Cleidocranial Dysplasia: A Review of Clinical, Radiological, Genetic Implications and a Guidelines Proposal

Emilie Farrow, MD, Romain Nicot, MD, MSd,* Axel Wiss, MD,*† Amélie Laborde, MD,* and Joël Ferri*†*

Abstract: In this review, we aimed to depict the clinical, radiological, and genetic features of cleidocranial dysplasia (CCD) and to suggest management guidelines, based on our experience of 8 cases, with an emphasis given to dental complications.

The most common craniofacial features of CCD that stand out are a patency of the anterior fontanelle, an inverted pear-shaped calvaria, a hypertelorism, a general midface retrusion, and a mandible prognathism, associated with an excessive mobility of the shoulders, a short stature, and teeth abnormalities such as supernumerary teeth and failure of eruption, in particular. *RUNX2* is the only gene in which mutation is known to cause CCD, but mutations are detected in only 65% of all patients with a clinical diagnosis of CCD. Panoramic radiography is a valuable adjunct in confirming the diagnosis of CCD.

Our experience allowed us to conclude that orthodontically aided eruption should always be attempted. However, to stabilize the occlusion and to improve facial esthetics, we recommend associated orthognathic surgery. When orthodontic treatment is partially efficient, prosthetic treatment options bring satisfactory results, in terms of occlusion. Nevertheless, when orthodontic treatment fails, we recommend to preserve as many native teeth as possible, and to combine orthognathic preprosthetic surgery and implant-supported prosthesis.

In any case, an individualized treatment protocol, depending on the needs and demand of the patient, the age at diagnosis and social and economic circumstances, should be put forward.

Key Words: Cleidocranial dysplasia, orthognathic surgery, tooth abnormalities

(*J Craniofac Surg* 2018;29: 382–389)

Cleidocranial dysplasia (CCD), also known as Scheuthauer syndrome, is a rare and underdiagnosed condition. The worldwide prevalence of CCD is generally estimated at about 1 per million,[1] without sex predilection. CCD is inherited as an autosomal dominant trait, with a high penetrance and a wide variation in clinical expressivity.[2]

The most typical clinical features observed in CCD are supernumerary teeth, delayed teeth eruption, hypoplastic maxilla, and hypoplastic clavicles, in >80% of cases,[3] and their association is highly characteristic.

The main issue in managing CCD is the early diagnosis. Yet, many patients are misdiagnosed for 3 main reasons: 30% to 40% of cases are caused by de novo mutations, the only gene (*RUNX2*: Runt-related transcription factor 2) in which mutation is known to cause CCD is not pathogenic in 30% of cases and most craniofacial features are age-related and do not become obvious before adolescence. Moreover, medical complications rarely occur.

It is admitted that dental and maxillofacial treatment strategies depend on the patients age and the earlier the treatment is set up, the higher the chances are of obtaining an aesthetic and long-term stable result using orthodontically aided eruption of natural permanent teeth.

The aim of this article is to depict the clinical, radiological, and genetic features of CCD and to suggest management guideline, based on our experience of 8 cases, with an emphasis given to dental and maxillofacial implications.

MATERIAL AND METHODS

Systematic Review

We intended to include as many pertinent studies as possible. The main inclusion criterion was that selected studies should present, at best, a complete collection of cases, or at least a single case report discussing treatment strategies. We excluded all studies that had not been written or accurately translated in either English or French language. The PubMed interface of Medline was searched using the following keywords: "Cleidocranial dysplasia," "Cleidocranial dysplasia," "Cleidocranial dysostosis," "Cleido-cranial dysostosis," and "Dysostose cléido-crânienne." The research was then completed by referring to the bibliographies and citation lists of selected papers.

Local Patient Cohort

Our study is based on 8 patients suffering from CCD. Each one of them was diagnosed and managed within the Maxillo-facial surgery and Stomatology Department, at the Lille University Hospital. Cases were found with the cooperation of the hospital's Medical Information Department using precise diagnosis and therapeutic keywords such as "Cleidocranial dysostosis," "Hypoplastic clavicle," but also keywords concerning wider fields such as "Cranio-facial malformation," "Maxillary bone osteotomy" all in French language.

From the *Department of Oral and Maxillofacial Surgery, University of Lille, CHU Lille; and †International Association of Oral and Maxillofacial Medicine (IAOMM), Villeneuve d'Ascq, France.

Received June 27, 2017.
Accepted for publication September 7, 2017.

Address correspondence and reprint requests to Emilie Farrow, MD, Service de Chirurgie Maxillo-Faciale et Stomatologie Hôpital Roger Salengro, Bd du Professeur Emile Laine – 59037 Lille, France; E-mail: farrow.emilie@gmail.com

The authors report no conflicts of interest.

Copyright © 2017 by Mutaz B. Habal, MD

ISSN: 1049-2275
DOI: 10.1097/SCS.0000000000004200

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

The study was approved by the local ethics committee at the University of Lille.

RESULTS

Main Features of CCD

Table 1 summarizes the major clinical and radiological features, which are described with more precision further.

