

Oro-facial considerations in a case of cleidocranial dysplasia– A review of the medical and dental management protocols

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ABSTRACT

Cleidocranial dysplasia (CCD) is a rare, hereditary, congenital disorder inherited in an autosomal dominant pattern and is characterised by cranio-facial, skeletal and oro-dental malformations. The typical patient is short, presents a brachiocephalic skull with bossing of the frontal and parietal bones. Cephalic sutures and fontanelles exhibit delayed closure. The mid-face is hypoplastic, giving a misleading appearance of mandibular prognathism. The development of the clavicles is often defective and may range from a small medial gap to total agenesis. Medical issues include delayed attainment of developmental milestones, scoliosis, skeletal, pelvic and thoracic abnormalities. However, oro-dental malformations are important and can be significant. A 17-year-old Malay girl presented to the National Dental centre with complaints of unsightly front teeth. General and radiographic examination revealed features consistent with CCD. Dental clinical findings corroborated radiographically utilising conventional radiography and Cone Beam Computed Tomography uncovered an intact, retained deciduous dentition with multiple unerupted permanent and supernumerary teeth. A diagnosis of CCD was made based on the typical clinical and radiographic features and various management options explored. This condition is of clinical significance to the medical profession and more so for the orthodontist due to involvement of the facial bones, altered teeth eruption patterns and presence of supernumerary teeth. These problems represent a challenge to the clinician who must often seek a multi-disciplinary approach for successful management of this anomaly. Various treatment protocols and their shortcomings with respect to the case are discussed.

Keywords: Cleidocranial dysplasia, orthodontics, dental anomalies, craniofacial morphology, Cone Beamed Computed Tomography

INTRODUCTION

Cleidocranial dysplasia ([Online Mendelian Inheritance in Man] # 119600) ¹ is a well-

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described congenital disorder inherited in an autosomal dominant pattern with high penetrance (but variable expressivity) and is characterised by cranio-facial, skeletal and oro-dental malformations (Table 1). It is now known that a spontaneous mutation in the

Table 1: Abnormal clinical findings in Cleidocranial dysplasia (CCD).

Examination	Area/ Organ system involved	Observations
Clinical	Cranio-Facial	Large brachio-cephalic skull, increased thickness of calvaria, wide forehead, frontal bossing, delayed closure of fontanelles, depressed nasal bridge and hypertelorism. Mid-face hypoplasia (under-developed maxilla), prognathic mandible with obtuse gonial angle, accentuated concavity of facial profile
	Skeletal	Short stature, aplastic or hypoplastic clavicles, narrow thorax, small arms and legs, Genua valga, Pes planus, Scoliosis, osteoporosis, asthma, hearing loss, awkward gait, long neck and narrow sloping shoulders, occasionally short middle phalanges of the second and fifth finger, wide pubic symphysis and pelvic abnormalities
	Oro-Dental	Delayed exfoliation of primary teeth, delayed eruption of permanent teeth, multiple supernumerary and/or supplemental teeth, crown and root abnormalities, Class III malocclusion, High arch palate, dentigerous cysts, alteration of dental hard tissue and occasionally cleft palate

Note: Not all features will be present in a case with CCD. A Combination of the above features corroborated radiographically should aid in diagnosis of the disorder.

core-binding factor alpha subunit-1 (CBFA-1) gene that codes for osteoblast transcription factor (located on Chromosome 6), is responsible for disturbances in osteoblast and dental cell differentiation. This directly affects bone and tooth formation. Studies have estimated the prevalence of this rare entity to vary between 1 per 200,000 to a million individuals worldwide.^{2, 3} Although hereditary transmission of the syndrome in a family was originally reported in 1898; the genetic connection remained unknown until genetic studies in families⁴ with Cleidocranial dysplasia (CCD) and experimental studies by Mundlos^{5, 6} on transgenic mice provided better insight into this mode of transmission. In majority of cases, the affected person inherits the trait from only one affected parent whereas others may result from new mutations in the gene. Shafer reported a high incidence of new mutations ranging from 20 up to 40% of all new cases.⁷ Such cases occur in people with no previous history of the disorder in their family.

