ORAL MANIFESTATIONS IN CLEIDOCRANIAL DYSPLASIA

Dorin Bratu[1], Florica Glavan[2], Cristina Bratu[2]

REZUMAT

Introducere: Displazia cleido-craniană este datorată unei mutații a cromozomului 6p21, în regiunea ce conține gena RUNX2 (CBFA1), ce codifică un factor de transcripție. Pe lângă cazurile tipice, cu transmitere a anomaliei autosomal dominant, există și situații în care boala apare la un copil cu ascendenți sănătoși (așa-zisele cazuri "de novo"), categorie în care se încadrează și cazul nostru. **Prezentare de caz:** Pacientul prezintă aplazie claviculară, întârzierea închiderii fontanelelor, poliincluzii (toți dinții frontali maxilari și doi supranumerari) care generează o edentație frontală aparentă. Din antecedentele copilului este demn de remarcat faptul că în perioada intrauterină a avut loc accidentul termonuclear de la Cernobîl (Ukraina) din 26 aprilie 1986. În etapa chirurgicală de tratament au fost descoperiți cei patru frontali superiori cu șanse de erupție și s-a realizat odontectomia lateralilor (cu malformații radiculare) și a supranumerarilor. A urmat etapa de terapie ortodontică fixă, finalizată în 18 luni. **Discuții:** Aspectul clinic postterapeutic seamănă cu simularea computerizată realizată de către noi înainte de debutul terapiei, satisface pacientul și anturajul. **Concluzii:** Un astfel de caz nu trebuie să ajungă până la vârsta de 17 ani pentru a fi rezolvat. La această vârstă terapia este una complexă și de muncă în echipă. Asistența de specialitate a copilului și prevenția în țara noastră lasă mult de dorit.
Cuvinte cheie: displazie cleido-craniană, RUNX2, dinți incluși

ABSTRACT

Introduction: Cleidocranial dysplasia is caused by a genetic disorder on 6p21 chromosome, in the region of RUNX2 (CBFA1) gene that encodes a transcription factor. The clinical aspects of the disease were described by Scheuthauer in 1871. Cleidocranial dysplasia is an autosomal dominant disease, but there are exceptions like the case we present, when the syndrome affects patients with healthy predecessors, the so-called "de novo" cases. **Case report:** For three generations none of the patient's ancestors presents any of the clinical signs of this genetic disorder. The patient has clavicular aplasia, delayed closing of fontanels, multiple impacted teeth (both upper canines, upper lateral and central incisors, two upper supernumerary teeth) generating an appearance of anterior partial edentulism. The medical history of the patient contains one troubling event which took place in the fourth month of intrauterine life: the thermonuclear accident at Chernobyl, Ukraine (April 26th, 1986). The treatment consists in a surgical phase for exposing the four upper impacted teeth (in order to promote their alignment), followed by odontectomy of the lateral incisors (due to root abnormalities) and supernumerary teeth. The fixed orthodontic treatment phase has been concluded within 18 months. **Discussions:** The final clinical aspect resembles our initial computer simulation, satisfies the patient and his social group. **Conclusions:** Such cases should receive therapy before reaching the age of 17, because at this age the treatment is very complex and involves a full therapeutic team. Paediatric medical assistance and prevention is still unsatisfactory in our country.

Key Words: cleidocranial dysplasia, RUNX2, impacted teeth

INTRODUCTION

Cleidocranial dysplasia (dysostosis) – CCD – also known as Marie–Sainton disease is a rare autosomal dominant genetic disorder. We prefer the term dysplasia because it includes dysostosis and covers a wider range (dysplasia - abnormal development of organs or cells; dysostosis - defective formation of bone). According to Genetic Information and Patient Services (GAPS) Index there are 18 names for CCD.[1] Pediatricians and physicians are identifying this disorder by premature coronal ossification, delayed closure of the fontanels and complete or partial absence of the clavicles. Oral manifestations appear in different components of the masticatory system: lips, jaws, palate, teeth etc.

