DIAGNOSTIC AND THERAPEUTIC APPROACH TO A PATIENT WITH CLEIDOCRANIAL DYSPLASIA - DENTAL ASPECT

Selma Ćosović[1]*, Mirjana Gojkov-Vukelić[2], Sanja Hadžić[2], Anela Hardaga-Muzurović[3], Džejma Suljić Hujić[4], Adisa Goga Filipović[5], Rijad Konjhodžić[6]

*Corresponding author

Dr. Selma Ćosović, DDM,
University of Sarajevo,
Faculty of Dentistry
with Dental Clinical Center ,
Reception and triage clinic
Bolnicka 4A, 71 000 Sarajevo,
Bosnia and Herzegovina
Phone: +387(33)407- 806,
e-mail: selmacosovic2@gmail.com

[1] Reception and triage clinic, Faculty of Dentistry with Dental Clinical Center, University of Sarajevo, Bosnia and Herzegovina

[2] Department of Oral Medicine and Periodontology, Faculty of Dentistry with Dental Clinical Center, University of Sarajevo, Bosnia and Herzegovina

[3] Clinic of Oral Surgery, Faculty of Dentistry with Dental Clinical Center, University of Sarajevo, Bosnia and Herzegovina

[4] Clinic of Oral Medicine and Periodontology, Faculty of Dentistry with Dental Clinical Center, University of Sarajevo, Bosnia and Herzegovina

[5] Public Health Center with Hospital in Kakanj, Bosnia and Herzegovina

[6] ALEA Genetic Center Sarajevo, Bosnia and Herzegovina

ABSTRACT

Cleidocranial dysplasia (CCD) is a rare autosomal dominant congenital syndrome occurring in approximately one in every million individuals worldwide, primarily affecting bones undergoing intramembranous ossification. Individuals with CCD exhibit hypoplasia or aplasia of the clavicles, open fontanelles and shorter stature, along with various forms of dental abnormalities. The gene RUNX2 plays an essential role in odontoblast and osteoblast differentiation, regulating the expression of many genes associated with the development of hard dental tissues. CCD is this accompanied by characteristic dental abnormalities such as supernumerary teeth, delayed eruption and impaction of permanent teeth. Intrafamilial variations of skeletal and dental abnormalities are well-known.

The aim of this study is to present a clinical case and provide a diagnostic approach as a guide for practicing dentists, thereby facilitating their future work with these patients.

Keywords: impacted teeth, supernumerary teeth, dental anomalies, cleidocranial dysplasia.

Introduction

Cleidocranial dysplasia (CCD), also known as Marie-Sainton's disease, is an autosomal dominant genetic disorder. Within members of a single family, there can be various clinical presentations of this syndrome [1]. The estimated prevalence of CCD is one in a million births, with no gender predilection [2, 3]. The clinical presentation varies from classic CCD, characterized by the triad of symptoms: delayed closure of the cranial sutures, hypoplastic or aplastic clavicles and dental anomalies which can be milder with isolated dental anomalies in the absence of skeletal abnormalities [4]. The spectrum of anomalies is wide and may encompass patients with only dental anomalies and clavicular anomalies to individuals with severe skeletal developmental defects.

Individuals with cleidocranial dysplasia may also have many other systemic disorders such as defects of vertebral bones in the cervical and thoracic regions, scoliosis/lordosis, defects of the pelvic region, supernumerary ribs and defects of hands, bones and joints [2, 5]. Dental anomalies include supernumerary retained deciduous teeth, teeth with delayed eruption, impacted permanent teeth and supernumerary permanent teeth [6, 7] being the characteristic of CCD. Dental anomalies are easily detected on panoramic radiographs, and for greater precision, computerized tomography (CBCT) can be used [8]. Specifically, CBCT allows for the assessment of precise locations of supernumerary teeth and their relationships with other teeth and important anatomical structures, which is particularly useful in treatment planning.