Clinical Diagnosis

CCD predominantly affects the bones formed through intramembranous ossification, such as the cranium and the clavicles, although bones formed through endochondral ossify.[4] The major general features are:

1. A short stature[5] (between 7.5 and 15 cm shorter, depending on the sex)
2. Clavicular hypoplasia or aplasia resulting in an excessive shoulder mobility, with shoulders that can typically be approximated anteriorly
3. Skeletal abnormalities, such as a narrow and cone-shaped thorax with short ribs, pes planus (flat feet), genu valgum (knock-knee deformity), and scoliosis
4. Hand abnormalities such as brachydactyly and short distal phalanges
5. Recurrent infections of the upper respiratory tract owing to maldevelopment of the sinuses, with a potential for conductive hearing loss consequent upon chronic otitis media[1]
6. General health is good, and intellect is unimpaired[1]
7. A familiar resemblance to most patients.[3]

The major craniofacial features are:

1. Patency of the anterior fontanelle (that may remain open throughout adulthood) associated with a wide-open metopic suture, that can produce a depression in the midline of the upper forehead, with a typical bulging aspect[6]
2. An inverted pear-shaped calvaria and generally, the head circumference is increased[6]
3. Hypertelorism and a broad flattened nasal bridge are also part of the characteristic facial appearance[7]
4. Hypoplastic maxillary bone with an ogival but non cleft palate,[7] that leads to a general midface retrusion and a relative mandible prognathism, as well as a diminished anterior facial height.[8]

The major dental features are:

1. Delayed exfoliation of deciduous teeth, secondary to delayed root resorption, and teeth shedding in primary dentition. This phenomenon can be explained by a generalized reduced bone resorption in the jaws and by the fact that the dental lamina in primary and permanent teeth, although normal, does not completely resolve at the expected time. The finding that deciduous teeth and permanent first molars always erupt normally may be explained by their superficial localization in the jaws, with minimal bone coverage.[9]
2. Delayed eruption or retention of permanent teeth, secondary to delayed bone resorption, reduced resorption of primary teeth roots and by the presence of multiple supernumerary teeth. The average delay of dental maturity in permanent teeth is 4 years.[7] Incomplete rhizogenesis,[3] malformed roots with marked deflections, taurodontia, and the presence of dentigerous cysts are common in delayed erupted teeth.[1] Their ectopic localization is caused by interference with supernumerary teeth.
3. Multiple supernumerary teeth, that could be secondary to reactivation of dental lamina, remnants at the time of completed crown formation of permanent teeth.[9] Supernumerary teeth are usually located in the anterior and premolar regions,[10] indeed deciduous teeth are absent in the molar/posterior region.[11] According to Jensen and Kreiborg,[9] the most common area for supernumerary teeth is the maxillary incisor region, the frequency of supernumerary teeth in the first premolar region is twice as high as in the second premolar region, but >1 supernumerary tooth per normal tooth was never observed.

Histological analysis led by Lukinmaa et al[12] found an excess of odontogenic epithelium in peridental tissues of developing as well as fully developed teeth, and that it could be related to the overproduction of acellular cementum, enamel pearls, and supernumerary teeth.

Generally, CCD should be suspected when primary dentition is present concurrently with erupted second permanent molars and wide spacing in the lower incisor area is observed.

TABLE 1. Major Clinical and Radiological Features of Cleidocranial Dysplasia

Major clinical and radiological features	
Craniofacial	Inverted pear-shaped calvaria
	Patency of the anterior fontanelle
	Hypertelorism
	Midface retrusion and relative mandible prognathism
	A familiar resemblance to most patients
Dental	Delayed exfoliation of deciduous teeth
	Retention of permanent teeth
	Supernumerary teeth
	Class III malocclusion
General	Clavicular hypoplasia/excessive shoulder mobility
	Short stature
	Frequent family history

Radiological Craniofacial Features

McNamara et al[13] reviewed the literature and studied the effect of dental panoramic radiography on the diagnosis of craniofacial and dental abnormalities in CCD patients. Their findings were as follows:

1. In the mandible, an abnormal shape of the ascending ramus with parallel-sided borders, a U-shaped sigmoid notch, and a slender pointed coronoid process directed upwards and posteriorly. This point is explained in an article by Furuuchi et al,[14] by hyperactivity of the temporal muscle, which has its insertion on the coronoid process, consequent to hypoplasia of the masseter muscle that could be caused by discontinuity of the zygomatic arch. In children, there often is a patent symphysis. Finally, trabeculation of the bone is coarse and density of the alveolar crestal bone overlying unerupted teeth is increased.
2. In the zygomatic bone, the arch is often thin or even discontinuous and presents a characteristic downward bend.
3. The paranasal sinus is narrow or absent with a poorly pneumatized aspect on the panoramic radiography. Moreover, the maxillary bone is hypoplastic, with a diminished distance between inferior rim of the orbit and the crowns of erupted teeth. The orbit is thus often mistaken for the maxillary antrum.
4. The head of the condyle is easily visible because of the downward bend in the zygomatic arch.

They concluded that dental panoramic radiography was a valuable adjunct in confirming the diagnosis of CCD.

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

Besides, on cephalometric radiographs, the most eloquent findings are persistence of Wormian bones in the cranial sutures,[3] poor or absent pneumatization of the paranasal, frontal, and mastoid sinuses,[8] and an anterior nasal spine that is hypoplastic and directed downwards.[6] This last point can actually be seen on the panoramic radiograph as a marked V-shape in the midline.

Genetic Findings

When CCD is suspected, the clinician should request a radiological assessment, including complete skull and chest projections, panoramic radiography, pelvic, lumbar spine, long bones, hands and feet projections. When the diagnosis of CCD is not clinically or radiologically obvious, genetic analysis can allow its confirmation.

RUNX2 is the only gene in which mutation is known to cause CCD. *RUNX2* codes for a transcription factor protein (CBFA1: core-binding factor alpha 1), which is involved in the differentiation of osteoblasts. Otto et al and Mundlos et al[15,16] showed that *Cbfa1* gene plays an essential role in osteoblast differentiation of the cellular periosteal mesenchyme and consequently in bone development.

RUNX2 plays an important role in tooth morphogenesis and histodifferentiation of the epithelial enamel organ.[5] Bufalino et al suggest that transcriptional deficiency of *RUNX2* could induce hyperactivity of dental lamina resulting in supernumerary teeth with subsequent impaction of the permanent dentition.