The disease occurs because of a mutation in 6p21 chromosome, region for RUNX2 gene (previously known as CBFA1). This gene encodes a transcription factor.[2]

The first to describe clinical aspects in CCD patients was G. Scheuthauer in 1871.[3] In 1897, P. Marie and P. Sainton wrote about the complete or partial absence of the clavicles, overdimensioned transversal

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cranial diameter and delayed closure of the fontanels in CCD patients. They were the first to name the disease hereditary cleidocranial dysplasia.[3]

Over 700 case reports of CCD were published in the scientific literature.[4]

For a century the disease was reevaluated by different authors, over 100 associated abnormalities were registered. In 1908, Hultkranz published the first complete morphological study about CCD, later completed by Fleischer-Peters and Schuch.[5-7] Many genetic familial studies were conducted during the last decades: Goodman (1975), Brueton (1992), Nienhaus (1993), Feldman (1995), Mundlos (1997 and 1999), Cooper (2001), Morava (2002) and Cogulu (2004).[8-17]

This article does not intend to insist on general manifestations known to appear in CCD, but on cranio-facial disorders which interest the dentist.

Usually, CCD patients present brachycephaly with bossing of the frontal, parietal and occipital bone, giving the head a large globular appearance. In contrast, the face is small because of the reduced size of the maxillary and zygomatic bones. Lips are poorly outlined, usually the upper lip is shorter. The hypoplastic maxilla is mostly generated by the poor development of the premaxilla, while the mandible is normal, causing a false progenic aspect. Fontanels are slowly closing and in some cases remain permanently open. Calvarian thickening in the supraorbital part of the frontal bone, squama of the temporal bone and occipital bone are present. Wormian bones are filling the cranian sutures. Dysplasia of the paranasal sinuses and mastoidian cells appears frequently. The nose is broad, with depressed bridge. Sometimes incomplete sinusal structures appear.

Usually the palate is deep. Medio-sagittal palatal suture and mandibular symphysis (considered to be an incomplete synostosis or synchondrosis) are delayed in closing, like the fontanels.

Until 1925 it has been believed that hypodontia, delayed eruption and malpositioning of the permanent teeth was generally present in CCD. This idea has proved to be wrong. Fleischer-Peters suggested that delayed eruption was caused by increased bone density.[6]

Sometimes teeth eruption occurs in abnormal positions (transpositions) due to persistence of the deciduous teeth. Winter observed that the teeth without deciduous predecessors had a greater chance to erupt.[18] Extraction of deciduous teeth did not seem to promote eruption of the impacted permanent teeth. Gemination and dilaceration of roots were also common. One of the most remarkable oral aspect is the number and shape of supernumerary teeth which appear usually. Wherever they are found their crown is similar to that of a premolar (bicuspid), severely deformed and with hypoplastic enamel. Their roots lack the layer of cellular cementum.

CASE REPORT

The patient M. M., male, born in Lugoj, on 13.09.1986, 1.76 m height, 75 kg, high-school student, presented to the Department of Paediatric Dentistry and Orthodontics of the Victor Babes University of Medicine and Pharmacy, Timisoara, requesting treatment of his upper anterior edentulous area. He had a chest radiograph (demonstrating complete bilateral aplasia of clavicles) and a lateral cephalograph. After performing a panoramic radiograph (Fig. 1) he has been refered from the Department of Pediatric Dentistry and Orthodontics to the Department of Prosthodontics for the surgical phase of treatment.