Advanced diagnostic methods during pregnancy can also indicate CCD. CCD can be suspected at an early age, even during fetal life, through prenatal ultrasound examination [9]. Genetically, CCD is caused by a mutation in the gene encoding the osteoblast-specific transcription factor, RUNX2, located on chromosome 6p21, which consists of a region of 223 kb (Chr6:45328317-45551082) and comprises eight exons [10, 11, 12]. Chromosome 6p21 is responsible for skeletal morphogenesis and also for the differentiation of specific cells such as osteoblasts [13]. RUNX2 is crucial for the proliferation of cells specialized in bone and tooth synthesis, as well as for osteoblast proliferation [14, 15, 16]. Mutations in the Runt domain are associated with dental anomalies such as supernumerary teeth, changes in eruption time, etc. [17].

CCD is usually diagnosed at birth but very often goes unrecognized because of its low incidence rate, and signs and symptoms are rarely seen at that age [18]. The craniofacial characteristics of the presented clinical case from our own casuistry manifest as minor skeletal changes in cranial bones and numerous impacted and supernumerary teeth. The diagnosis was confirmed after analyzing orthopantomograms and finding genetic testing results, where DNA isolation was performed using the QIAamp DNA Mini kit. The platform on which the analysis was performed is the NextSeq System Illumina allowing comprehensive analysis of more than 4800 genes.

In cases of diverse and complex dental anomalies, patients sometimes require intervention from a multidisciplinary team of dental specialists from early childhood. When treatment is approached in a timely manner with appropriate therapy provided by pediatric dentists, orthodontists, maxillofacial and oral surgeons, periodontists and prosthodontists, a harmonious dentoalveolar relationship can be achieved. [19-27]

The aim of this study is to present a clinical case and provide a diagnostic approach as a guide for practicing dentists by facilitating and providing guidelines for their future work with these patients.

Case Presentation:

A 73-year-old male patient of short stature and medium osteomuscular build presented to the receptione and triage clinic of the Faculty of Dentistry with Dental Clinical Center following a referral from the Emergency Medical Services Department of the Sarajevo Canton, with a referral diagnosis of post-hemorrhagic gingivitis in the region of tooth 25. During the patient's anamnesis, we noticed that bleeding in the oral cavity occurred spontaneously during the previous night. After emergency medical intervention with gingival tamponade and intramuscular Dicynone injections, the bleeding was stopped. Further anamnestic examination of the

patient and review of medical documentation revealed that the patient had been diagnosed with osteoporosis and was receiving oral bisphosphonate therapy, medication named Promass.

On extraoral examination, we observed a shortened lower third of the face and a concave profile (Figure 1). Intraoral clinical examination revealed partial edentulism in the upper and lower jaws, limited mouth opening, high-arched hard palate, carious teeth with significant hard and soft deposits on the teeth (Figure 2).

After performing an orthopantomogram, analysis revealed twenty impacted, retained, and supernumerary teeth in both jaws (Figure 3). For more precise diagnosis, a 3D CBCT was performed, allowing for a detailed examination of tooth position and morphology, as well as their relationship with other anatomical structures in the jaws (Figure 4).

This approach facilitated the diagnosis of periodontitis et dentes supernumerarii cum impactio dentis and the development of a treatment plan.

According to the planned therapeutic protocol, the patient was first referred to the Clinic of Oral Medicine and Periodontology for the removal of supragingival and subgingival dental deposits. After obtaining the patient's medical history and analyzing radiographic images and laboratory findings (bleeding time and coagulation time), which were within reference values, initial periodontal therapy was performed, and no subsequent prolonged bleeding was observed. The patient was given instructions on maintaining oral hygiene.

After achieving optimal periodontal status, the patient was referred to the Clinic of Oral Surgery for further treatment.

Figure 1
Extraoral view of the patient showing a typical concave facial profile, and evident pseudoprognathism

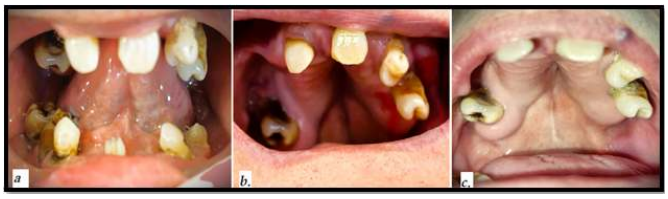

Figure 2
Intraoral view; a. Presence of a larger number of carious teeth with hard and soft deposits;
b. Hypotonic maxilla and looseness in the dental arch;
c. High-positioned hard palate.