However, not all *RUNX2* mutations are identified on standard DNA sequencing.[6] Indeed, mutations are detected in approximately 65% of all patients with a clinical diagnosis of CCD. Therefore, in patients with CCD phenotype, for whom standard DNA sequencing does not indicate a causative *RUNX2* mutation, screening for intragenic deletions and duplications of RUNX2 by quantitative polymerase chain reaction and multiple ligation-dependent probe amplification methods should be considered.[17]

Other conditions share some characteristics with CCD. In particular, at an early stage, abnormally wide sutures and patent fontanelles are found in pycnodysostosis, osteogenesis imperfecta, hypophosphatasia, and congenital hypothyroidism. These manifestations are associated with dysplastic or hypoplastic clavicles in 3 other syndromes: mandibuloacral dysplasia, Yunis Veron syndrome, and CDAGS syndrome (craniosynostosis, delayed closure of the fontanelle, anal, genitourinary, and skin abnormalities). However, in the latter, these symptoms are seldom isolated and are usually associated with severe malformations in other systems. Later in childhood, hyperdontia can either be part of a specific genetic syndrome such as Gardner, Hallerman-Streiff, and orofaciodigital type I syndromes. But more frequently, hyperdontia can be sporadic or hereditary and is an isolated autosomal dominant trait.

Case Series

Our study is based on 8 patients suffering from CCD. All were seen at the Maxillofacial surgery and Stomatology Department of Lille University Hospital.

In our series, there were 4 males and 4 females, all white, aged between 8 and 45 years at the time of our study, included between November 1998 and May 2017.

Diagnosis was based on clinical and radiological analysis with particular reference to the morphological features, described by Jensen and Kreiborg[6,9]: the typical craniofacial features such as the inverted pear-shaped calvaria, the patency of the anterior fontanelle, the hypertelorism, the general midface retrusion and the mandible prognathism, the undue mobility of the shoulders, the short stature and teeth abnormalities like supernumerary teeth, and failure of eruption in particular. A family history of the syndrome was sought-after.

The main characteristics and treatment plans for each case are summarized in Table 2.

Case 1

C.L. was a male subject first seen at the age of 2 months by a clinical geneticist because of delayed cranial ossification with wide anterior fontanel and bilateral metatarsus varus (Fig. 1). x-rays were performed and showed hypoplasia of both clavicles. There were no other cases in the family. The first surgical management, at the age of 10 years, consisted of extractions of deciduous maxillary and mandibular incisors. Spontaneous eruption, however, did not occur. A second surgery was performed at the age of 12 to extract the remaining nonexfoliated deciduous teeth and the supernumerary teeth (12′ 22′), and expose the retained teeth (11 13 21 23 32 42) with placement of orthodontic tractions. The first results are extremely convincing with the latter teeth partially or completely erupted.

Case 2

B.L. was a male subject first seen at age the age of 2 weeks by a pediatrician because of enlarged metopic suture (Fig. 2). The skeletal x-rays found abnormal clavicles and a cone-shaped thorax with pectus excavatus. CCD diagnosis was confirmed by genetic analysis of *RUNX2* that was mutated. No family history of the syndrome was found. From the age of 4, the patient presented repeated respiratory and ENT infections. The first surgery took place at the age of 11 years to extract the supernumerary maxillary incisors (11′ 12′) and expose the retained teeth (11 21) with bonding of orthodontic attachment. It should be noted that there were no supernumerary teeth in the mandible. Orthodontic treatment is currently in progress, with convincing results.

Case 3

A.M. was also a male subject, first seen at the age of 5 years by a clinical geneticist because of partial hearing loss, strabismus, and language delay (Fig. 3). Though cranial abnormalities such as patent fontanel were not found, x-rays showed overdeveloped Wormian bones. Skeletal x-rays were asked for and showed hypoplasia of the right clavicle exclusively. Soon after he was sent to our department because of numerous « dental abnormalities » and more specifically delayed exfoliation of deciduous teeth. Similar dental features were found within family members. CCD was suspected. In this case, genetic analysis allowed confirmation of CCD diagnosis: *RUNX2* was mutated and the same mutation was found in the patient's sister and mother. The panoramic x-ray found 3 supernumerary teeth and all permanent teeth retained except for the lateral maxillary incisors. No

TABLE 2. Patients Dental Characteristics and Treatment Plan

Cases	1*	2*	3*	4	5	6	7	8†
Supernumerary teeth‡	10	2	3	2	0	1	?	7
Orthodontic treatment§	+	+	0	−	+	+	0	+
Orthognathic surgery‖				0	+	+	+	
Prosthesis¶				+	+	−	++	−

*Cases 1, 2, and 3 represent 3 young patients, still in the process of the orthodontic treatment, with probable secondary orthognathic surgery to be planed.

†Case 8 is planned for surgery in 2018.

‡Number of supernumerary teeth.

§Orthodontic treatment: + indicates successful; −, failed; 0, none undertaken.

‖Orthognathic surgery: + indicates successful; 0, none undertaken.

¶Prosthesis: + indicates removable prosthesis; ++, fixed prosthesis; −, none needed.

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

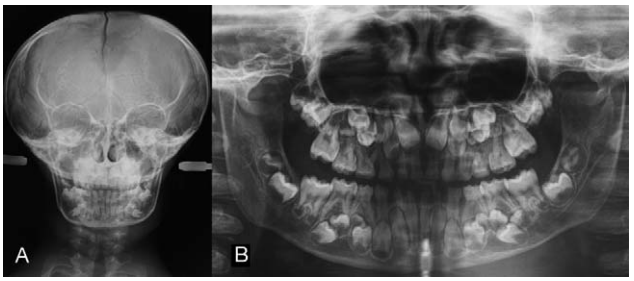

FIGURE 1. Case 1. (A) Front teleradiography (age 8) showing typical signs of open metopic suture, patent anterior fontanel, inverted pear-shaped calvaria (brachycephaly), invisible paranasal sinuses. (B) First panoramic x-ray showing typical signs of parallel ramis, supernumerary teeth, and nonexfoliated deciduous teeth.

treatment has yet been undertaken. Nevertheless, we plan to extract the nonexfoliated mandibular deciduous teeth and expose the retained anterior teeth with combined orthodontic traction.