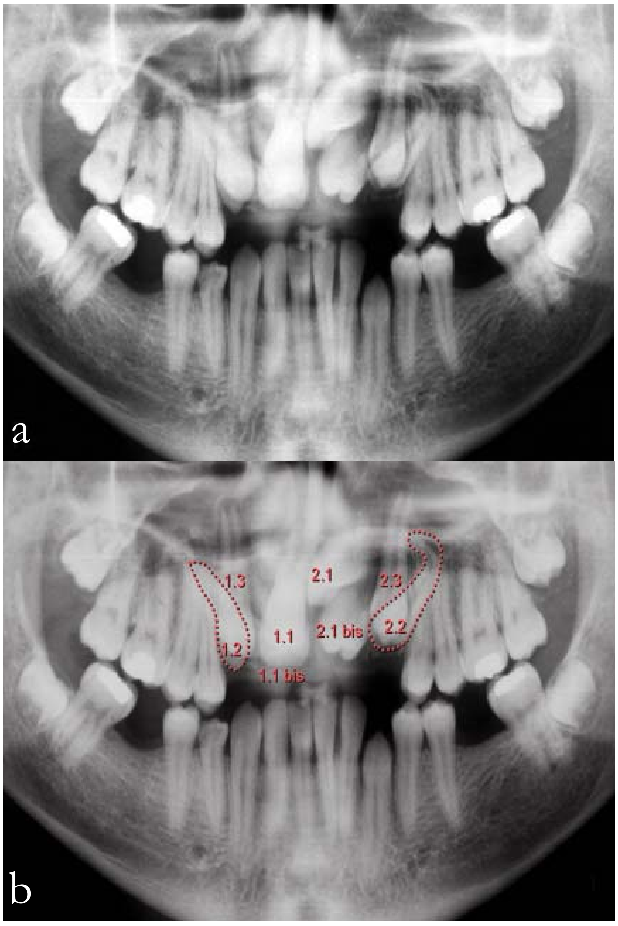

Figure 1. Panoramic radiographs revealing the impacted teeth, superposition of the impacted teeth makes their recognition difficult.

Heredo-colateral medical history did not reveal any important information. None of his grand-parents, parents or sibblings (one brother and one sister) presented any of the clinical aspects associated with CCD.

Personal medical history is showing normal birth, breast feeding, opened fontanels until 15 years old, abnormal shoulder movement due to clavicular aplasia. The patient could place his shoulders adjacent to each other. (Fig. 2)

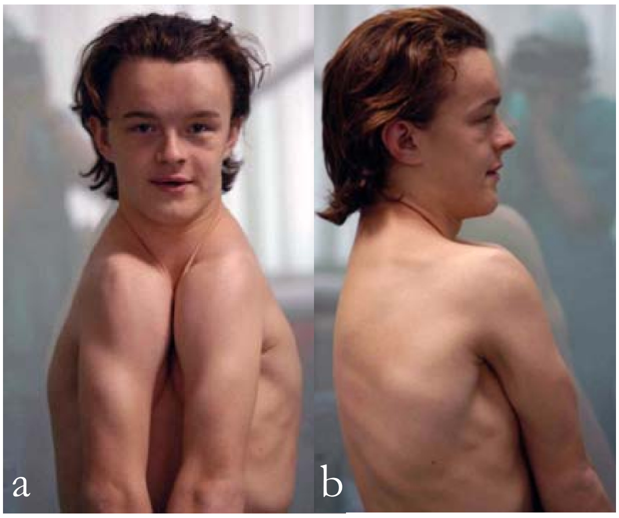

Figure 2. Placing the shoulders adjacent to each other reveals the lack of clavicles.

Dental medical history is showing delayed eruption interesting both deciduous and permanent teeth. First lower molars (3.6, 4.6) were lost because of complicated caries. At the age of 14 years he received 2 amalgam fillings on his second lower molars (3.7, 4.7). Strangely, his upper anterior edentulism was not investigated or treated. He presented good oral hygiene.

Patient has light brown hair, blue eyes; his skin texture, muscular tonus and lymphatic system are normal.

