Abstract: A family case of Cleidocranial Dysplasia is presented. A mother and two adolescent girls were examined. In all three cases, a radiological series was performed over the entire body. Generalized dysplasia in bones, prolonged retention of primary teeth, and delayed eruption of permanent, as well as supernumerary teeth was diagnosed. The citogenetic study with GTG band showed normal 46, XX. Bilateral audiometry in the mother demonstrated a mild to moderate hypoacoustic condition. Radiological findings are presented and the importance of early diagnosis is discussed. (J. Oral Sci. 46, 259-266, 2004)

Key words: cleidocranial dysplasia; hypoplastic; aplastic clavicles; delayed eruption; supernumerary teeth.

Introduction

Cleidocranial dysplasia (CCD) is a dominant, inherited autosomal bone disorder with a wide range of expressivities, primarily affecting bones undergoing intramembranous ossification characterized by clavicular aplasia or hypoplasia, retarded cranial ossification, supernumerary teeth, short stature and a variety of other skeletal abnormalities (1,2).

The CCD gene has been mapped to chromosome 6 p 21 (3-6) within a region containing the CBFA1 gene, a member of the Runt family of transcription factors (7,8). CBFA1 controls differentiation of precursor cells into osteoblasts and is thus essential for membranous as well as endochondral bone formation, which may be related to delayed ossification of the skull, teeth, pelvis and extremities in CCD (9). However, Brueton et al. (10) described rearrangements of chromosome 8 q 22 which may be a factor to consider in the genetic heterogeneity in CCD.

According to Yoshida et al. (11), the genotype–phenotype correlations in mutational studies of the RUNX2 domain show a variable clinical spectrum, suggesting that skeletal growth and dental development could be related to the type of changes in the RUNX2 activity in regards to all patients with an intact Runt domain, although they presented the classical phenotype showing higher stature. Yoshida et al. (11) suggested that the presence of short stature and supernumerary teeth may have important implications in the prognosis and treatment of CCD patients.

CCD is highly polymorphic, therefore a complete radiological study is necessary to establish a reliable diagnosis, mainly in those cases with low expressivity (12).

Golan et al. (13), in a study of the craniofacial findings of 289 cases of CCD, reported that the prevalence of supernumerary teeth, delayed eruption or failure of eruption of the permanent teeth, and hypoplastic maxilla was high. Additionally, delayed tooth development associated with the presence of supernumerary teeth has been reported in CCD patients (14). Less frequently, eruption cysts, alterations of hard dental tissues, a high propensity for caries and narrow high palate have been found (15-17).

According to Ishii et al (18), young CCD patients show relatively normal proportions and morphology of the mandible, while older CCD individuals tended to express
the typical signs of CCD. These abnormalities can be attributed to pronounced horizontal mandibular growth resulting from lack of vertical maxillary growth and impaired eruption of permanent teeth.

The aim of this paper is to describe the findings of a rare familiar case of CCD and to compare it with other reported patients. Early diagnosis and dental care are discussed as well.

**Materials and Methods**

Radiological examination regarding osseous malformations was carried out in all three patients. Lateral cephalometric, anteroposterior and panoramic radiographs were taken to examine the skeletal morphology of the skull and face, and to evaluate dental development. The GTG band cariotype was developed and bilateral audiometry was performed in the three cases. The pedigree was constructed through the patient’s reference.

**Patients**

Two females (ages sixteen and seventeen) and their parents in their late thirties were the subject of this study. There was no parental consanguinity. The daughters are product G II P 0 C II A 0. The GTG band cariotype showed normal result of 46, XX. According to the pedigree, the maternal line was affected predominantly in the female gender (Fig. 1).

Fig. 1 Pedigree of the family □ males, ○ females, white symbols are for unaffected offspring, blackened symbols indicate affected individuals, ♀ proband.

Fig. 2 Narrow and drooped shoulders, wide range of shoulder movement. a) mother, b) younger daughter, c) elder daughter.

Fig. 3 Chest radiograph demonstrating hypoplastic clavicles. a) mother, b) younger daughter.

Fig. 4 Mother, anteroposterior view: underdeveloped maxilla and paranasal, mandible prognathism.