Case 4

M.M. was a female subject and the elder sibling of case #3. CCD was confirmed by genetic analysis (Fig. 4). Alike her brother, she presented a hypoplastic right clavicle. When we first met the patient, all deciduous teeth had unfortunately already been extracted, at the age of 14. We then performed the extractions of the 2 supernumerary teeth (12′ 45′) and the exposure of the retained permanent teeth with placement of orthodontic tractions. Still, 2 years after a specialized orthodontic management, most permanent teeth were still retained. At the age of 18, a new management plan was proposed. The first stage, consisting of extractions of all retained permanent teeth and preservation of the erupted ones, was performed at age 19. The second, consisting of Lefort I maxillary down graft followed by dental implants placement and

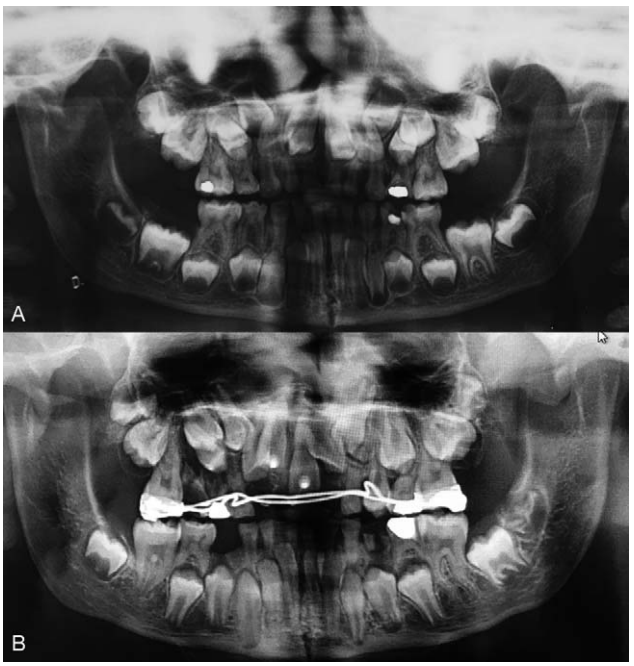

FIGURE 2. Case 2. (A) First panoramic x-ray showing typical signs of patent symphysis, parallel ramis, pointed and posteriorly directed coronoid processes. (B) Panoramic x-ray during orthodontic treatment (age 12).

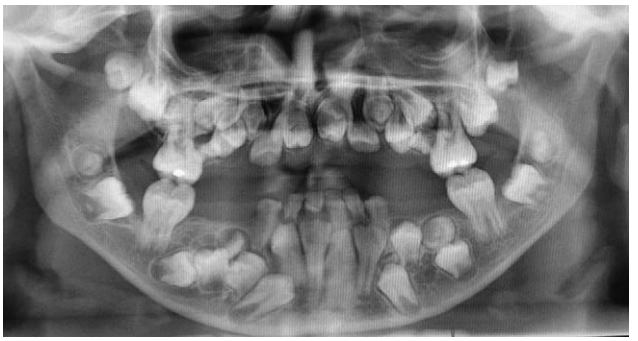

FIGURE 3. Case 3. Panoramic x-ray showing typical dental abnormalities (nonexfoliated deciduous teeth, retained permanent teeth, supernumerary teeth).

subsequently, setting up an implant supported prosthesis. However, the latter treatment was not chosen because the patient could not afford dental implants. She currently wears removable denture.

Case 5

D.B. was a female subject, first seen at the age of 19 years. She was addressed to our department for surgical management of unerupted teeth. The diagnosis of CCD was established according to the usual clinical features, but no record of genetic analysis was found. In addition, no family history was reported. Luckily, this patient did not present any supernumerary teeth at all. The treatment plan was as follows: extractions of carious and dystrophic permanent teeth (33 35 43 46) and exposure of the only retained tooth,[12] followed by orthodontic traction and preparation for surgery. At the age of 25, the patient underwent orthognathic surgery consisting of Lefort I advancement osteotomy and setback genioplasty. The missing teeth in the mandible were replaced by removable prosthesis.

Case 6

A.R. was also a female subject sent to our department by orthodontist at the age of 18 years for orthognathic surgery to correct a class III malocclusion (Fig. 5). The diagnosis of CCD was clinically obvious, with characteristic craniofacial and clavicular features. The patient presented only 1 supernumerary tooth (45′) and only a few permanent teeth were retained. Orthodontic treatment was rapidly efficient. Orthognathic surgery took place at the age of 21 and consisted of a Lefort I advancement osteotomy and a mandibular bilateral sagittal split osteotomy (BSSO).

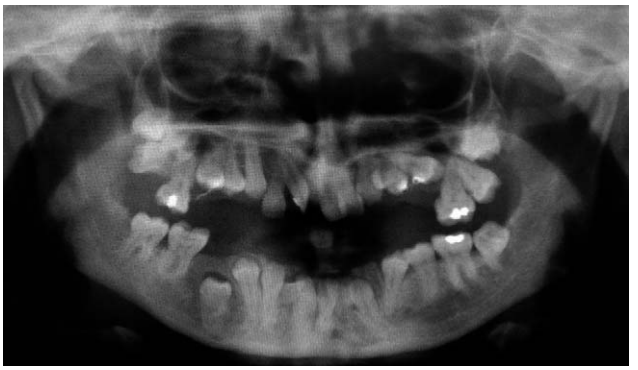

FIGURE 4. Case 4. Panoramic x-ray showing the persistent retained teeth despite the 2-year orthodontic treatment.