Moderate brachycephaly, with slightly prominent frontal, parietal and occipital bossing, and the triangular face conferred the head a globular aspect. (Figures 3,4)

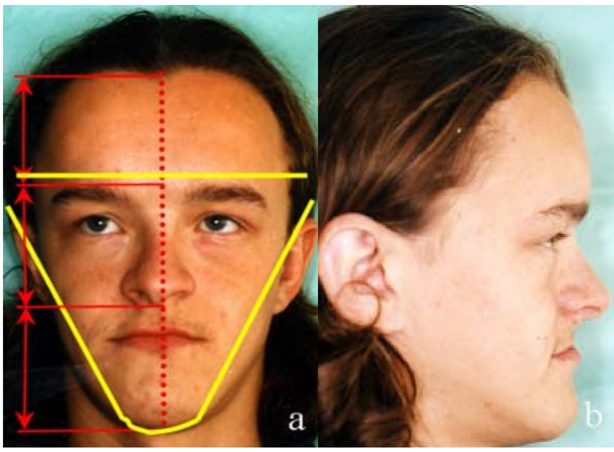

Figure 3. Front and lateral facial aspect.

Figure 4. Frontal and occipital bossing.

Maxillary hypoplasia and the slightly overgrown mandible concurred to a progenic profile. (Fig. 3b)

Fontanels were almost closed and cranial sutures were still open until 2 years previously.

The supraorbital ridge is thicker than normal, the nose broad. (Fig. 3)

The frontal analysis of the head reveals that the upper and lower figure segments were almost equal in height and the middle segment was slightly shorter. (Fig. 3a) The lateral view showed an almost straight profile.

Temporo-mandibular joint examination: mouth opening 37 mm, straight chin excursion, physical examination of the temporo-mandibular joint did not reveal any pain or unusual noise.

Intraoral examination: unstable occlusion, a reduced number as well as unequal and asymmetric occlusal contacts were noticed. The Angle's classification of the occlusion was impossible in the molar as well as in the canine area, because of lacking lower first permanent molars (3.6, 4.6) and impacted upper permanent canines (1.3, 2.3). A normal relationship between the existing teeth was present in the horizontal plane. Normal vertical relations were obseved in the posterior zones of the dental arches.

Functional examination of the stomatognathic system revealed prolonged bilateral chewing, with reduced efficiency; normal adult swallowing; esthetics and fonation are deficient; breathing and mimics, as well as the muscular tonus (except the sterno-cleido-mastoidian muscle) are normal.

Mucosa is normotrophic, the palate high. The tongue, floor of the mouth and soft palate are normal in size and movement.

Examination of the dental arches revealed: large carious distructions on 4.4; 3.3 was blocked in eruption; Black class I amalgam fillings on 1.6, 2.6, 3.7, 4.7; Kennedy class IV upper edentulism caused by impacted anterior teeth and modified Kennedy class III edentulism on the lower dental arch. (Fig. 5)

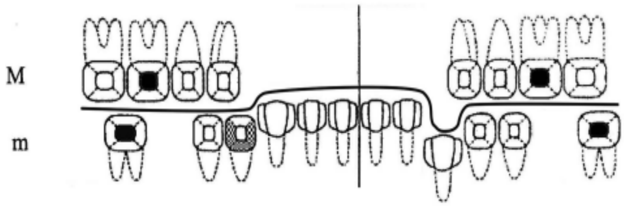

Figure 5. Intraoral clinical examination

Radiographic examination (panoramic radiograph) revealed multiple impacted teeth in the upper anterior area (6 anterior permanent teeth and 2 supernumerary teeth) (Fig. 1); the 4 wisdom teeth showed normal development according to the age of the patient; 3.3 had a normally developed root, but was blocked in eruption. Coronal morphology of the supernumerary teeth resembled one of a premolar. Both upper lateral permanent incisors (1.2, 2.2) have curved roots, mostly in the apical third.

General examination could lead to the diagnosis of CCD, caused by a "de novo" mutation, considering the normal ascendancy of the patient.

Oral diagnosis was: 4 Black class I amalgam filings (1.6, 2.6, 3.7, 4.7); modified Kennedy class III edentulism on the lower arch; false Kennedy class IV edentulism on the upper arch caused by the 8 impacted teeth; 3.3 blocked in eruption; unstable occlusion; false progenic aspect (by hypoplastic premaxilla) combined with a minor progenic mandible (concluded after analyses of the lateral cephalograph).