Fig. 5 Mother, lateral view: wormian bones (dark arrow), calvaria thickening sinuses (white arrow).
Mild to moderate bilateral hypoacusia was detected only in the mother. Clinical and radiological studies revealed as coincidental data the following findings: slow growth and moderately short stature. Clavicle bilateral hypoplasia involving the medial third distal, as well as muscular defects associated with abnormal motion of the shoulders (Fig. 2). Other clinical findings include defects of the cervical and lumbar vertebrae, cervical ribs, and deformities of the thorax (Fig. 3). Hypoplasia of the pelvis, total absence of pubic symphesis in the younger daughter, and hypoplasia in the other two patients was observed as well. The arms and legs were abnormally short to a moderate degree with genu valgum. Furthermore, abnormalities in hands, feet and nails, were observed.

The craniofacial findings included delayed closing of the fontanels until the age of 7 or 8, brachicephalia and moderate thickness of the calvaria of the skull. In the mother, wormian bones, aplasia of the frontal sinuses and hypoplasia of maxillary sinuses were observed (Figs. 4,5). Frontal and parietal bossing with a groove along the metopic suture, depressed nasal bridge and hypertelorism being remarkable in the younger daughter due to the

Table 1 Cephalometric analysis

<table>
<thead>
<tr>
<th>LINEAR ANALYSIS (mm)</th>
<th>Younger daughter</th>
<th>Elder daughter</th>
<th>MEAN*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAGITAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-S</td>
<td>65</td>
<td>63</td>
<td>67.74</td>
</tr>
<tr>
<td>A'-Ptm'</td>
<td>55</td>
<td>58</td>
<td>50.45</td>
</tr>
<tr>
<td>Pog-Go'</td>
<td>79</td>
<td>78</td>
<td>77.76</td>
</tr>
<tr>
<td>N perp to A</td>
<td>12</td>
<td>11</td>
<td>3.31</td>
</tr>
<tr>
<td>Pog to Np</td>
<td>15</td>
<td>16</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>VERTICAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Me</td>
<td>108</td>
<td>107</td>
<td>119.34</td>
</tr>
<tr>
<td>N-ANS</td>
<td>49</td>
<td>48</td>
<td>54.90</td>
</tr>
<tr>
<td>Ans-Me</td>
<td>61</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Gn-Cd</td>
<td>118</td>
<td>120</td>
<td>118.53</td>
</tr>
<tr>
<td>Cd-Go</td>
<td>64</td>
<td>65</td>
<td>60.15</td>
</tr>
</tbody>
</table>

Parameters of normal Mexican female 15-17 year old.

<table>
<thead>
<tr>
<th>ANGULAR ANALYSIS (grades)</th>
<th>Younger daughter</th>
<th>Elder daughter</th>
<th>MEAN*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNA</td>
<td>97</td>
<td>93</td>
<td>82.45</td>
</tr>
<tr>
<td>SNB</td>
<td>93</td>
<td>90</td>
<td>79.99</td>
</tr>
<tr>
<td>Facial angle</td>
<td>94</td>
<td>99</td>
<td>90.46</td>
</tr>
<tr>
<td>Y axis (FH)</td>
<td>52</td>
<td>52</td>
<td>58.61</td>
</tr>
<tr>
<td>Ramus incl (FH)</td>
<td>73</td>
<td>75</td>
<td>83.30</td>
</tr>
<tr>
<td>Gonial angle</td>
<td>120</td>
<td>122</td>
<td>118.47</td>
</tr>
<tr>
<td>Mandibular plane</td>
<td>12</td>
<td>11</td>
<td>21.7</td>
</tr>
</tbody>
</table>

* Parameters of normal Mexican female 15-17 year old.
increase of skull width was observed (Fig. 6).

According to the cephalometric analysis (Table 1), the two daughters showed reduction of the superior facial depth (N-S), thus increasing middle facial depth (A’-Ptm’), and a resultant protrusion of the maxilla (SNA y N perp to A). The mandibular length was normal in both girls (Pog-Go), however the posterior facial height was greater than in the normal group (Cd-Go), as well as the anterior facial height that was shorter (N-Me). These changes caused a counter clockwise rotation of the mandible resulting in mandibular protrusion (SNB, Facial angle and Pog to Np) as shown in (Fig. 7).

Intra oral inspection showed that the mother was partially edentulous with only a few teeth in the maxilla and mandible. The two daughters presented roots of primary teeth as well as prolonged retention of their primary teeth and clinical absence of some permanent teeth as well as high palate and anterior cross-bite (Fig. 8). Radiological examination showed permanent teeth mainly in the incisive pre-molar region as well as supernumerary teeth being retained in all three patients (Fig. 9).

Discussion

A rare family case of CCD is presented that was not previously diagnosed, though the patients were partially edentulous with prolonged retention of primary teeth and a history of dental extractions as the result of caries. A mother and two daughters were studied. As the rest of the relatives lived in another state of the country, they were not examined. Although CCD is an autosomal syndrome, in this family case the maternal line is affected predominantly in the females.