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

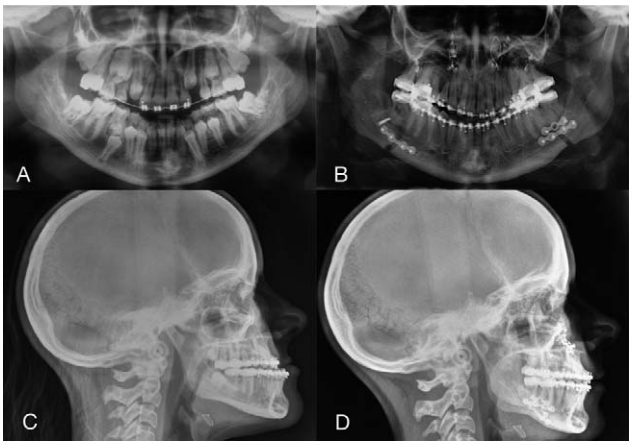

FIGURE 5. Case 6. Presurgical (A) and postsurgical (B) panoramic x-rays. Presurgical (C) and postsurgical (D) profile teleradiographies.

Case 7

R.C. was a male subject, first sent to our department at the age of 31 years for delayed healing after mandibular cyst curettage (Fig. 6). There again, CCD was immediately suspected in view of the typical signs. Panoramic radiography showed 7 retained permanent teeth in the mandible, notably in the symphysis area. The first operation was organized to extract the latter teeth (31 32 33 41 42). Removable maxillary and mandibular prosthesis were set up, but the patient met stability issues. Therefore, as in case 4, the treatment plan consisted of extractions of the remaining maxillary teeth and Lefort I maxillary down graft. Second, 10 dental implants were placed and subsequently, implant supported prosthesis was set up in both jaws.

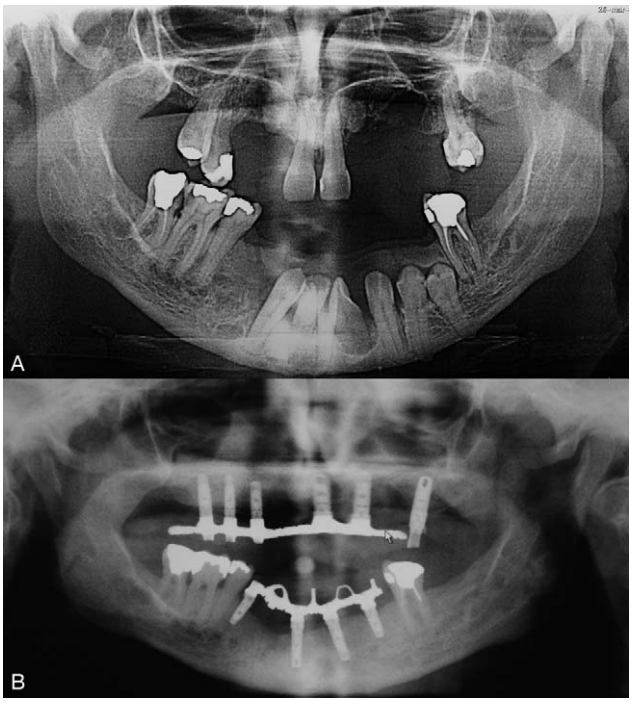

FIGURE 6. Case 7. (A) Initial panoramic x-ray showing unerupted teeth in the mandible with cystic complication. (B) Postoperative panoramic x-ray showing the implant borne denture in both jaws.

Case 8

N.J. was a female subject first addressed to our department at the age of 16 years for delayed exfoliation of temporary denture (Fig. 7). CCD diagnosis was, once more, clinically and radiologically obvious. *RUNX2* mutation was found in the patient and her father. The patient presented with 7 supernumerary teeth. Treatment consisted of extractions of all deciduous teeth and supernumerary teeth, and exposure of the retained teeth combined with orthodontic tractions, in 2 stages (anterior teeth first, posterior teeth secondly). The treatment is conclusive and about to come to its end, yet, teeth #13 and 24 were extracted secondarily because of their major dystrophic aspect. We plan a bimaxillary orthognathic surgery to close the patient's anterior open-bite, once all the teeth are completely erupted.

DISCUSSION AND MANAGEMENT GUIDELINES PROPOSAL

Diagnosis

Every maxillofacial surgeon should be aware of the main features of CCD to avoid misdiagnosing the condition (Table 1).

When CCD is suspected, the clinician should request a radiological assessment, in particular, cephalometric teleradiographies and a panoramic radiography, and should send the patient to a clinical geneticist, a pediatrician, and an orthopedic surgeon experienced in the symptom, as part of the multidisciplinary assessment and management.[18]

When the diagnosis of CCD is not clinically or radiologically obvious, genetically analysis of *RUNX2* mutations should be asked for.

Family history should always be sought for because CCD has an autosomal dominant transmission and because it can help with reaching the diagnosis especially when the main features are missing. Besides it is important to search for the condition in siblings, parents, and offspring to allow the earliest possible management of the latter.

The maxillofacial surgeon must make sure he works with a team made up of orthodontists, implantologists, and prosthodontists that are well experienced in the condition.

The goal of treatment is to provide a functioning masticatory mechanism and to improve appearance. Dental and craniofacial abnormalities found in CCD are indeed responsible for speech, mastication, swallowing, and breathing disorders. Furthermore, the typical premature aging appearance can have a heavy psychological impact.

Timing of Orthodontic-surgical Management

When treatment is planned during childhood, dental management generally consists of the surgical exposure of permanent retained teeth with orthodontic-guided eruption.