The treatment plan was established after space evaluation between the first upper permanent premolars, according to the age of the patient and his economical situation.

The surgical phase of treatment started with exposing the upper impacted permanent teeth, (Fig. 6,7) extraction of the upper lateral permanent incisors and supernumerary teeth. (Fig. 8) The remaining upper permanent teeth (1.3, 1.1, 2.1, 2.3) were then covered by a muco-periosteal flap. (Fig. 9) Six months later, eruption of 1.3, 1.1 and 2.3 is observed, 2.1 is still in submucosal position. (Fig. 10) The incisal edge of 2.1 was electrosurgically exposed. (Fig. 11) One month later the patient is referred to the Department of Paediatric Dentistry and Orthodontics. He attends a fixed orthodontic treatment using Rothomni brackets (slot 0,18 - 5-5 CSHK) - Prof. Florica Glavan, Dr. Cristina Bratu. After fixed orthodontic treatment using straight-wire technique a positive result is obtained. (Fig. 12) The four formerly impacted teeth closed the anterior edentulous area. Final clinical aspect (Fig. 13) is similar to the computer-aided simulation. (Fig. 14)

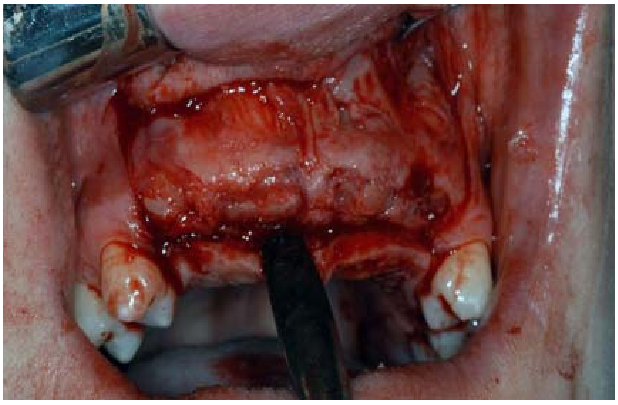

Figure 6. Large vestibular incision.

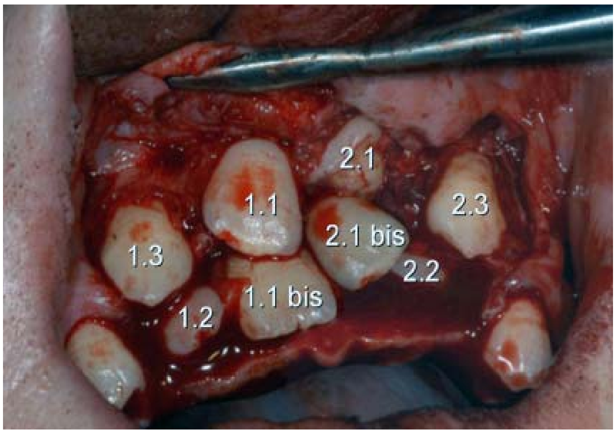

Figure 7. After removal of the covering bone, identification of the impacted teeth is necessary.

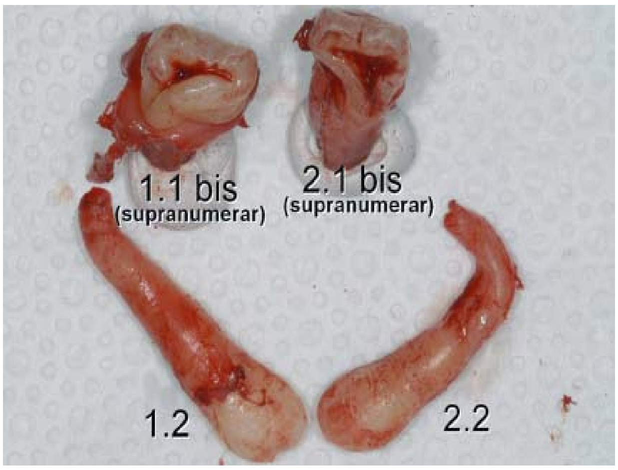

Figure 8. The two supernumerary teeth and the upper lateral incisors after extraction.

