European Review for Medical and Pharmacological Sciences 2020; 24: 8281-8287

Audiological evaluation of patients with cleidocranial dysplasia (CCD)

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Abstract. – OBJECTIVE: The description of clinical manifestation of hearing problems in cleidocranial dysplasia (CCD) remains limited and incomplete, since CCD constitutes a rare congenital disorder. The study aims to provide a complex panel analysis of the auditory system in patients suffering from the disease.

PATIENTS AND METHODS: The study group consisted of 4 children with CCD (aged: 12-15), who underwent orthodontic treatment. A full panel analysis of their auditory systems was performed, including high-frequency audiometry and a new method of middle ear assessment – WBT (Wideband Tympanometry).

RESULTS: A slight conductive hearing loss was diagnosed in 3 out of 4 patients. While high frequency audiometry has shown a deterioration of hearing in 3 patients, in one case, the obtained thresholds were within the normal range. A decrease of absorbance in low frequencies has been observed in one or both ears. Only one patient has had a shift of maximum absorbance towards high frequencies in the left ear.

CONCLUSIONS: The presented manuscript is the first with a complete evaluation of the auditory system comprising 4 cases of children in a similar age group. All of the examined patients presented an air-bone gap indicating conductive disorders.

Key Words:
Cleidocranial dysplasia, Hearing, Children, Genetic disease, Hearing loss.

Introduction

Cleidocranial dysplasia (CCD) constitutes a rare genetic disease which consists in an autosomal-dominant inheritance. The mutation responsible for the condition is located on the 6th chromosome, in the RUNX2 (CBFA1) gene, involved in the development of osseous structures[1]. The most common symptoms of cleidocranial dysplasia include low stature, with the average height in males fluctuating between 156.6 cm to 168.8 cm, and between 144.6 cm to 148.5 cm in women. Additionally, the disease entails facial dysmorphia, as well as unilateral or bilateral complete, or partial aplasia of clavicles[2]. Furthermore, the patient's face appears to be small, since both the maxilla and the zygomatic bone are hypoplastic, while the nose is broad, with an indented base. On the other hand, the skull is large, with broad sutures and large, occasionally incompletely fused fontanels[2,3].

Additionally, other osseous defects may be present, such as clawed hip joints, deviation of the vertebral column, scapular hypoplasia, abnormal number of ribs etc.[2,4]. In terms of the oral cavity, it usually shows a high palate and a small maxilla, whereas the teeth exhibit an abnormal anatomical structure, and are supernumerary[2,5,6].

The clinical symptoms of CCD are generally well-known, and include the standard pathognomonic triad-aplasia, or hypoplasia of the clavicles, multiple retained teeth, and delayed closure of fontanels. However, hearing loss remains a defect which tends to be insufficiently diagnosed and to which little attention has been given in scientific reports[3]. Nevertheless, the existing literature suggests that hearing impairment may be the first symptom of CCD[4,5], which makes it particularly important to uncover any instances of hearing loss in children at school age, in order to ensure their proper psycho-social development.

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Patients with CCD present an elevated risk of hypoacusis (38%)[3]. Auditory system disorders may involve structural, or functional lesions within the temporal bone, resulting in abnormalities in the outer and middle ear, dysfunction in the Eustachian tube[4], as well as cochlea and auditory nerve dysfunctions[5]. The Eustachian tube disorders and narrow auditory canals frequently lead to recurring infections and inflammations of the middle ear, with as many as 62% of patients with CCD suffering from acute, or chronic otitis media[3]. Additionally, deformations of the auditory ossicles are observed causing mobility disorders. The most frequently manifested symptoms comprise a progressive bilateral conductive, or mixed hearing loss, commonly affecting lower frequencies[4]. Unfortunately, our current knowledge of hearing impairment in CCD patients is based mostly on case reports, or limited case series[7-9]. In fact, up to date, only one international study has been conducted including patients from the USA, Canada, and Australia which has indicated the need for hearing assessment since birth to childhood.

The present study provides a full panel hearing system assessment of patients with CCD in an active phase of orthodontic treatment, who undergo comprehensive audiological examinations, including both objective and subjective tests. The diagnosis additionally comprises Wideband Tympanometry.