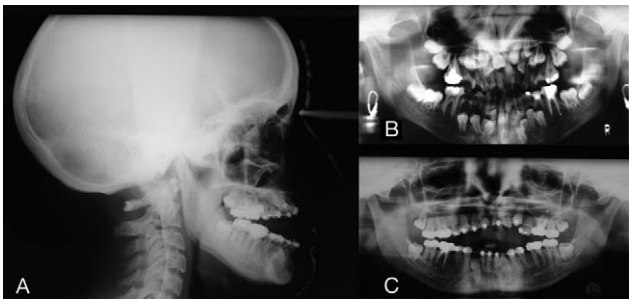

FIGURE 7. Case 8. (A) Profile teleradiography showing a typical anterior open bite and a class III malocclusion with a retruded and hypoplastic maxillary bone. (B and C) Panoramic x-rays before and during orthodontic treatment.

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

The most approved orthodontic-surgical protocols in the literature are the Toronto-Melbourne, Jerusalem, Bronx, and Belfast-Hamburgh methods. In the first 3 methods, the timing for surgery is based on the root development of the permanent unerupted teeth (two-thirds of their expected length). In the Toronto-Melbourne procedure, several operations are performed, from the age of 6, to facilitate the spontaneous eruption of the unerupted permanent teeth.[19] In the Jerusalem procedure, 2 stages are planned, ideally, at age 10 years, to extract anterior deciduous teeth and all supernumerary teeth with exposure of the permanent anterior teeth. Meanwhile, orthodontic tractions are bonded and surgical flaps are closed. Then at age $\geq$13, the posterior deciduous teeth are extracted, unerupted canines and premolars are exposed, and orthodontic processes are completed.[20,21] In the Bronx method, the age is not specified; however, it initially favors spontaneous eruption and swings to an orthodontically aided eruption rapidly. In addition to the other approaches, this method uses an intermediate removable partial prosthesis for functional and esthetic reasons and plans a final surgical step consisting of a Lefort I maxillary down graft and dental implants placement, to address any eruption failure.[22] The Belfast-Hamburgh method, unlike the others, pleads for a single surgical procedure during which all deciduous and supernumerary teeth are extracted and unerupted permanent teeth are exposed. Moreover, orthodontic devices are placed only after healing by secondary intention has occurred.[23]

In our series, in children, we modeled our dental management, closely on the Jerusalem approach, as seen in cases 1, 2, and 3. The only point we did not follow was the extractions of the posterior supernumerary teeth at the same time as the anterior ones. We deliberately chose to avoid multiple surgical approaches, for the patient's comfort. Moreover, no scientific evidence was found concerning the appropriate time for managing supernumerary teeth.

As regards the teeth exposure, the literature privileges closed eruption methods. Closed eruption surgical technique, which returns the mucoperiosteol flap to its original location following the attachment on impacted teeth,[24] seems to allow acceptable periodontal result[25] and enables limited wound contamination and infection, by promoting healing by primary intention, as opposed to surgical packs. Moreover, the surgery should be aimed at preserving, rather than removing bone. Indeed, its lack would be a greater drawback in terms of bone support and thus in terms of periodontal prognosis of the future erupted.[20]

In cases 6 and 8, who were 2 female subjects that had reached puberty, the orthodontic management turned out to be quite efficient. Our experience as well as the case study by Zhang et al[24] suggests that orthodontic aided eruption should be attempted, regardless of the age. As to waiting for spontaneous eruption, in our experience, the only case (#1) in which this was tested, the method failed. This point is in agreement with Becker and Roberts studies.[1,21] However, Zhang and al.[19] found that when the patient is young enough (up to 12 years) and the root development of the impacted incisors are two-thirds of their expected length, and if the alveolar bone overlying the teeth is removed as well as the local supernumerary teeth, high the chances are of the teeth erupting spontaneously.

During orthodontic traction, Becker et al[21] promote bringing anterior teeth into the mouth first and tipped the incisors labially to establish a normal arch shape and to offer bony support for the upper lip, to improve self-image fast.

Besides, we support the view of the Bronx approach, offering at an early age a removable partial prosthesis to improve children's quality of life, by acting on esthetic and functional factors,[22] although this should not interfere with the orthodontic treatment being well-lead.

The major difficulty in dental managing in CCD is when eruption of retained teeth delays to occur. The lack of eruption of retained permanent teeth is mostly explained by mechanical obstruction such as the presence of supernumerary teeth, roots malformation in these retained teeth, and their ectopic localization.[26] Besides, it can be explained by iatrogenic events: tooth buds may be damaged by the trauma of their exposure while they are still at an early development stage and premature surgical removal of a follicle that surrounds an immature and deeply impacted tooth can lead to replacement resorption, with secondarily risk of ankyloses.[20]

In addition, several articles describe histological factors to explain this lack of eruption. Although, it has been long admitted that the absence of cellular cementum at the root apices is one of the factors for failure or delayed eruption,[12,27] Jensen and Kreiborg[9] privilege the abnormal bone resorption as the main responsible factor. Moreover, Manjunath et al[26] consider that the absence of cellular cementum is unlikely to have any influence on the eruption process and their findings suggest that an abnormal resorption pattern in the bone and the increased percentage of the gap type of C-E junctions can explain the delayed eruption in CCD.

In our study, case #4 illustrates the problem: although there were only 2 supernumerary teeth and despite a well-lead orthodontic treatment, no eruption of retained permanent teeth occurred. This patient had deciduous teeth extractions in imprecise conditions and was 16 when we first treated her.

The major unanswered question in managing retained teeth is: when should we admit that orthodontic traction has failed? Or that the tooth is ankylosed? It seems crucial that further studies are needed to clarify this essential point.

Nevertheless, when eruption does not occur, management options may include removal of nonfunctional deciduous teeth and of teeth that could eventually cause complications (carious, infected, cystic, or submucous). Edentulous areas can then be managed either with removable prostheses or by means of implant-supported prosthesis.

The advantages of the latter option include prevention of jaw bone resorption, stabilization of a removable prosthesis, and the possibility of delivering fixed or dentist-removable restorations.