Originally known as Marie-Sainton syndrome or Scheuthauer-Marie Sainton syndrome, it was first reported by Meckel in

1760 and, later by Martin in 1765.⁸ Prior to reclassification of the disorder as CCD by Index Medicus in 1985, it was also known as 'Cleidocranial dysostosis' or 'Osteo-dental dysplasia'. The characteristic manifestations of this disorder were however, first described by Pierre Marie and Paul Sainton in 1898.⁹ In the early years, it was erroneously dubbed 'mutational dysostosis' because the disorder was initially thought to involve only the bones of intra-membranous origin; although, it is now well established that endochondral ossification too is affected. From the medical literature available it is evident that this condition is usually not diagnosed at birth (except when one of the parents is known to have CCD). Initial diagnosis is usually made many years later by the child's paediatrician or orthopaedist, although sometimes the discovery has been made at a dental examination.

Corroborative evidence from a detailed clinical, wider radiological examinations and more recently genetic mapping of the individual's chromosomes for presence of CBFA-1 or Runt-related transcription factor 2 (RUNX2) on Chromosome 6 (6p 21.1) will

help confirm the anomaly in the absence of other positive findings.^{10,11} Our patient, the first such case to be documented in Brunei Darussalam, was diagnosed as having the disorder, only when she presented to the dental clinic to have her dental needs addressed and was herself quite oblivious of her general condition. The clinical and radiographic findings in the case along with a review of various treatment protocols and their shortcomings are discussed.

CASE REPORT

A 17-year-old Malay girl was referred from the out-patient clinic to the Orthodontic unit of the National Dental Centre, complaining of 'unsightly front teeth'. Her main concern was the poor appearance of teeth that she knew was due to retained 'milk (deciduous) teeth'. Her medical history was unremarkable. Her mother admitted that she was legally adopted and was hence not her biologic child. As such, the presence or absence of a similar anomaly in her biologic parents could not be ascertained. Her mother reported that she was evaluated earlier by a dentist for the unerupted front teeth at 10 years; but, was then advised to wait for definitive treatment. However, they failed to keep subsequent

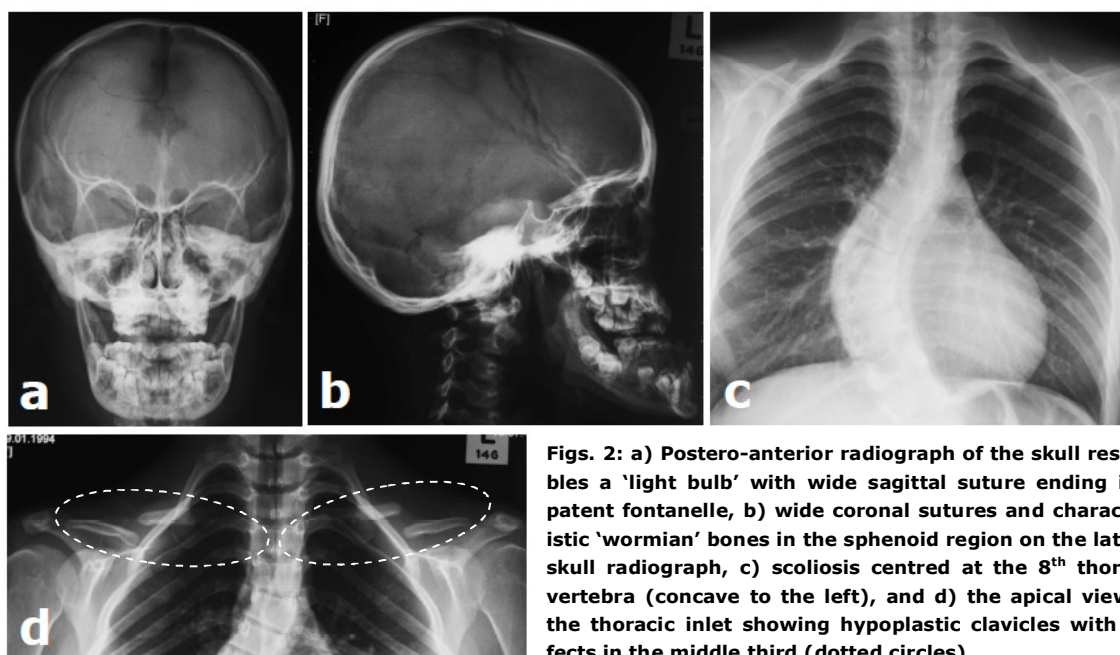
appointments with the dentist.