Patients and Methods

4 children diagnosed with CCD participated in the study, i.e., 3 girls and 1 boy, aged 12-15 years (average age: 13 years and 2 months). 2 of the girls were 12 and one was 15 years old, whereas the boy was 14 years of age. All the patients were in an active phase of orthodontic treatment. Clinical manifestations observed in the presented cases are compared with Gorlin's Syndromes of the Head and Neck in Table I[10].

Hearing Evaluation

The complete audiometric evaluation consisted of subjective tests based on the patient's respons-

Table I. Clinical manifestations observed in the 4 presented cases as compared to ones listed in Gorlin's Syndromes of the Head and Neck[10].

Gorlin's Syndromes of the Head and Neck	Patient 1 Female 12 y.o.	Patient 2 Female 15 y.o.	Patient 3 Female 12 y.o.	Patient 4 Male 14 y.o.
Height (cm)	+ 135	+ 152	+ 128	+ 140
Weight (kg)	+ 30	+ 41	+ 24	+ 42
Brachycephalic skull	+	+	+	+
Glabellar groove	+	+	+	-
Frontal and parietal bossing	+	-	+	-
Broad nasal base	+	-	+	+
Hypertelorism	+	-	+	+
Long neck	+	+	+	+
Narrow shoulders	+	+	+	+
Delayed closure of fontanels	+	+	+	+
Thick supraorbital portion of the frontal bone	+	+	+	-
Short sagittal diameter of the cranial base	+	-	-	-
Increased mandibular length	+	+	+	+
Maxilla short vertically	+	-	-	+
Hypoplastic maxilla with underdevelopment of premaxilla	+	+	+	+
High palate	+	+	+	+
Normal development of deciduous dentition	+	+	+	+
Multiple supernumerary permanent teeth	+	+	+	+
Malposed permanent teeth germs	+	+	+	+
Delayed dental age	+	+	+	+
Underdeveloped paranasal sinuses	+	+	+	+
Aplasia or hypoplasia of clavicles	+	+	+	+
Brachydactylia	+	-	-	+
Defects of vertebrae	-	-	+	-
Normal mental development	+	+	+	+
Other skeletal and congenital defects	+	-	+	+

es, and objective electrophysiological tests. The electrophysiological audiometric tests were based on responses recorded for each of the levels of the auditory pathway, whereas subjective audiometry provided supplementary information regarding auditory perception, including the sound processing centers in the brain. The test set was constructed on the basis of Jerger's Cross-Modality Matching Method, since the application of the cross-check principle method stipulates taking into account the results of both objective and subjective clinical examinations.

The clinical interview included a medical interview related to hearing problems, otolaryngologic consultations, as well as recognizing previous problems with communication or education. Before conducting all the tests, the patient underwent otoscopic examination for establishing the patency of external auditory meatus and for a tympanic membrane evaluation.

We performed the otoscopic examination of the external auditory canal and tympanic membrane with Heine 300 otoscope (HEINE Optotechnik, Herrsching, Germany), and Inventis Delfino video-otoscope (Inventis, Padua, Italy). Next, audiometric hearing threshold levels were determined, which included both standard pure tone audiometry and high-frequency tests. Air conduction thresholds were tested for the range of frequencies from 125 to 16000 Hz, and bone conduction thresholds for the range of frequencies from 250 to 4000 Hz. Thresholds of air and bone conduction were tested using the ascending 2/3 method. Madsen Astera 2 clinical audiometer (Otometrics, Taastrup, Denmark), TDH39, and HDA 300 headphones, as well as a bone vibrator B71 were used.

The objective evaluations included distortion product of otoacoustic emissions (DPOAE) tests, performed by means of Madsen Capella 2 (Otometrics, Taastrup, Denmark). Classic tympanometry with a probe frequency of 226 Hz was performed using Madsen Zodiac 901 clinical tympanometer (Otometrics, Taastrup, Denmark), and the wideband tympanometry (WBT) was performed with the Titan Interacoustics Wideband Tympanometer (Interacoustics, Middelfart, Denmark). Auditory brainstem response (ABR) test with a 2-4 kHz click stimulus was performed by means of ABR ICS Charter EP 200, (Otometrics, Taastrup, Denmark). For the purpose of the study, insert earphones were used.