Moreover, it has been demonstrated histologically and clinically that implants osseointegration is not affected in patients with CCD.[23]

Orthognathic Surgery

Orthognathic surgery represents a key stage in the overall management. It allows improvement in functional results as well as in esthetic results. Indeed, despite orthodontic treatment, the decreased midfacial height aspect, owing to an underdeveloped maxillary bone, persists.[28] This leads to a general premature aging appearance. Moreover, a skeletal class III malocclusion and an anterior open bite are typical.

In our series, when growth was completed, Lefort I advancement osteotomy with combined mandibular BSSO were performed in case #6. The class III malocclusion and the anterior open bite were corrected and a facial rejuvenation effect was brought to the patient. An identical treatment is planned for case #8. In case #5, Lefort I osteotomy combined with a setback genioplasty was performed. Because of a severe buccal tilt of the mandibular incisors, mandibular BSSO was not appropriate to correct the skeletal class III malocclusion. Madeira et al performed the placement of malar prostheses to correct midface deficiency, in addition to maxillary and mandibular orthognathic surgery.[29]

In our experience, orthognathic surgery turns out to be inevitable when implant therapy is opted for. It allows to compensate for maxillary bone atrophy and retrusion. In that case, the surgery consists of Lefort I maxillary down graft with combined dental implants placement, in a 1 or 2-stage surgery management. In case

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

#7, partial edentulousness was long established and therefore the maxillary bone was atrophic. Orthognathic surgery allowed a satisfactory implant anchorage and the implant borne dentures are stable and comfortable.

In our opinion, preprosthetic orthognathic surgery should always be considered in adults suffering from CCD, to correct maxillary atrophy as well as maxillary retrusion. Noh et al[30] consider that telescopic detachable prostheses are an alternative treatment option to orthognathic surgery to correct occlusal vertical dimension. However, their case was not edentulous and therefore, bone atrophy was absent. Moreover, the global midfacial retrusion aspect persisted after treatment.

Personalized Management

It seems important to point out that these procedures are all undertaken over a long period. Hence, it is crucial for the practitioners to precisely inform the patient of the treatment scheme, its extended duration, the expected results, the unpredictability of achieving them, especially in more severe cases, and the alternative treatment options. The commitment of the patient to the treatment plan is also essential.

Unluckily, in our series, case #4 revealed a lack of information. Indeed, after a 2-year orthodontic treatment had failed to expose any retained teeth, all submucous and complicated retained teeth were extracted to plan orthognathic surgery and dental implants placement. However, the patient could not afford the last treatment stage. She ended up wearing removable maxillary and mandibular dentures, which are fortunately stable and fairly comfortable. Leaving the retained teeth in place would have prevented early bone resorption and would probably have not compromised prosthesis stability.

To conclude, it stands out from our experience that the treatment should be planned on a case-by-case basis, depending on the needs and demand of the patient, the age at diagnosis, and social and economic circumstances.

Figure 8 represents our management guidelines proposal.

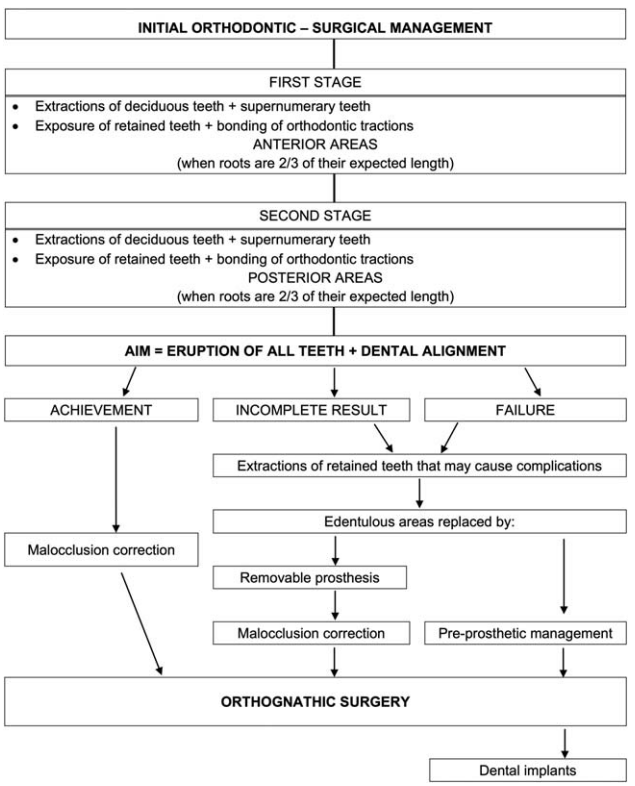

FIGURE 8. Management guidelines proposal.

CONCLUSION

We agree that the main issue in managing CCD is the early diagnosis. Therefore, every maxillofacial surgeon should be aware of the major clinical characteristics of CCD to avoid missing its diagnosis and to allow the most adapted management, whether it be in an infant or an adult.

Although results are not always convincing even after a long waiting period, it stands out that orthodontically aided eruption should always be attempted because natural dentition is spared.

However, to stabilize the occlusion and to improve facial esthetics, we recommend associated orthognathic surgery.

When orthodontic treatment was partially efficient, in our experience, prosthetic treatment options brought satisfactory results, in terms of occlusion. Nevertheless, when orthodontic treatment fails, we recommend to preserve as many native teeth as possible, and to combine orthognathic preprosthetic surgery and implant-supported prosthesis.

In any case, we offered an individualized treatment protocol, depending on the needs and demand of the patient, the age at diagnosis, and social and economic circumstances.

The treatment was based on our guidelines proposal and it was obvious that patient compliance was essential to a favorable outcome for any of these modalities.