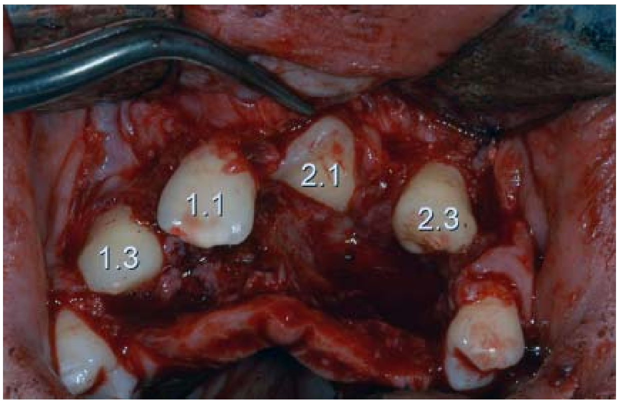

Figure 9. The four remaining teeth were covered with the muco-periosteal flap.

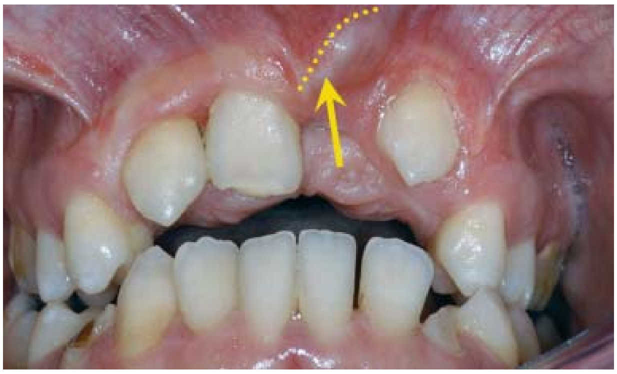

Figure 10. Six months after the surgical phase of treatment 1.1, 1.3, 2.3 are pting, 2.1 is still present under the mucosa.

Figure 11. Incisal edge or 2.1 is electrosurgically exposed.

DISCUSSIONS

CCD was genetically investigated during the last decades. Recently, Mundlos et al. (1997) were the first to discover that the defective RUNX2 (CBFA1) gene is responsible for CCD.[14] Submicroscopic deletions of this gene were shown in CCD families. Other CCD cases show insertions, missense and nonsense mutations.