The performed tests allowed for a comprehensive assessment of the patients' hearing: the degree and the type of hearing loss, the function of the cochlea, as well as the middle ear. Wideband tympanometry made it possible to identify slight abnormalities in the tympanic cavity, as it involves a frequency range of 226-8000 Hz and a broadband stimulus (a click). Due to such a broad range of frequencies, this method of measurement is more accurate than the classic tympanometry, and remains independent of outer disturbances, such as noise or patient movements. In the case of tests involving children, this property is critical[11]. In addition, the equipment allowed for absorbance measurement, which determines the value of acoustic energy absorbed by structures within the middle ear, as well as the resonance frequency of the middle ear. The method gives information regarding the frequency at which the mass and rigidity of the auditory ossicles exert the same effect on the admittance value of the middle ear, thus, facilitating an evaluation of abnormalities in the chain of auditory ossicles[11,12]. Moreover, a broadband tympanometer was also used to examine reflexes from the stapedius muscle, as well as the involuntary defensive reflex of the hearing organ, protecting the basilar membrane of the labyrinth from loud sounds.

Ethical Aspect

The study was reviewed and approved by the Institutional Ethics Committee (consent of Bioethics Committee at Poznań University of Medical Sciences Poznań No. 645/16). All procedures performed in the study were performed under the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration with its later amendments, or comparable ethical standards.

Results

The medical interview allowed to establish that patients 3 and 4 suffered from multiple otitis media. Since the 4th year of age, both ears of patient 4 were subject to drainage. Between the age of 6 and 8, patient 4 would wear hearing aids due to exudative otitis media linked to hypoacusis (the threshold of hearing in the right ear amounted to 70 dB_{HL}). Drainage was repeated after 2 years following a fitting of hearing aids, after which Patient 4 ceased to use hearing aids. The later drainages had been applied 2 years before current audiological tests. There were no contraindications to conduct audiological tests on patients

1, 2, and 3. Otoscopic examination of patient 4 demonstrated occlusion of the drain and an exudate deposited in the left middle ear. The patient was referred for further laryngological treatment.

Pure Tone Audiometry

The average hearing thresholds measured using pure tone audiometry and calculated according to the World Health Organization 1997 standards show normal values. The result of the audiometric test for patient 1 was 25 dB HL for the right ear, and 10 dB HL for the left ear. The hearing threshold for patient 2 for both ears was the same, and it was estimated at 15 dB HL. For patient 3, it was 25 dB HL. Only the hearing threshold for the left ear in patient 4 slightly deviated from normal, as it amounted to 35 dB HL, whereas in the right ear it was 20 dB HL. All of the examined children had an air-bone gap, which indicates conductive disorders. High frequencies audiometry (8000 to 16000 Hz) showed a deterioration of hearing in 3 patients (patients 1, 2, and 3).

Tympanometry

A reduced eardrum compliance was noticed in all female patients. The impedance audiometry for patients 1 and 2 showed a small decrease of eardrum mobility in both ears, with the tympanometric curves classified as Type A. The tympanograms of patient 3 were classified as Type B for both ears. Reduced compliance of the tympanic membrane in the left ear was observed for all patients. Ear drainage in patient 4 prevented the performance of a tympanometry test. Therefore, only an absorbance test (without pressure change) was conducted on both ears. Each patient manifested conductive disorders. In case of two patients, it was impossible to register tympanic muscle reflexes for all stimuli. However, in the right ear of patient 1 it was observed for all frequencies, whereas in the left ear of patient 3 it was detected for 500 Hz and 2 000 Hz. A decrease of absorbance for low frequencies was presented in one (patients 1 and 2) or both ears (patient 3). In view of the data above, such results can be associated with otosclerosis. Results of patient 4 obtained for the right ear were consistent with the normal value for the age of 11-16 years. However, a shift of absorbance maximum toward lower frequencies was noted. In the left ear, very low values of absorbance (between 5% and 25%) were observed in the 250 Hz-4000 Hz frequency range. Furthermore, the peak of absorbance was found within a high-frequency range (Figure 1).