REFERENCES

1. Roberts T, Stephen L, Beighton P. Cleidocranial dysplasia: a review of the dental, historical, and practical implications with an overview of the South African experience. *Oral Sur Oral Med Oral Pathol Oral Radiol* 2013;115:46–55
2. Bufalino A, Paranaíba LMR, Gouvêa AF, et al. Cleidocranial dysplasia: oral features and genetic analysis of 11 patients. *Oral Dis* 2012;18: 184–190
3. Golan I, Baumert U, Hrala BP, et al. Dentomaxillofacial variability of cleidocranial dysplasia: clinicoradiological presentation and systematic review. *Dentomaxillofac Radiol* 2003;32:347–354
4. Kreiborg S, Jensen BL, Larsen P, et al. Anomalies of craniofacial skeleton and teeth in cleidocranial dysplasia. *J Craniofac Genet Dev Biol* 1999;19:75–79
5. Cooper SC, Flaitz CM, Johnston DA, et al. A natural history of cleidocranial dysplasia. *Am J Med Genet* 2001;104:1–6
6. Jensen BL, Kreiborg S. Craniofacial abnormalities in 52 school-age and adult patients with cleidocranial dysplasia. *J Craniofac Genet Dev Biol* 1993;13:98–108
7. Martins RB, de Souza RS, Giovani EM. Cleidocranial dysplasia: report of six clinical cases. *Special Care Dent* 2014;34:144–150
8. Jensen BL, Kreiborg S. Craniofacial growth in cleidocranial dysplasia–a roentgencephalometric study. *J Craniofac Genet Dev Biol* 1995;15:35–43
9. Jensen BL, Kreiborg S. Development of the dentition in cleidocranial dysplasia. *J Oral Pathol Med* 1990;19:89–93
10. Atasu M, Dumlu A, Ozbayrak S. Multiple supernumerary teeth in association with cleidocranial dysplasia. *J Clin Pediatr Dent* 1996;21:85–91
11. Tanaka JLO, Ono E, Filho EM, et al. Cleidocranial dysplasia: importance of radiographic images in diagnosis of the condition. *J Oral Sci* 2006;48:161–166
12. Lukinmaa PL, Jensen BL, Thesleff I, et al. Histological observations of teeth and peridental tissues in cleidocranial dysplasia imply increased activity of odontogenic epithelium and abnormal bone remodeling. *J Craniofac Genet Dev Biol* 1995;15:212–221
13. McNamara CM, O'Riordan BC, Blake M, et al. Cleidocranial dysplasia: radiological appearances on dental panoramic radiography. *Dentomaxillofac Radiol* 1999;28:89–97

© 2017 Mutaz B. Habal, MD

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

14. Furuuchi T, Kochi S, Sasano T, et al. Morphologic characteristics of masseter muscle in cleidocranial dysplasia: a report of 3 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodont* 2005;99: 185–190
15. Otto F, Thornell AP, Crompton T, et al. Cbfa1, a candidate gene for cleidocranial dysplasia syndrome, is essential for osteoblast differentiation and bone development. *Cell* 1997;89:765–771
16. Mundlos S, Otto F, Mundlos C, et al. Mutations involving the transcription factor CBFA1 cause cleidocranial dysplasia. *Cell* 1997;89:773–779
17. Ott CE, Leschik G, Trotier F, et al. Deletions of the RUNX2 gene are present in about 10% of individuals with cleidocranial dysplasia. *Hum Mut* 2010;31:E1587–E1593
18. Lewandowski B, Martula-Gala K, Brodowski R, et al. Multiple, supernumerary retained teeth in the course of cleido-cranial dysplasia. A case report. *Dev Period Med* 2015;19:503–507
19. Hall RK, Hyland AL. Combined surgical and orthodontic management of the oral abnormalities in children with cleidocranial dysplasia. *Int J Oral Surg* 1978;7:267–273
20. Becker A, Lustmann J, Shteyer A. Cleidocranial dysplasia: part 1—general principles of the orthodontic and surgical treatment modality. *Am J Orthod Dentofacial Orthop* 1997;111:28–33
21. Becker A, Shteyer A, Bimstein E, et al. Cleidocranial dysplasia: Part 2–Treatment protocol for the orthodontic and surgical modality. *Am J Orthod Dentofacial Orthop* 1997;111:173–183
22. Berg RW, Kurtz KS, Watanabe I, et al. Interim prosthetic phase of multidisciplinary management of cleidocranial dysplasia: "the Bronx Approach. *J Prosthod* 2011;20(suppl 2):S20–S25
23. Schnutenhaus S, Luthardt RG, Rudolph H, et al. Histological examination and clinical evaluation of the jawbone of an adult patient with cleidocranial dysplasia: a case report. *Int J Clin Exp Pathol* 2015;8:8521–8531
24. Zhang CY, Si Y, Wang XZ, et al. Early dental treatments for patients with cleidocranial dysplasia. *Chin J Dental Res* 2015;18:51–57
25. Vermette ME, Kokich VG, Kennedy DB. Uncovering labially impacted teeth: apically positioned flap and closed-eruption techniques. *Angle Orthod* 1995;65:23–32
26. Manjunath K, Kavitha B, Saraswathi TR, et al. Cementum analysis in cleidocranial dysostosis. *Indian J Dent Resh* 2008;19:253–256
27. Lee KW, Pillay VK. Hereditary cleido-cranial dysostosis. With a note on the anomaly of cementum. *Singapore Med J* 1964;4:3–9
28. D'Alessandro G, Tagariello T, Piana G. Craniofacial changes and treatment of the stomatognathic system in subjects with cleidocranial dysplasia. *Eur J Paediatr Dent* 2010;11:39–43
29. Madeira MFC, Caetano IM, Dias-Ribeiro E, et al. Orthognathic surgery in patients with cleidocranial dysplasia. *J Craniofac Surg* 2015;26: 792–795
30. Noh K, Kwon K-R, Ahn H, et al. Prosthetic rehabilitation of a cleidocranial dysplasia patient with vertical maxillofacial deficiency: a clinical report. *J Prosthodont* 2014;23:64–70

This year, the meeting is November 2–4, 2018.

Copyright © 2017 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.