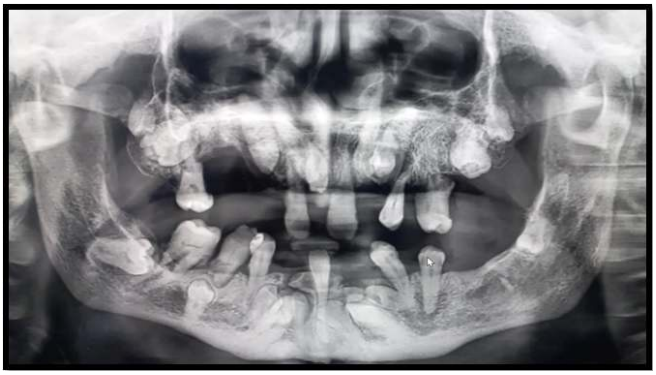

Figure 3
Orthopantomograph

Considering the analysis of OPG and 3D CBCT images revealing a larger number of impacted and supernumerary teeth, both in the upper and lower jaws, with atypical shape and position, and noting the radiolucency suggestive of a dentigerous cyst in the apical region of impacted tooth 13, a decision was made to adopt a multi-session approach to the patient's treatment protocol. After completing a detailed anamnesis, clinical examination, and radiographic diagnostics, and considering the referral diagnosis of post-hemorrhagic gingivitis in the region of tooth 25, an indication for the extraction of teeth 25 and 45 was set as the primary phase of surgical treatment to address the patient's oral cavity sanitation. Additionally, before the oral-surgical procedure, an assessment was made to determine whether there was a risk of impaired healing of extraction wounds due to the patient's bisphosphonate therapy. Considering that the patient takes bisphosphonate medication orally and that the potency of the drug is not significantly pronounced due to this route of administration and