Otoemission

Results of DPOAE otoemission for both ears are presented in Table II. Otoemission of patient 1 in the right ear was not recorded for the entire range of frequencies, while in the left ear, it was recorded only for the frequency range of 1000 Hz to 4000 Hz. Nevertheless, these results are consistent with the results obtained in the course of the audiometric examination. From 4000 Hz to 8000 Hz frequency range, DPOAE was not recorded. In this range, hearing levels in pure tone audiometry varied between 40 dB_{HL} to 70 dB_{HL}. The results of patient 2 in terms of DPOAE were

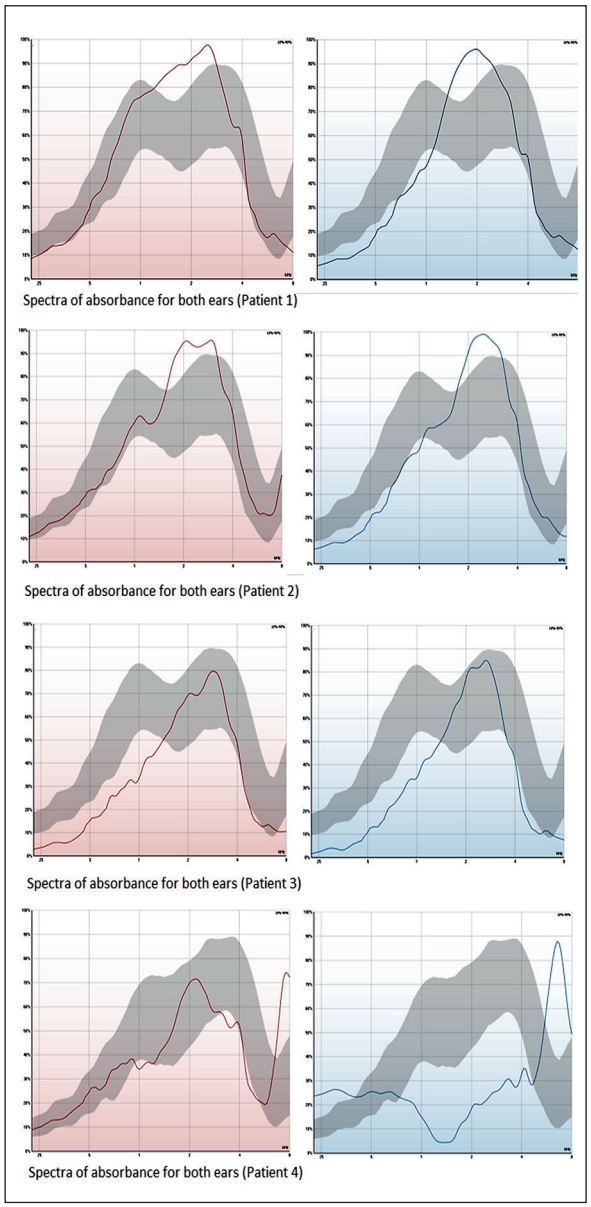

Figure 1. Spectra of absorbance for both ears.

Table II. DPOAE results.

Frequency [Hz]	Patient 1		Patient 2		Patient 3	
	Right	Left	Right	Left	Right	Left
996 +	-	+	+	+	-	
1191 -	+	-	+	+	-	
1416 +	-	+	+	-	-	
1679 -	+	+	+	-	-	
2001 -	+	+	+	-	-	
2382 -	+	+	+	-	+	
2832 -	+	+	+	+	+	
3359 -	+	+	+	+	-	
4003 -	+	+	+	+	-	
4755 -	-	+	+	-	+	
5654 -	-	+	+	+	-	
6728 -	+	+	+	-	+	
7998 +	-	+	+	-	+	
+ Accepted; - Rejected						

normal. Patient 3 DPOAEs were recorded in the left ear only for high frequencies (above 2000 Hz), and in the right ear selectively for both low and high frequencies.