General physical examination revealed an individual of short stature who appeared to be well oriented and of normal intelligence. Her overall countenance presented a brachiocephalic skull with a wide prominent forehead, frontal bossing and a depressed nasal bridge (Figure 1a). Hypertelorism was also observed. The mid-face exhibited marked malar hypoplasia due to an underdeveloped maxilla. A prognathic mandible with an obtuse gonial angle served to accentuate her concave facial profile. She had narrow, sloping shoulders and notable excessive mobility of the joints by virtue of the fact that she could painlessly and effortlessly approximate both her shoulders towards the middle of the chest. No dysplasia was noted on her fingers or nails. Intraoral examination revealed an almost intact retained deciduous dentition. Permanent upper and lower anteriors were clinically absent; but, bulges of the unerupted permanent upper right and left central incisors were visible and palpable (Figure 1b). Only the permanent upper and lower first molars had erupted and could be seen clinically. No mobility was noted for any of the deciduous teeth. The maxilla was severely



Figs. 1: a) Profile showing frontal bossing and mid-face deficiency, b) intra-oral frontal view shows the retained deciduous dentition. Note the visible bulges of the un-erupted permanent incisors (arrows), and c) intra-oral left lateral view shows Class III with severe reverse overjet.



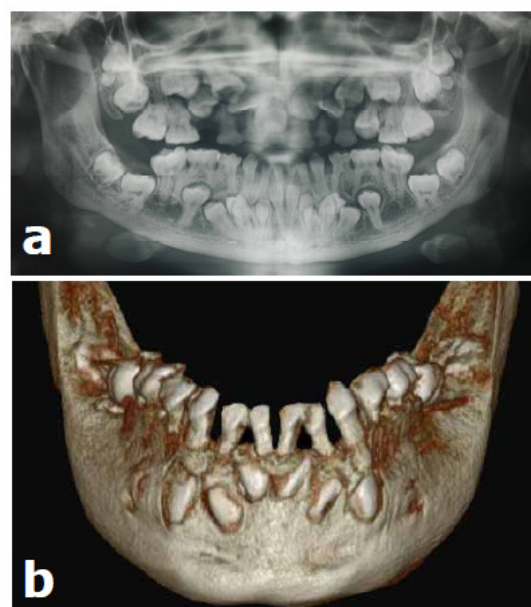


Figs. 2: a) Postero-anterior radiograph of the skull resembles a 'light bulb' with wide sagittal suture ending in a patent fontanelle, b) wide coronal sutures and characteristic 'wormian' bones in the sphenoid region on the lateral skull radiograph, c) scoliosis centred at the 8th thoracic vertebra (concave to the left), and d) the apical view of the thoracic inlet showing hypoplastic clavicles with defects in the middle third (dotted circles).

underdeveloped that the patient had a reverse overjet of 11mm (Figure 1c). The palate was high and narrow. Based on these clinical findings; the patient was provisionally diagnosed as having CCD and therefore subjected to detailed radiological scrutiny.