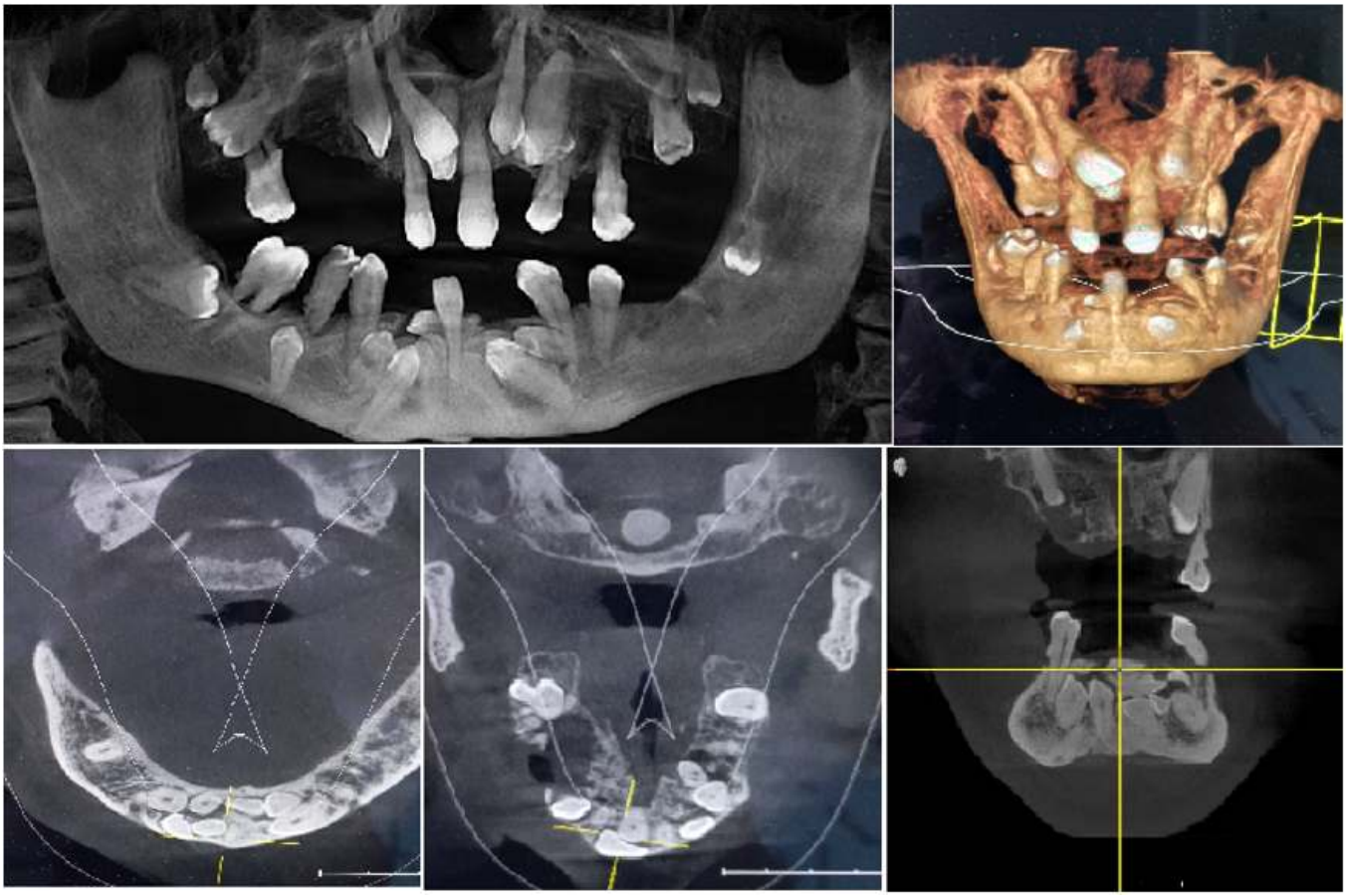

Figure 4
3D CBCT

that the patient has been on bisphosphonate therapy for less than three years, the intervention was carried out.

Under local anesthesia, tooth extraction of 25 and 45 was performed, followed by alveolar curettage, extensive wound irrigation and placement of a mattress suture in the region of tooth 25. The extraction socket in the region of tooth 45 was left to heal by secondary intention. The wound in the region of tooth 25 was primarily sutured with absorbable suture material. A broad-spectrum antibiotic (Amoxicillin caps. 500mg 2x2) was prescribed for 7 days.

The oral surgical procedure, involving tooth extraction, proceeded smoothly, with minor complaints of post-extraction pain and swelling. The extraction wounds healed well, as evidenced by follow-up examinations (Figure 5).

The patient is regularly monitored through clinical examinations and further surgical treatment planning is scheduled involving the operative removal of supernumerary and impacted teeth for which indications are set.

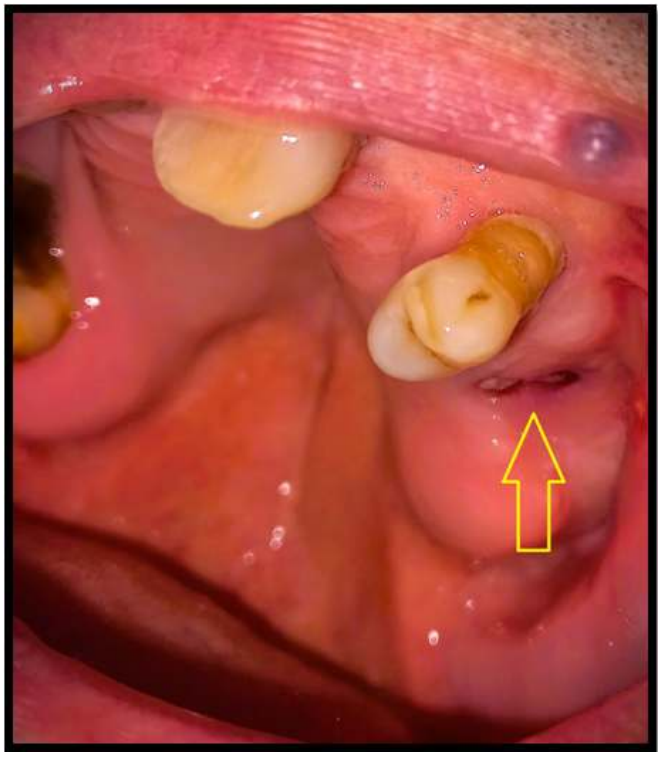

Figure 5
Normal healing of the extraction socket

Based on the extraoral and intraoral examination and suspicion of Cleidocranial dysostosis syndrome, the patient was referred for laboratory and genetic verification, confirming the existence of the mentioned syndrome.