ABR

The results of pure tone audiometry confirm auditory brainstem evoked potentials tests. Elongated latency of wave V is typical for the conductive hearing loss. Elongation was recorded for one ear (patient 4), or for both ears (patients 1 and 3). Only the results of patient 2 demonstrated normal hearing.

Discussion

The patients presented in this study were diagnosed with a mild to moderate conductive or mixed hearing loss. The air-bone gap indicates that conductive disorders were found for all patients; furthermore, objective tests additionally confirmed conductive disorders. Elongated latency in ABR, reduced compliance of tympanic membrane, and abnormal absorbance in tympanometry were also found.

A review of CCD case reports from the last seven years identified five cases providing information about the hearing of a child affected by CCD. In the case described by Candamourty et al[7], a 12-year-old girl's hearing was examined using pure tone audiometry, as a result of which conductive hearing loss in the right ear was diagnosed. However, no information regarding the degree of hearing loss was available. In another case study, the hearing of 13-year-old twin boys was found to be normal[13]. Nevertheless, there was no information regarding the testing methods. The case description presented by Butnariu et al[14] highlighted the increased risk of acute middle ear infection in a CCD patient. The only two detailed case reports presented by Matthews-Brzozowska et al[8] and by Turska-Malinska et al[9] described two girls, aged 12 and 15 diagnosed with conductive hearing loss. The diagnosis was made on the basis of both subjective and objective tests, such as pure tone audiometry, ABR, tympanometry, as well as otoemission.

Scientific papers regarding CCD published in the last years did not contain information about the patients' hearing condition. The following case studies did not present the analysis of hearing condition: Broeks et al[15] – a 12-year-old girl; Nagarathna et al[16] – a 15-year-old girl; Vij et al[17] – a 15-year-old boy; Kolokitha et al[18] – a 13-year-old boy; Park et al[19] – a 12-year-old boy; Martins et al[20] – a 7-year-old boy and a 4-year-old girl; Bechtold et al[21] – a 9-year-old boy; Singhal et al[22] – a 10-year-old boy; Zhang et al[23] – a 16-year-old girl; a 15-year-old boy and a 10-year-old boy; Lewandowski et al[24] – a 12-year-old boy; Bharti et al[25] – 10 and 14 years old boys; Morikava et al[26] – a 11-year-old boy; Medina et al[27] – a 3-year-old boy; and Zhu et al[28] – a 16-year-old girl.

The medical interview demonstrated frequent infections and inflammatory conditions in the middle ear in 2 out of 4 patients. Some studies[29,30] have indicated that patients with CCD may be prone to acute or chronic otitis media, which is consistent with our observations.

Hearing disorders in CCD patients may develop not only due to structural, or functional lesions in the temporal bone, but also due to auditory tube dysfunction, as well as may be induced by the improper shape of the palate, narrowed auditory canals, or abnormalities associated with the formation of the auditory ossicles chain[12,31]. Literature data[31,32] also demonstrate progressive conductive hearing loss. In fact, 3 out of 4 examined patients manifested slight conductive hearing loss. Additionally, we have registered the air-bone gap in all audiograms, which is consistent with prior findings[17,18,29]. It is worth noting that in patients 1 and 4 the hearing thresholds for frequencies below 1000 Hz reach border values for normal hearing. In the CCD study conducted by Gonzalez et al[5] the patient manifested a progressive hearing loss within low frequencies, which is consistent with our observations. Therefore, due to the risk of future hypoacusis development, it is worth continuing the monitoring of the patients' hearing condition. High-frequency audiometry showed a deterioration of hearing in three patients. The results of one patient were consistent with the normal thresholds obtained in the normative group by Gierek[33]. Even though literature indicates an elevated risk of sensorineural hearing loss occurrence, no signs of it were observed, except for hearing deterioration for higher frequencies[5].