The postero-anterior view of the skull (Figure 2a) showed an open sagittal suture extending anteriorly to a still patent fontanelle. A perceived degree of flattening was also observed at the vertex of the cranial vault. The frontal view presented a characteristic 'light bulb' appearance. A poor pneumatization of the frontal and mastoid air cells was evident. Lateral view of the skull revealed wide coronal sutures and characteristic 'wormian' bones in the sphenoid and lambdoid regions (Figure 2b). Chest radiograph revealed a barrel shaped chest, rudimentary clavicles with bilateral hypoplastic defects in the middle third (Figure 2d). An obvious scoliosis was observed in the thoracic region

(concave to the left) centred at the eighth thoracic vertebra (T₈) (Figure 2c). Spina bifida occulta was observed in the lower cervical and thoracic vertebrae. Dental orthopantomom-



Figs. 3: a) Orthopantomogram shows multiple unerupted supplemental and supernumerary teeth and b) CBCT of the mandible. CBCT of both jaws helped to confirm the number of impacted supplemental and supernumerary teeth

graph (OPG) showed multiple unerupted permanent teeth (Figure 3a). Multiple supplemental teeth (teeth that are additional to the normal complement and, with identical morphology) could be observed in the lower canine-premolar regions bilaterally along with supernumerary teeth (teeth that are additional to the normal complement but with varied morphology) in the maxillary 3rd molar regions. The root morphology of the permanent molars appeared less developed than normal with an accentuated curvature in the distal roots of lower permanent second molars. Cone Beam Computed Tomography (CBCT) (Figure 3b) helped to confirm the number of anomalous (supplemental and supernumerary) teeth in both jaws – ten in total, of which 7 were supplemental and 3 supernumerary accounting for a total of 36 unerupted entities. Thus, the total number of retained, erupted and unerupted teeth was determined to be 61.

A diagnosis of CCD was made on the basis of the clinical and radiographic findings. The patient is currently under follow-up.

DISCUSSION

Although CCD is primarily inherited in an autosomal dominant manner, recessive inheritance^{21, 22} and mosaicism²³ have also been reported. Detailed genetic screenings of individuals manifesting this disorder and studies on mice have revealed that the *Cbfa-1* gene located in area 6p21 on chromosome 6 is responsible for the syndrome. This factor is important for the normal osteoblastic differentiation in the development and growth of bones. Experimental studies have shown that due to the insufficiency of transcription factor

Cbfa-1, its target genes are not activated; namely the genes for osteocalcin,²⁴ Vascular Endothelial Growth Factor (VEGF), Matrix Metallo-Proteinase 13 (MMP 13), collagen type 10a1, osteopontin²⁵ and alkaline phosphatase,²⁵ which are all characteristic products of osteoblasts. This could account for the osteopenia and subsequent development of osteoporosis in patients with CCD.

Apart from the effects on the skeleton, this gene additionally regulates expression of the mesenchymal cells of the dental epithelium.²⁶ In this manner, its deficiency leads to the manifestation of dental and associated skeletal anomalies observed in patients with CCD. Studies on the cellular mechanisms of dental eruption by introducing mutations of the *Cbfa1* gene in homozygotic and heterozygotic test animals showed a decrease in the number of osteoclasts that contribute to normal resorption of alveolar bone during tooth eruption. The decreased number of osteoclasts in patients with CCD leads to delayed eruption and increased number of impacted teeth.²⁷ In short, the deficiency of transcription factor *Cbfa1* in CCD leads to a deregulation of the morphogenetic mechanisms controlling skeletal and dental development and subsequent growth.

Medical implications and management:

Although the signs and symptoms of this rare condition are quite distinct, they are entirely benign in that there is no debilitation or progression of the manifestations. Most organ systems remain virtually unaffected and the patient is not usually physically or mentally challenged. Young children with this condition however, are mildly delayed in the development of motor skills such as crawling, and

walking. Women with CCD have an increased risk of requiring a Caesarean section during delivery due to a narrow pelvis. Few CCD patients may present less common features such as scoliosis of varying degrees of severity, particularly the progressive type which may be associated with an increased risk of syringomyelia. Such cases will require sophisticated imaging and medical or surgical intervention in order to prevent cardio-pulmonary and neurological complications.³

The dysmorphic features, especially of the face and the unsightly dentition too could have varying degrees of psychological impact on patients which may need to be addressed by psychological counselling. Genetic counselling is also recommended for patients with a family history of CCD. Counselling for our patient may be beneficial even though her genetic profile was uncertain. A neurosurgical consultation has been scheduled for our patient to evaluate the severity of scoliosis. This notwithstanding, osteopenia and development of osteoporosis coupled with the laxity of joints increases the risk of musculoskeletal injuries like fractures at a relatively early age and these patients may benefit from an orthopaedic consultation.