Discussion

The most common manifestations of CCD are skeletal anomalies and atypical dentition. The most significant dental anomalies include multiple supernumerary teeth, impacted and retained teeth and the occurrence of cystic changes [17] compromising the aesthetic appearance and function of dentition [28]. The formation of supernumerary teeth can result from incomplete or delayed resorption of the dental lamina, leading to the reactivation and formation of supernumerary teeth [29]. Other dental anomalies include retention of deciduous teeth and delayed eruption with subsequent impaction of permanent teeth. Some patients, later in life, due to the need for prosthetic rehabilitation, decide to consult a dentist. Dentists often may be the first healthcare professionals to encounter patients with this potential diagnosis. The most common sites where supernumerary teeth are present include the maxillary incisor region, as well as the maxillary and mandibular canine and premolar regions [30]. The presence of supernumerary teeth can inhibit the eruption of permanent teeth and cause resorption of the roots of adjacent teeth. In our presented case, supernumerary and impacted teeth were identified in the following regions of the upper jaw: right maxillary region 18 and 17, intermaxillary region 13, 12, 11, 23, 24, 25, left maxillary region 27 and 28, and in the area of the right upper canine along with a dentigerous cyst. In the lower jaw, supernumerary and impacted teeth were identified in the following regions: in the anterior region 44, 43, 42, 31, 32, 33, 34, and in the ramus of the mandible on the left side 38 and on the right side 48.

A particularity of this case report is that the patient exhibits all the clinical characteristics of dysostosis (flat forehead, short stature, irregular relationship between the upper and lower jaws as a consequence of abnormal jaw development, etc.) and has multiple supernumerary teeth, yet there was never an expressed suspicion of CCD's presence.

For these patients, dental radiography can provide valuable diagnostic information to the dentist. Additionally, early diagnosis will increase the possibility of selecting appropriate treatment, reducing the likelihood of complications and obtaining genetic counseling for patients [1, 15]. In most cases, panoramic radiographs are often used as the initial imaging for further diagnosis, which has the specific advantages of low radiation dose and broad coverage of anatomical details of the jaws [31]. Besides assessing dentition, panoramic radiography can provide visualization of adjacent structures, such as the mandible, maxilla, zygomatic bone, and temporomandibular joints. For dentists, a significant question is whether panoramic radiography can provide a reliable assessment of CCD.

Although there are no specific therapeutic guidelines for dental treatment in patients with CCD syndrome, we believe that after the anamnestic-diagnostic procedure and suspicion of CCD syndrome, the patient should be referred for genetic analysis, which we also conducted. Osteoporosis diagnosed earlier in our patient is not associated with CCD through genetic testing. A heterozygous mutation c.2680C>T (p.Arg 894Ter) associated with Congenital Myotonia was detected, corresponding to the musculoskeletal appearance of the patient.

Therapeutic protocols depend on the patient's age, craniofacial characteristics, dental anomalies and social and economic circumstances [32]. Treatment of dental abnormalities depends on the dental and chronological age of the patient requiring a multidisciplinary approach like in our case (general dentistry specialists, periodontist and oral surgeon) with further prosthetic rehabilitation planned.

Conclusion

Based on the presented case, we can conclude that detailed anamnestic-diagnostic data (medical history, extraoral and intraoral clinical examination and radiographic analysis of orthopantomogram) can provide sufficient information for establishing a working diagnosis of CCD requiring appropriate genetic testing to confirm the diagnosis. The therapeutic protocol for dental treatment should be tailored to the patient's age with a multidisciplinary approach to treatment which may last for many years.

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