Tympanometric curves may indicate otosclerosis, and may suggest the auditory ossicles malformations, which are likely to occur in the skeletal defect syndrome in CCD patients[4]. A decrease of absorbance for low frequencies was observed in 3 out of 4 patients (patients 1, 2, and 3), which can also be associated with otosclerosis. The curve of absorbance recorded for the right ear of patient 4, with a shift of maximum toward lower frequencies, resembled in shape the curves recorded in patients with the tympanic membrane perforation. The absorbance curve determined for the left ear of patient 4 is consistent with the curves recorded in the presence of fluid in the tympanic cavity[11,12].

Patients with CCD should be covered by a medical care from an early age and both diagnosis, as well as therapy should be conducted by collaborating units specializing in stomatology, audiology, radiology, surgery, and orthodontics. The cooperation between professionals may result in a more effective rehabilitation process. The patients included in the current study were under regular orthodontic care and therapy.

Conclusions

The present study is the first with a full diagnosis of the auditory system on a group of four young patients of a similar age. All examined children presented an air-bone gap indicating conductive disorders. Furthermore, we also observed a decrease of absorbance for low frequencies in 3 out of 4 patients, indicating abnormal mobility of the ossicles. Additionally, evidence suggests that with age, progressive hearing loss may occur in the low-frequency range as well. No sensorineural hearing loss was observed in any of the presented cases.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Lewandowski B, Martula-Gala K, Brodowski R. Multiple, supernumerary retained teeth in the course of cleido-cranial dysplasia. A case report. Dev Period Med 2015; 19: 503-507.
2) Szczepkowska A, Osica P, Janas-Naze A. Aspekt chirurgiczny opieki nad pacjentem z dysplazją obojczykowo-czaszkową – opis przypadku (in Polish). J Educ Health Sport 2016; 6: 355-363.
3) Segal N, Puterman M. Cleidocranialdysplasia--review with anemphasis on otological and audiological manifestations. Int J Pediatr Otorhinolaryngol 2007; 71: 523-526.
4) Segal N, Moshe P. Cleidocranial dysplasia--review with an emphasis on otological and audiological manifestations. Int J Pediatr Otorhinolaryngol 2007; 71: 523-526.
5) Gonzalez GE, Caruso PA, Small JE, Jyung RW, Troulis MJ, Curtin HD. Craniofacial and temporal bone CT findings in cleidocranial dysplasia. Pediatr Radiol 2008; 38: 892-897.
6) Cooper SC, Flaitz CM, Johnston DA, Lee B, Hecht JT. A natural history of cleidocranial dysplasia. Am J Med Genet A 2001; 104: 1-6.
7) Candamourty R, Venkatachalam S, Yuvaraj V, Kumar GS. Cleidocranial dysplasia with hearing loss. J Nat Sci Biol Med 2013; 4: 245-249.
8) Matthews-Brzozowska T, Hojan-Jezierska D, Loba W, Worona M, Matthews-Brzozowski A. Cleidocranial dysplasia-dental disorder treatment and audiology diagnosis. Open Med J 2018; 13: 1-8.
9) Turska-Malinska R, Matthews-Brzozowska T, Hojan-Jezierska D, Komar D. Audiological diagnostics and treatment of craniofacial abnormalities in cleidocranial dysplasia CCD. J Interdiscipl Med Dent Sci 2017; 5: 2.

10) Hennekam RCM, Krantz ID, Allanson JE. Gorlin's syndromes of the head and neck. Oxford University Press, 2010.

11) Voss SE, Merchant GR, Horton NJ. Effects of middle-ear disorders on power reflectance measured in cadaveric ear canals. Ear Hear 2012; 33: 195-208.

12) Nakajima, HH, Rosowski JJ, Shahnaz N, Voss SE. Assessment of ear disorders using power reflectance. Ear Hear 2013; 34: 48-53.

13) Wang J, Xinwen H, Lai C, Jiang K. Clinical spectrum of cleidocranial dysplasia in a family with twins. Pediatr Int 2013; 392-395.

14) Butnariu LI, Rusu C, Pânzaru M, Caba L, Popescu R, Gorduza EV. Cleidocranial dysplasia: a case report. Rom J Funct Clin, Macro Microsc Anat Anthropol 2017; 16: 163-167.

15) Broeks I, Veenstra-Knol IE, Kamps AW. A rare presentation of cleidocranial dysplasia. Case Reports 2012; 2012: bcr0320126101.