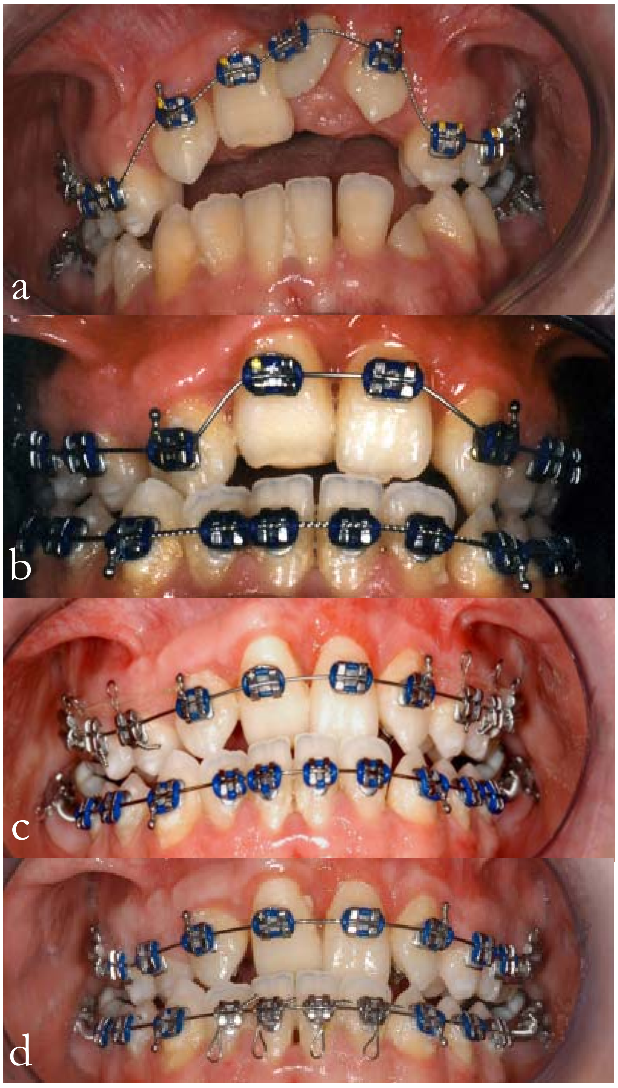

Figure 12. clinical aspects during the fixed orthodontic treatment, straight-wire technique using Rothomni brackets (slot 0,18 - 5-5 CSHK).

Figure 13. Final clinical aspect.

Figure 14. Computer aided simulation of the final result.

Mundlos et al. concluded that heterozygous loss of function was sufficient to produce the characteristic clinical findings of CCD.[13]

In 1999, Quack et al. analyzed the RUNX2 (CBFA1) gene in 42 unrelated patients.[19] In 18 patients, they detected mutations in the coding region, including 8 frameshift, 2 nonsense and 9 missense, as well as 2 novel polymorphisms. A missense mutation identified in a patient with supernumerary teeth and a radiological normal skeleton indicated that certain mutations in the RUNX2 (CBFA1) gene can be associated exclusively with a dental phenotype.

Zhou et al. (1999) studied 26 independent cases of CCD, and a total of 16 new mutations were identified in 17 families.[20] Data collected by Zhou showed that variable loss of function in CBFA1 gene may rise to clinical variability, including classic CCD, mild CCD and isolated primary dental anomalies.

Yoshida et al. (2002) performed mutation analysis of RUNX2 on 24 unrelated patients with CCD.[21] In 17 patients, 16 distinct mutations were detected in the coding region of RUNX2. There was a significant correlation between short stature and the number of supernumerary teeth.

In 2003, Irma Thesleff was the first to determine the connection between loss of function in RUNX2 gene and the possibility to generate the third dentition in humans.[22] Complete malfunctioning of this gene induces lack of all bones and teeth formation but certain anomalies in RUNX2 generates supernumerary teeth.

Zhou describes cases of CCD patients with normal ancestors and relatives.[20] Our case is similar, because for three generations none of his ancestors presented CCD. Pathogenesis of this cases is to be discovered.

Dento-maxillar anomalies in our patient appear only in his anterior maxillary region, the development of the rest of his jaws and teeth was normal.

The only important event in the patient's medical history is the termonuclear accident in Cernobil (26th April 1986). His mother was 4 months pregnant at that time. Development of the permanent incisors, canines, premolars and molars takes place between the 4^{th} and 9^{th} month of the intrauterine life.[23] One cannot say for sure that this event caused CCD in our patient but it rises some questions.

The teamwork that was necessary for dental treatment in this patient is worthy for recognition. The patient has been socially reintegrated in a short period of time, considering his dental anomalies. The most difficult part of the treatment was to radiologically and clinically identify the 8 impacted teeth. It was hard deciding odontectomy of the two impacted upper lateral incisors, but their curved roots could not support orthodontic repositioning.

The big problem of our case is how a patient with a wide frontal edentulous area was treated for simple caries and no questions were raised regarding the lack of the upper anterior permanent teeth.

CONCLUSIONS

1. CCD patients should receive special dental care beginning with childhood because of the dento-maxillar anomalies common in this syndrome.
2. If treated correctly, the final results are remarkable.
3. Teamwork of surgeons, orthodontists and prosthodontists is necessary to obtain a good final result.
4. It is not acceptable that a pacient with such a condition is not forwarded for treatment until the age of 17, when the therapeutic costs are much higher. Paedriatic dental assistance in our country is unsatisfactory.

