. It can arise spontaneously or by an autosomal dominant inheritance pattern, with high genetic penetrance and variable clinical manifestations. It mainly affects bones that undergo intramembranous ossification, with no gender or ethnicity predilection [1]. The intellect is unimpaired, and the patient usually is fit and well [2].

The main characteristic features are short stature, delayed closure of the fontanelles, brachycephaly [3], hypertelorism,

bell-shaped thorax, and a partial or complete absence of clavicles leading to excessive mobility of shoulders on one or both sides. The vertebral column, the pelvis, and the hands and feet bones may also be affected [4].

CCD has distinctive importance to dental practitioners because of the involvement of facial bones, dental problems such as prolonged retention of deciduous teeth, delayed eruption of permanent teeth, and the presence of multiple unerupted supernumerary teeth [5].

Ehlers-Danlos syndrome (EDS) is a spectrum of inherited heterogeneous connective tissue disorders [6]. The most common type of EDS is hypermobile Ehlers-Danlos (hEDS) [7]. Connective tissue, joints, and muscles are mainly affected in hEDS

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**Fig. 1 – Panoramic radiograph: multiple impacted supernumerary teeth, U-shaped sigmoid notch, and paralleled ramus.**

causing skin hyper-elasticity and joint hypermobility [8]. The oral and dental manifestations of hEDS may include high or narrow palate, dental crowding, ectopic eruption, and short roots [9,10]. Temporomandibular joint hypermobility is also common [11].

This article describes the clinical and radiographic features of a 31-year-old male with cleidocranial dysplasia and hypermobile Ehlers-Danlos.

### Case presentation

A 31-year-old male presented to the Department of Oral Medicine, Faculty of Dental Medicine, with a chief complaint of halitosis and an unpleasant fixed full-arches prostheses. The patient reported that many of his teeth had been extracted before placing the full dental restoration.

Intraoral examination revealed poor oral hygiene, a high arched palate, and fissured tongue. We also observed the presence of a partially erupted tooth at the right of the upper labial frenum.

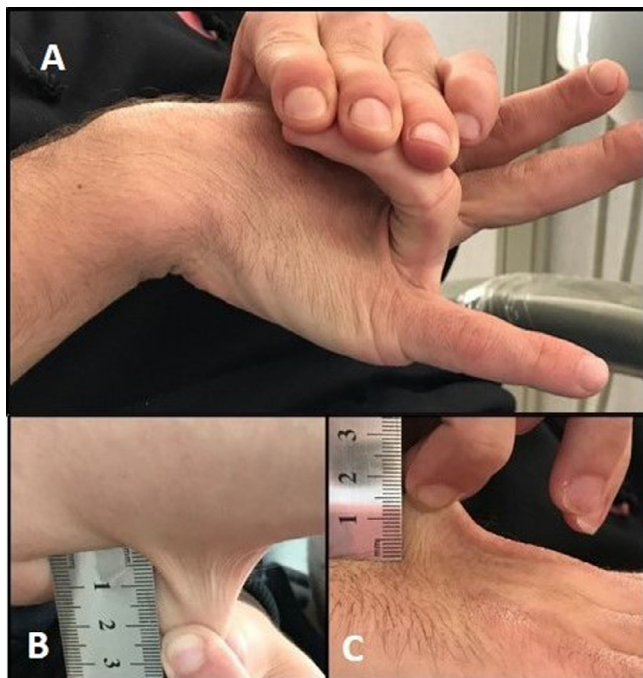
A panoramic radiograph was requested to evaluate the dental situation and the fixed prosthesis, which showed that both the maxillary and mandibular fixed prostheses have few abutments with inadequate endodontic treatments. Also, many unerupted and supernumerary teeth were observed in the maxilla and mandible. The maxillary sinuses were underdeveloped. The gonial angles were round, and the rami were parallel, with a U-shaped sigmoid notch. In addition, coarse osseous trabeculation was noticed (Fig. 1).

Physical examination revealed short stature, a central depression on the forehead, frontal and parietal prominence, a flattened nasal bridge, hypertelorism, exophthalmos, lobeless ears, hypoplastic maxilla, and mandible prognathism with no symmetry. The patient was able to bring his shoulders in front of his chest (Fig. 2). Flat feet and genu valgum were also observed.

The joint mobility was examined using Brighton criteria [12]. His fifth finger in both hands has more than 90 degrees



**Fig. 2 – (A, B) Frontal and lateral view of the patient face demonstrating depressed large anterior fontanelle, broad nasal bridge, hypertelorism; (C) the general appearance of the patient; (D) shoulders hypermobility.**



**Fig. 3 – (A) Joint hypermobility; (B, C) Skin laxity.**

of passive dorsiflexion. The thumb in the right hand could be passively flexed to the forearm. Both knees can hyperextend more than ten degrees. However, he could not hyperextend his elbows beyond ten degrees nor forward flexion his trunk with knees fully extended and palm resting on the floor. The overall Brighton criteria score was 5, which dictates generalized hypermobility of the joints. The patient's skin can easily extend more than the normal range (Fig. 3). However, there was no bruising all over his skin.

