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Case Report
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First Clinical Evaluation of Combined Cleidocranial Dysplasia (CCD) and Thyroid Gland Agenesis

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Abstract

Cleidocranial dysplasia (CCD) is a rare autosomal dominant skeletal dysplasia associated with clavicle hypoplasia or aplasia and serious, complex dental abnormalities. It has been associated with thyroid disorders: CCD with hyperthyroidism and neonatal hyperbilirubinemia has previously been reported. We hereby report the first case of CCD with absent thyroid gland and propose a comprehensive orthodontic treatment plan for this patient.

Keywords: Autosomal dominant; Skeletal dysplasia; Dental abnormalities; Hyperthyroidism; Neonatal hyperbilirubinemia; Orthodontic treatment; Endochondral bone; Brachycephalic skull; Midface hypoplasia; Delayed closure of fontanelles; Supernumerary teeth

Abbreviations: CCD: Cleidocranial Dysplasia; DVT: Digital Volume Tomography; CBFA1: Core Binding Factor α-1

Introduction

One of the earliest descriptions of cleidocranial dysplasia (CCD) in scientific literature dates to 1760 and was reported by anatomist Johann Friedrich Meckel, who described an infant with a missing collarbone. Shortly after in 1765 Martin described some clinical features of CCD [1]. The name "dysostoses cléido-crânienne hereditary" was originally given by Marie & Sainton in [2], but Scheuthauer was probably the first in 1871 to describe the syndrome accurately.

CCD is a rare autosomal dominant skeletal dysplasia affecting both membranous and endochondral bone formation and it is characterised by hypoplastic/aplastic clavicles, a brachycephalic skull, midface hypoplasia, delayed closure of fontanelles, supernumerary teeth and moderately short stature. More recent and detailed clinical investigations have shown that CCD is a generalised skeletal dysplasia affecting not only the clavicles and the skull but the entire skeleton. CCD is therefore considered to be a dysplasia rather than a dysostosis [3]. The condition is caused by mutations in the CBFA1 gene, a transcription factor that activates osteoblast differentiation [4].

The estimated prevalence of CCD is one per million, but it may be more common and under-diagnosed due to the relatively low rate of medical complications in comparison to other skeletal dysplasia's [5]. CCD is reported in all ethnic groups and there is no sex predilection [6,7].

Patient history, examination and investigations

Figure 1: Frontal image of the patient, L.

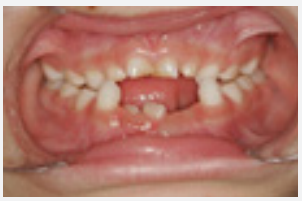

Figure 2: Intraoral frontal view, anterior open bite, negative overjet.

L., a 10-year-old happy and cooperative girl (Figures 1-5), presented at our centre for the first time at the age of 9. She is the second child of healthy parents living in non-consanguineous relationship. At birth, L.´s mother was 28 years old and her father was 46. L. was born full term, spontaneously in cephalic

position. She has a sister aged 11 years, who was unaffected by the disease.

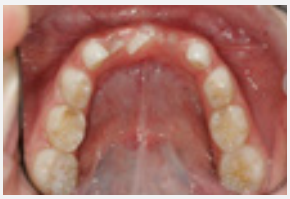

Figure 3: Lower jaw with primary crowding.

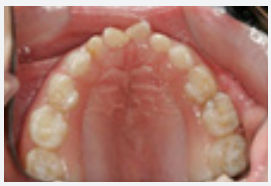

Figure 4: Upper jaw showing moderate anterior crowding.

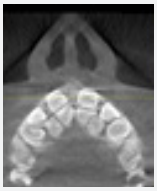

Figure 5: Digital volume tomography (DVT), depicting the patient's Supernumerary teeth 11 and 21.

L. was diagnosed with CCD and complete absence of the thyroid gland shortly after birth. Following endocrinologic assessment she has been treated with L-thyroxine ever since. L. has a family history of multiple thyroid malfunctions in the females in both her mother's and father's side of the family.