Dental implications and management:

Since patients with CCD seek treatment primarily for dental problems, the dental community has for decades tried to develop therapeutic protocols which could improve and rehabilitate the functional and aesthetic needs of the patients. Often, it is when the dentist has diagnosed this benign condition of such extra-ordinary therapeutic magnitude that he is faced with an even greater dilemma that there is no single treatment protocol that

could be followed. The complex nature of the dento-facial skeleton and the abnormal eruption pattern of teeth in such patients undermines the predictability of the ultimate treatment outcome. Often, the alternatives are (a) to offer no treatment at all, (b) to suggest a more radical approach of extraction of many teeth, followed by prosthetic replacement, or (c) to offer an orthodontic-surgical procedure, with an unknown level of confidence in the result. Non-treatment becomes less of an option as the patient grows older owing to the attrition and progressive morbidity of the deciduous dentition. Appearance too suffers due to the reduced lower face height and impaired masticatory function that contributes to the increasing overclosed appearance. Any treatment undertaken should therefore be directed towards improving the above parameters. Failure to treat these patients early could lead to possible emotional, social, and self-esteem issues. The literature reveals that the most popular approach to treating this anomaly is to provide the patient with dental prostheses that would fulfil the immediate needs of the patient.

Many authors have suggested surgical removal of all the deciduous and unerupted permanent and supernumerary teeth followed by prosthetic rehabilitation with dentures.^{12,13} This was based on the assumption that all the impacted teeth could potentially create extensive cysts and bone defects. Others^{7,14,15} have recommended using the remaining standing teeth together with surgical exposure of unerupted teeth to serve as supports for an over-denture. The premise here is to minimise the likelihood of further ridge resorption, but carries the risk of morbidity of the remaining teeth and periodontium. As the

alveolar bone will not have developed to the extent that one would see in normal circumstances, contemporary management using implants may not be a viable option in all cases.

The prognosis of the surgical approach and the problems of conventional prosthodontic rehabilitation like relining or replacement of the denture several times during the lifetime of the patient led to a combined treatment involving surgical and orthodontic management¹⁶. Orthodontic management of these cases can prove to be a daunting task for the clinician who must often plan the treatment in phases. Three major orthodontic approaches have been described in the literature based on the cities where they were promulgated.

The Toronto-Melbourne Approach: originated by Smylski et al.¹⁷ in 1974 and further developed by Hall and Hyland¹⁸ in Melbourne. Surgery is performed in stages under general anaesthesia, with the degree of root development of permanent teeth dictating timing for each stage. Treatment is initiated at 6 years. Supernumerary teeth overlying crypts of unerupted permanent teeth are removed together with substantial amounts of bone to uncover the crowns of teeth leaving them widely exposed. Surgical packs are used to maintain patency of the surgical exposure and safeguard access for bonding. The packs are left in place until complete healing and are removed just before commencing orthodontic treatment using conventional fixed attachments designed to apply vertical traction to extrude teeth. The limitation of this approach is that the patient commences on treatment early and continues for many years

and will require multiple, fairly extensive surgical interventions.

The Belfast-Hamburg Approach: Richardson and Swinson¹⁹ of Belfast and Behlftet of Hamburg, independent of each other but, simultaneously proposed a diametrically opposite method for treatment of CCD. They proposed that the extraction of all deciduous teeth, supernumerary entities and exposure of all the unerupted permanent teeth could be completed in a single surgery under general anaesthesia. As with the earlier approach, surgical packs need to remain in place to encourage epithelialisation of the exposed tissue. Orthodontic fixed appliances to vertically develop the alveolar bone by extrusion of partially erupted teeth are used at a later stage. Although there is a clear advantage from the patient's perspective in terms of the number of surgical interventions, a fine balance has to be struck in terms of timing of this surgery. Accordingly, Behlftet recommends that the one-time comprehensive surgical management be timed between 12 to 14 years of age. These options may not be viable if the patient is diagnosed much later or reports after 16 years. Frequent changing of surgical packs is necessary and this could cause pain, halitosis (bad breath) and could compromise oral hygiene and function.