TMJ and muscles examination revealed tenderness of the right and left masseter and the left lateral pterygoid. There was apparent atrophy in the left and right masseter. On the other hand, the temporalis muscles were noticeably enlarged and not tender on palpation. No hypermobility or subluxation was found.

Chest radiography demonstrated aplasia of the right clavicle, a hypoplastic left clavicle, and a narrow bell-shaped thorax with oblique ribs. The pelvis X-ray showed a wide pubic symphysis and coxa vara. Feet radiograph revealed hypoplasia of distal phalanges (Fig. 4). The family history revealed that 3 of 6 of the patient's siblings and the father have analogous phenotypic.

Computed tomography (CT) of the skull with 3-dimensional reconstruction revealed extreme open sutures and plagiocephaly. Each of the anterior fontanelle, posterior fontanelle and the posterolateral fontanelles are widely open. Wormian bones are noticed in the cranial sutures. Malformations in the orbit bones and the absence of nasal bone were also detected (Fig. 5).

The CT also revealed a patent mandibular symphysis, cleft palate, and discontinuous zygomatic arch on both the right and left sides. Many unerupted teeth were observed; 26 of them were in the maxilla and 15 teeth in the mandible. Several

dentigerous cysts around the unerupted teeth in the mandible and maxilla were noticed (Fig. 6).

Based on the previous clinical and radiographic features, the patient was diagnosed with 2 syndromes cleidocranial dysplasia and hypermobile Ehlers-Danlos syndrome.

## Discussion

CCD is mainly caused by heterozygous mutations in the runt-related transcription factor 2 (RUNX2) gene, which is located on locus 21 of the short arm(p) of chromosome VI (6p21) [13], which plays a significant role in the differentiation and maturation of osteoblasts and osteoclasts and recession of the dental lamina [14]. Nevertheless, the genetic mutations cannot be detected in approximately 40% of the cases [15].

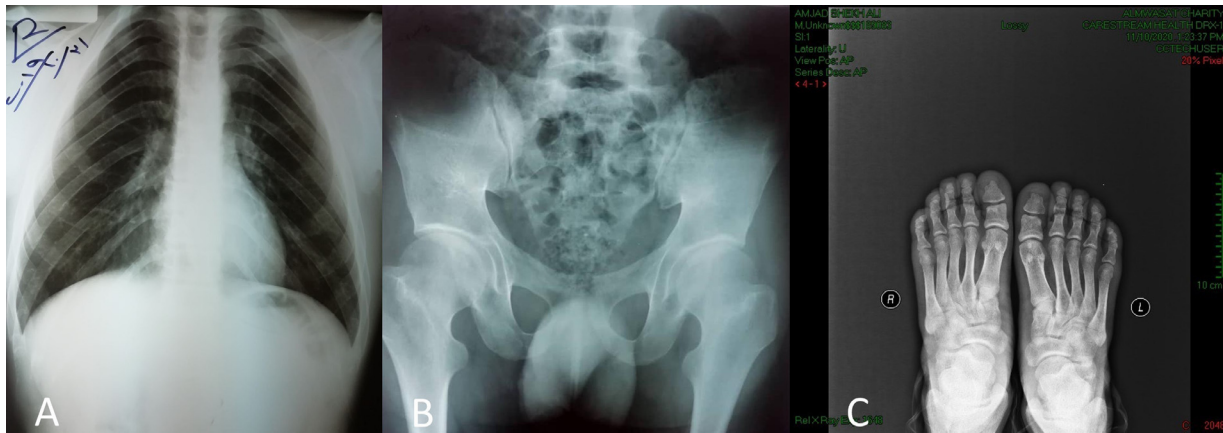
The pathognomonic features for diagnosis of CCD are open fontanelles, broad sutures, frontal and parietal bossing, wormian bones [16], a narrow thoracic cage, and hypoplasia or aplasia of clavicles which leads to excessive mobility of the shoulder girdle. Other skeletal abnormalities like short stature [2], coxa vara, short femoral neck, wide pubic symphysis, genu valgum, pes planus, and vertebral column deformity, including scoliosis kyphosis or lordosis could be observed. Hands and feet can also be affected; the abnormalities may include brachydactyly, tapering fingers, and absence of carpal bones [15].

The Craniofacial features found with CCD are hypoplasia of the maxillary bone, high vaulted palate, decreased face height, malformed paranasal sinuses, hypoplastic nasal bones, hypertelorism, and a slender or even discontinuous zygomatic arch. The mandible is relatively prognathic with a patent symphysis and u-shaped sigmoid notch [17,18].