REFERENCES

1. The GAPS (Genetic Information and Patient Services, Inc.) Index – Cleidocranial Dysplasia. Internet: http://www.icomm.ca/geneinfo/cleidocran.htm
2. Karsenty G. Minireview: transcriptional control of osteoblast differentiation. Endocrinology 2001;42:2731-3.
3. Gorlin RJ, Pindborg JJ, Cohen MM. Syndromes of the head and neck. New York: Blackstone, 1976.
4. Terry RJ. Rudimentary clavicles and other abnormalities of the skeleton of a white woman. J Anat Physiol 1899;33:413-22.
5. Hultkranz JW. Über Dysostosis cleidocranialis. Z Morphol Anthropol 1908;11:385-528.
6. Fleischer-Peters A. Zur Pathohistologie des alveolarknochens bei dysostosis cleidocranialis. Stoma (Heidelberg) 1970;23:212-5.
7. Schuch P, Fleischer-Peters A. Zur klinik der dysostosis cleidocranialis. Z Kinderheilkd 1967;98:107-32.
8. Goodman RM, Tadmor R, Zaritsky A et al. Evidence for an autosomal recessive form of cleidocranial dysostosis. Clin Genet 1975;8:20-9.
9. Brueton LA, Reeve A, Ellis R et al. Apparent cleidocranial dysplasia associated with abnormalities of 8q22 in three individuals. Am J Med Genet 1992;43:612-8.
10. Nienhaus H, Mau U, Zang KD et al. Pericentric inversion of chromosome 6 in a patient with cleidocranial dysplasia. Am J Med Genet 1993;46:630-1.
11. Feldman GJ, Robin NH, Brueton LA et al. A gene for cleidocranial dysplasia maps to the short arm of chromosome 6. Am J Hum Genet 1995;56:938-43.
12. Mundlos S. Cleidocranial dysplasia: clinical and molecular genetics. J Med Genet 1999;36:177-82.
13. Mundlos S, Mulliken JB, Abramson DL et al. Genetic mapping of cleidocranial dysplasia and evidence of a microdeletion in one family. Hum Molec Genet 1995;4:71-5.
14. Mundlos S, Otto F, Mundlos C et al. Mutations involving the transcription factor CBFA1 cause cleidocranial dysplasia. Cell 1997;89:773-9.

15. Cooper SC, Flaitz CM, Johnston DA et al. A natural history of cleidocranial dysplasia. Am J Med Genet 2001;104:1-6.
16. Morava E, Karteszi J, Weisenbach J et al. Cleidocranial dysplasia with decreased bone density and biochemical findings of hypophosphatasia. Europ J Pediat 2002;161:619-22.
17. Cogulu O, Munanoglu D, Karaca E et al. Cleidocranial dysplasia with new additional findings. Genet Counsel 2004;15:229-31.
18. Winter GR. Dental conditions in cleidocranial dysostosis. Am J Orthod 1943;29:61-89.
19. Quack I, Vonderstrass B, Stock M et al. Mutation analysis of core binding factor A1 in patients with cleidocranial dysplasia. Am J Hum Genet 1999;65: 1268-78.
20. Zhou G, Chen Y, Zhou L et al. CBFA1 mutation analysis and functional correlation with phenotypic variability in cleidocranial dysplasia. Hum Molec Genet 1999;8:2311-6.
21. Yoshida T, Kanegane H, Osato M et al. Functional analysis of RUNX2 mutations in Japanese patients with cleidocranial dysplasia demonstrates novel genotype-phenotype correlations. Am J Hum Genet 2002;71:724-38.
22. Thesleff I, Mikkola M. The role of growth factors in tooth development. Int Rev Cytol 2002;217:93-135.
23. Rominu M, Bratu D, Uram-Tuculescu S et al. Aparatul dento-maxilar. Date de morfologie functionala clinica. Timisoara: Helicon, 1997.