16) Nagarathna C, Bethur SS, Somy M, Krishnamurthy NH, Yumkham R. Cleidocranial dysplasia presenting with retained deciduous teeth in a 15-year-old girl: a case report. J Med Case Rep 2012, 6.

17) Vij R, Batra P, Vij H. Cleidocranial dysplasia: complete clinical, radiological and histological profiles. Case Reports 2013; 2013: bcr2013009015.

18) Kolokitha OE, Ioannidou I. A 13-year-old Caucasian boy with cleidocranial dysplasia: case report. BMC Res Not 2013; 6.

19) Park TKN, Vargervik K, Oberoi S. Orthodontic and surgical management of cleidocranial dysplasia. Korean J Orthod 2013; 43: 248-260.

20) Martins RB, de Souza RS, Giovani EM. Cleidocranial dysplasia: report of six clinical cases. Spec Care Dentist 2014; 34: 144-150.

21) Bechtold TE, Lee KJ, Park YC, Berneburg M, Goz GR. A Simultaneous mobilization of four impacted upper incisors in a case of an adolescent patient with cleidocranial dysplasia (CCD). Dentistry 2014; 4: 1-8.

22) Singhal P, Singhal A, Jayam C, Bandlapalli A. Cleidocranial dysplasia syndrome (CCD) with an unusual finding in a young patient. Case Reports 2015; 2015: bcr201521051

23) Zhang CY, Si Y, Wang XZ, Sun XY, Yan WJ, Zheng SG. Early dental treatments for patients with cleidocranial dysplasia. Chin J Dent Res 2015; 18: 51-57.

24) Lewandowski B, Martula-Gala K, Brodowski R, Zych B. Multiple, Supernumerary retained teeth in the course of cleido-cranial dysplasia. A Case Report. Dev Period Med 2015; 19: 503-507.

25) Bharti K, Goswami M. Cleidocranial dysplasia: a report of 2 cases with brief review. Intractable Rare Dis Res 2016; 5: 117-120.

26) Morikava FS, Scariot R, Morisini IAC. Cleidocranial dysplasia: diagnostic, surgical and orthodonic planning and interventions in a pediatric patient. Int J Odontostomatol 2016; 10: 325-331.

27) Medina O, Muñoz N, Moneriz C. Cleidocranial dysplasia: a case report. Rev Chil Pediatr 2017; 88: 517-523.

28) Zhu Y, Zou Y, Yu Q, Sun H, Mou S, Xu S, Zhu M. Combined surgical-orthodontic treatment of patients with cleidocranial dysplasia: case report and review of the literature. Orphanet J Rare Dis 2018; 13: 217.

29) Pawlowska E, Wójcik KA, Synowiec E, SzczepaÐska J, Błasiak J. Expression of RUNX2 and its signaling partners TCF7, FGFR1/2 in cleidocranial dysplasia. Acta Biochim Pol 2015; 62: 123-126.

30) Shibata A, Machida J, Yamaguchi S, Kimura M, Tatematsu T, Miyachi H, Matsushita M, Kitoh H, Ishiguro N, Nakayama A, Higashi Y, Shimozato K, Tokita Y. Characterisation of novel RUNX2 mutation with alanine tract expansion from Japanese cleidocranial dysplasia patient. Mutagenesis 2016; 31: 61-67.

31) Visosky AMB, Johnson J, Bingea B, Gurney T, Lalwani AK. Otolaryngological Manifestations of cleidocranial dysplasia, concentrating on audiological findings. Laryngoscope 2003; 113: 1508-1514.

32) Cimen E, Dereci Ö, Tüzüner-Öncül AM, YazicioÐlu D, Özdiler E, ÐenoL A, Sayan NB. Combined surgical-orthodontic rehabilitation of cleidocranial dysplasia: 5 years follow-up. World J Clin Cases 2015; 3: 751-756.

33) Gierek T. Ocena wydolności narządu słuchu dla zakresów częstotliwości od 250 Hz – 20 kHz w procesie starzenia się organizmu człowieka. Otolaryngol Pol 1979; 33: 95-104.