She also suffered from a congenital hip dysplasia which has been successfully treated with a hip abduction bandage and physiotherapy from 8 weeks of life. Her motor development has been delayed.

The patient needed nasal surgery after birth. No further complications have been reported. At the age of six she underwent additional surgery to remove the remaining nasal polyps. These upper respiratory complications may relate to midface hypoplasia and underdeveloped sinuses which are common in CCD.

At the ages of 6- and 8-years L. received logopaedic treatment to improve indistinct pronunciation and s-sound disturbances. These were most likely related to hearing impairment, which was detected following ENT assessment.

Figures 2-5 clearly shows that L. has two supernumerary teeth in the anterior midline of the maxillary arch. It is well documented that CCD is associated with the presence of supernumerary teeth.

L. still breathes through her mouth most of the time, especially during sleep. She was in the habit of chewing her fingernails and hair until a year ago. Her oral hygiene is very good: her mother paid early attention to healthy food and oral hygiene as well as regular visits to the dentist for prophylaxis.

Treatment

Following a panoramic radiograph on 17 January 2007and digital volume tomography (DVT) (Figure 5) in January 2008, in accordance with the Jerusalem concept, it was decided to extract all deciduous incisors and supernumerary incisors under general anaesthesia in approximately one year's time from now after a subsequent panoramic radiograph or DVT [8,9]. The intention is to concurrently expose the permanent incisors which will- after bonding eyelets with chains-then be orthodontically erupted with heavy extrusion arches secured with ministries for additional anchorage, if necessary. At the age of 14 or 15, when her incisors are in place, the premolars and molars in both arches will be exposed, attachments will be placed, and the teeth will be erupted and aligned orthodontically.

Differential Diagnosis

Genetics of cleidocranial dysplasia

The gene for CCD, core binding factor α-1 (CBFA1/RUNX2), is located on the short arm of chromosome 6p21 and is composed of nine exons. As well as controlling the differentiation of precursor cells into osteoblasts during development of the skeleton, CBFA1/RUNX2 is also essential for membranous and endochondral bone formation [4-10]. Insertions, deletions, nonsense mutations, and missense mutations have been identified in CCD families [4,11-13].

In an animal model, Otto et al. [10] introduced a germline mutation in mice resulting in inability to produce a CBFA-1 gene product. Mice homozygous for this mutation show a block in osteoblast development from mesenchyme and thus no ossification. These mice died of respiratory failure shortly after birth; analysis of their skeletons revealed an absence of osteoblasts and mature bone. In additional investigations Otto et al. [10] created a mutation in only one of the chromosomes resulting in heterozygous mice. Those animals showed specific bone defects like the phenotype of CCD. Possible genetic links between CCD and the complete absence of the thyroid gland have not yet been reported.

Features of cleidocranial dysplasia

The features of CCD can be divided into four groups, relating to severity of disease.

a) Group 1: Skeletal features

b) Group 2: Dental features

c) Group 3: ENT features

d) Group 4: Other features

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Skeletal features

The clinical and radiological features have been reported by several authors and are summarised in Table 1 below [14-17]. L.'s symptoms include hypertelorisms, wide nasal bridge, and projecting forehead.

Dental features

Dental malformations occur frequently and are very characteristic of CCD. Retention of the deciduous dentition with delayed eruption of the permanent teeth is a common finding [18].

Permanent teeth may show a delay of root development but in all cases their eruptive potential is very weak [19]. Despite surgical procedures to promote eruption including the extraction of all deciduous teeth and the removal of bone overlying the crypts of the unerupted teeth the permanent teeth usually require orthodontic disimpassion.

Table 1: Clinical and radiological features of cleidocranial dysplasia.