The Jerusalem Approach: was first described by Becker et al.^{16, 20} in 1987 and is different from either of the two earlier approaches. Two surgical interventions are planned at distinct points in time; the first at dental age 7-8 years and the second at dental age 10-11 years. Both surgical interventions require extraction of the supernumerary teeth by raising intra-oral surgical

flaps and these flaps must be completely closed after immediate bonding of orthodontic attachments. In this approach, a clear distinction is sought between the dental age and chronologic age; as the stages of root development is a critical factor in timing surgery. Only enough bone is removed to gain access for bonding while maintaining the integrity of the buccal and lingual cortical plates. Preparation of anchorage during orthodontic treatment too is paramount. For this reason, a rigid cast appliance framework is fabricated and is additionally reinforced by heavy wires welded on the buccal surfaces of the molar bands to help in extruding impacted teeth.

It is clear that all the above approaches rely principally on the fact that the patient be diagnosed early so that treatment can be commenced as early as possible. Any of these protocols can be followed in a CCD patient if they are diagnosed early; but, as in our case, the patient was already 17-years old and beyond the scope of any of these specific protocols. Whatever the treatment decided will have to be tailored to suit the specific needs of the patient. Nevertheless, a multi-disciplinary approach has to be opted for successful mitigation of her aesthetic and functional problems.

The dental aspects of the condition paint a very singular picture of the serious ramifications of CCD as they affect the face and contiguous structures. The delay in eruption of permanent teeth usually drives the patients to seek treatment with the dentist. Otherwise, the syndrome can remain undiagnosed until relatively old age or may have been previously misdiagnosed, because of findings similar to other syndromes. Often,

the major reason why these patients are often left untreated dentally is because of the protracted and complex nature of envisaged treatment. The outstanding oro-dental finding is the prolonged retention of the deciduous teeth and the subsequent delay in eruption of the succedaneous teeth. This has been attributed variously to; a) lack of cellular cementum, b) defective post-cementum formation, c) presence of thick connective tissue between oral epithelium and dental follicle, d) delayed tooth formation and maturation although no one factor has been definitively implicated.^{28, 29}

Additionally, supernumerary teeth have been reported to develop in the successional teeth areas that usually varies from none to around 12 in general, though the highest recorded number ever found was 63.³⁰ These are more prominent in the premolar and incisor areas. Again the reasons for development of these supernumeraries and the relative predilection for these sites are still obscure. CBCT is an invaluable tool in such patients whose benefits include localisation of ectopic teeth. Accurate localisation of ectopic, impacted and supernumerary teeth is vital to the development of a patient-specific treatment plan with the best chance of success.

Ultimately, the availability of resources both in terms of facilities and interdisciplinary expertise required in dealing with cranio-facial anomalies is also an important measure of the outcome and options for treatment. The dentist plays an important role in the early diagnosis of CCD which will facilitate timely referral to the orthodontist as treatment options and outcomes are directly dependent on such referrals. Because of the

presenting age of our patient, and the non-availability of the required comprehensive surgical expertise required to manage such a case, the likely treatment options for our patient were limited. This being the case, we planned and embarked on employing a conservative approach for treating her immediate concerns.

In conclusion, although not a life threatening condition, CCD is associated with significant morbidity. Among these, the dysmorphic features, especially of the face and the unsightly dentition could have varying degrees of psychological impact on patients which may need to be addressed by psychological counselling. From the dental perspective, treatment planning is largely dependent on both the chronological and dental ages of the patient, which due to the frequency of eruption in this condition, are never coincident. Thus, it is vital to develop a patient-specific treatment plan. Although a few treatment protocols have been described over the years, individual treatment plans have to be tailor-made for the patient with overall goals of successful aesthetic and functional rehabilitation of the teeth and face in mind. With continuing evolution of the dental specialities, it is all the more essential to have an organised and multi-faceted treatment approach for these patients; ideally by a team of specialists, where in each one can contribute with their expertise for the best possible treatment outcome.

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