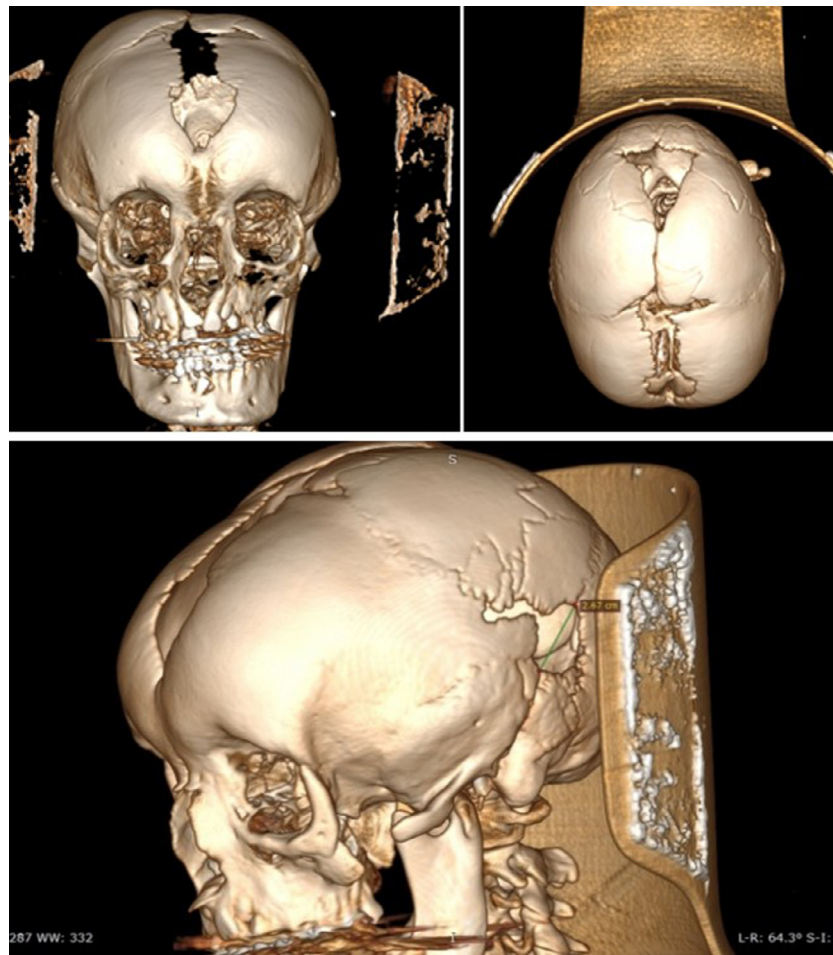
Patients with CCD also have several dental abnormalities, including teeth formation and eruption. The dental abnormalities are manifested by multiple supernumerary teeth as a result of the lack of recession of succeeding dental lamina and the distal extension of the primary dental lamina. This regression is a crucial mechanism for preventing the development of supernumerary teeth. The disturbing of osteoclastogenesis in the dental follicle and the periodontal ligament leads to impair resorption of bone and roots of primary teeth; as a result, a delayed shedding of primary teeth and delayed eruption of permanent teeth occur [19]. In addition to the presence of supernumerary teeth as physical obstacles in the eruption path [20], dentigerous cysts may develop due to the presence of retained teeth [18].

Early diagnosis of CCD is important for the dental treatment plan to obtain satisfactory results. It is possible to predict the presence of supernumerary teeth when the crowns of successional teeth complete their formation. The early intervention aims to promote spontaneous eruption by removing the primary teeth, supernumerary teeth, and overlaying bone covering the permanent unerupted teeth. These should be done when the root formation of the permanent tooth reaches half to two-thirds of its final length. The treatment may also include orthodontic traction, fixed prostheses, implants, or even orthognathic surgery if indicated [15,21].





**Fig. 4 – (A) Chest radiograph (PA view): hypoplastic clavicles and narrow thoracic cage; (B) Hip X-ray: wide pubic symphysis, broad femoral heads, and short femoral neck; (C) feet X-ray: hypoplasia of distal phalanges.**



**Fig. 5 – Open frontal suture, wormian bones, malformation of the zygomatic arch, and absence of nasal bone.**



**Fig. 6 – Supernumerary teeth and cysts in the mandible and maxilla.**

The patient had other unique signs and symptoms which do not usually exist in CCD, like generalized joint hypermobility, excessive skin laxity, smooth skin, prominent eyes, lobeless ears, and limb pain. This indicates the patient has another syndrome in addition to CCD. The suspected syndrome was hEDS since the patient met sufficient criteria to set the diagnosis [6].

## Conclusion

To our knowledge, this is the first documented case that describes the clinical and radiographic features of a patient with 2 rare syndromes, CCD and hEDS. The relationship between the 2 syndromes needs further future research. We also emphasize the fundamental role of radiological examination in the early detection of the syndrome, which allows the dentist to start a better treatment plan and obtain satisfactory results.

The early intervention will also improve the patient's quality of life and reduce the care burden.

## Patient consent

Written and informed consent was obtained from the patient to publish this case. The patient was aware that no personal information will be revealed in the manuscript.

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