Clinical	Radiological
Skull	**Skull**
Brachycephaly	Multiple wormian bones
Frontal and parietal bossing	Segmental calvarial thickening
Open sutures and fontanelles	Unossified sutures and patent fontanelles
Delayed closure of fontanelles	Dysplastic changes in the basiocciput
Relative prognathism	Hypoplasia of maxilla
Soft skull in infancy	Delayed mineralisation
Depressed nasal bridge	Calcification of nasal bone delayed or missing
Hypertelorism	Hypoplastic sinuses (paranasal, frontal, mastoid)
Thorax and Shoulders	**Thorax and Shoulders**
Ability to bring shoulders together	Hypoplastic, aplastic, or discontinuous clavicles
Narrow, sloping shoulders	Cone shaped thorax
Respiratory distress at early age	Cervical ribs, missing ribs
Increased mobility	Hypoplastic scapulae
Pelvis and Hips	**Pelvis and Hips**
Caesarean section	Delayed ossification of pubic bone
	Hypoplasia of iliac wings
	Widening of sacroiliac joints
	Large femoral neck, large epiphyses
Spine	**Spine**
Scoliosis	Hemivertebrae, posterior wedging
Kyphosis	Spondylolysis and spondylolisthesis
	Spina bifida occulta
Hands	**Hands**
Brachydactyly	Short middle phalanges and metacarpals/tarsals III-V
Tapering of fingers	Hypoplastic distal phalanges
Nail dysplasia/hypoplasia	Accessory epiphyses especially of 2nd metacarpal
Short, broad thumbs	Long 2nd metacarpal
Clinodactyly of 5th finger	Cone-shaped epiphyses

Among the devices suggested for the orthodontic eruption are magnets [20], and removable appliances [20,21], thick oral/buccal extrusion arches [8,9,22,23], with or without implant anchorage [24], and rather conventional orthodontic appliances [20,21].

The situation may be complicated by the presence of multiple supernumerary teeth obstructing the eruption of permanent teeth, as is the case with our patient, L. (Figure 5). The frequency of supernumeraries in patients with CCD ranges from 22% in the maxillary incisor region to 5% in the molar region [25].

The large number of supernumerary teeth that may even form a complete third dentition (up to 30 extra teeth in some cases) is one of the most striking findings in CCD.

Occasionally, however these patients have no extra teeth or even have congenitally missing teeth [19]. Morphologically

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and functionally, supernumerary teeth resemble their normal counterparts [25]. L. has only two supernumerary teeth (upper central incisors, 12, 11,) Digital volume tomography (DVT) Siemens, (Figure 5).

Dentine formation in CCD is normal but a lack of cellular root cementum has been reported [26]. Long term orthodontic and surgical treatment is usually necessary and aims to provide active support for eruption and aligning of the impacted permanent teeth [8,9,27].

The dental development of CCD patients is approximately 3 years behind that of unaffected children [18]. As the first permanent molars are required for orthodontic anchorage, the treatment is usually not initiated before the age of 9.

ENT features

It has recently been reported that patients suffering from CCD show anatomical malformations within the ENT area as well as many functional problems in the ear, nose and throat area. Several studies reported narrowed external auditory canals in CD patients, increased rates of recurrent childhood ear infections and various degrees of hearing loss [28]. Midface hypoplasia may contribute to these complications.

Other features

These include mental retardation and epilepsy [29], and exophthalmos [1]. Thyroid gland problems (including hypo- and hyperthyroidism) have been reported to occur in association with CCD. Chen et al. [30] reported a rare case of CCD associated with congenital hypothyroidism and severe neonatal hyperbilirubinemia. It is of great interest to present here the first documented case of CCD with total absence of the thyroid gland.

Comment

This is the first reported case of combined cleidocranial dysplasia and complete thyroid gland agenesis. Although one case of CCD with congenital hyperthyroidism and severe neonatal hyperbilirubinemia has previously been reported, there are no reports in the literature discussing CCD in association with the absence of the thyroid gland. We therefore propose to investigate possible genetic links between CCD and complete thyroid gland agenesis.

From the clinical point of view, early diagnosis and multidisciplinary management of all aspects of CCD (dental/orthodontic and endocrine) are important in order to give the patient the best chance of an improved quality of life. This was the case with our patient L., who had undergone surgery and endocrine management of the thyroid deficiency by the time she was just 8 weeks old.

With the further dental treatment planned for L. we expect her dentition in due course to approach that of a normal permanent dentition.

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