Although the mutational analysis of RUNX2 was not carried out as proposed by Yoshida et al. (11), it is possible that the Run domain was affected since the patients showed short stature. Furthermore, the number of supernumerary teeth was high in these patients. Yoshida et al. (11) pointed out that there is a significant correlation between the number of supernumerary teeth and short stature with the gene dosage RUNX2 effect in the RUNX2 activity.

In this family clinical case, the number and severity of alterations were different in each patient. The genotype-phenotype correlation has been discussed widely. It is possible that the extreme clinical diversities of CCD could be explained by the type of mutation in the codin region of RUNX2 (11,19-22). The skeletal anomalies as well as the oral manifestations of the syndrome in the three patients were similar to those described in the literature (23-29).

The clinical findings of CCD, although present at birth, could be easily missed due to its extreme low frequency and to the variety of clinical manifestations as was true in this family case (30,31). On other hand, some atypical forms of CCD could be misdiagnosed or diagnosed at a much later date (32).

Less frequently, CCD may be associated to congenital hypothyroidism and neonatal hyperbilirubinemia (33), acute upper limb ischemia (34), syringomyelia (35) and Yunis Varon Syndrome (36).

The cephalometric features of the two girls compared with parameters of normal occlusion of their age group (37) suggest reduced superior facial depth (N-S) due to abnormal growth of the cranial base. Additionally, increased middle facial depth (A’-Ptm’), as a result of higher growth of this region, produced a protrusion of the maxilla (SNA y Np to A). Though the mandible length was normal, the posterior facial height increased due to a higher growth of the ascending mandible ramus and reduced anterior facial height as a result of a lack of growth of the anterior superior facial height (N-Ans). Disturbances of the permanent teeth


![Fig. 8 Intraoral view: a) mother, b) younger daughter, c) elder daughter.](image2)
eruptions can be related to the lower anterior inferior height (Ans-Me). These irregular changes result in mandible rotation (Y axis-FH), ramus inclination (FH), and the mandibular plane (FH) being forward with a counter clockwise rotation, causing a mandible protrusion as has been proposed by Ishii et al. (18) and Richardson (38).

According to Golan (39), the indicators of CCD are age related, and their expression should be taken into consideration for early diagnosis. Apparently, signs only manifest during growth, when the ideal timeframe for beginning treatment has already passed. In our case, the unique treatment option for the mother was the surgical management of the retained teeth and the use of full dentures, whereas both daughters underwent orthodontic treatment. Selected retained permanent teeth, supernumerary and primary teeth were extracted to allow occlusion of the remaining teeth. The reduced anterior supero facial height will require surgical treatment. McNamara et al. (40) proposed that in addition to the usual dental complications of eruption failure of the permanent dentition and multiple supernumerary teeth, morphological abnormalities of the maxilla and mandible, particularly the ascending ramus and the coronoid process, may be detected by using panoramic radiography.

Early identification of the syndrome permits the planning of dental treatment by selecting the teeth that should be removed. Sato (41) suggests the use of a three-dimensional method of locating the position of impacted supernumerary

Fig. 9 Panoramic X-ray and tracing. a) mother, b) younger daughter, c) elder daughter. primary teeth (dark), supernumerary teeth (gray), permanent teeth (white).
teeth, insisting upon the importance of the removal of the supernumerary teeth and the planning of an orthodontic treatment that will allow for occlusion of the retained teeth. Davies (42) recommends a method where orthodontic forces may be applied to un-erupted permanent teeth moving them into a satisfactory, functional and aesthetic position. Occasionally, when the teeth fail to erupt after the removal of supernumerary teeth and orthodontic traction, a combination of orthodontic-prosthodontic treatments is necessary (43,44).

The cases having vertical maxillofacial deficiency require coordinated surgical-orthodontic management (45). Lombardas (46) has advised the use of osseointegrated implants in the maxillary arch in an attempt to provide a retentive and esthetic over denture.

Conclusion

Despite the variable expressivity of CCD, early diagnosis through the oral findings can be achieved by clinicians. In addition to the oral findings, diagnosis of this rare disease requires a reliable skeletal evaluation. Furthermore, confirmation by molecular genetic analysis is also recommended. A well-functioning permanent dentition, as well as an aesthetically satisfying facial appearance may be achieved by interdisciplinary treatment when CCD is diagnosed in the early stages of childhood development.

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References

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