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MALOCCLUSIONS AND CRANIOFACIAL ANOMALIES IN A CHILD WITH VELO-CARDIO-FACIAL SYNDROME

ZABURZENIA ZGRYZU I ZMIANY WYSTĘPUJĄCE W OBRĘBIE CZĘŚCI TWARZOWEJ CZASZKI U DZIECKA Z ZESPOŁEM PODNIEBIENNO-SERCOWO-TWARZOWYM

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Abstract
Velo-Cardio-Facial syndrome (VCFS), also called 22q11.2 microdeletion syndrome, is a rare pathology. The syndrome is caused by 22q11.2 deletion, recognized as one of the most frequent pathogenic human microdeletions. The scope and severity of the phenotypic expression of 22q11.2 microdeletion is characterised by high variability, although cleft palate and congenital conotruncal malformations are among the clinical features often associated with that syndrome. In the presented case of a boy patient with submucous cleft palate and congenital cardiac defect, 22q11.2 microdeletion was identified at the age of 13 months. In the presented paper particular emphasis was placed on the issue of dental and orthodontic care in patients with changes in the oral cavity and the craniofacial area, as well as on the possibilities of treatment and prophylaxis. The necessity to perform a thorough examination of the oral cavity in infants was also underlined as a vital element of clinical assessment, in particular in the case of co-occurring structural defects of internal organs.

Key words: velo-cardio-facial syndrome, 22q11.2 microdeletion, cleft palate

Streszczenie
Zespół podniebienno-sercowo-twarzowy (Velo-Cardio-Facial Syndrome – VCFS), zwany również zespołem mikrodelecji 22q11.2, jest rzadko występującą jednostką chorobową. Przyczyną zespołu jest delecja 22q11.2, zaliczana do jednej z najczęściej występujących patogennych mikrodelcji u człowieka. Stopień ekspresji fenotypowej mikrodelecji 22q11.2 charakteryzuje się ogromną różnorodnością, aczkolwiek rozszczep podniebienia oraz wady wrodzone stożka naczyniowego serca należą do cech klinicznych często występujących w tym zespole. W przedstawionym przypadku obecność mikrodelecji 22q11.2 stwierdzono u 13-miesięcznego chłopca z podśluzówkowym rozszczepem podniebienia oraz wadą serca. W pracy zwrócono szczególną uwagę na aspekt opieki stomatologiczno-ortodontycznej u pacjentów ze zmianami w obrębie jamy ustnej i części twarzowej czaszki oraz na możliwości ich leczenia. Wskazano również na konieczność bardzo dokładnego badania jamy ustnej u wszystkich noworodków jako istotnego elementu oceny klinicznej, w szczególności w przypadku współistnienia wad strukturalnych narządów wewnętrznych.

Słowa kluczowe: zespół podniebienno-sercowo-twarzowy, mikrodelecja 22q11.2, rozszczep podniebienia

INTRODUCTION

Velo-Cardio-Facial syndrome (VCFS), also called Shprintzen syndrome (OMIM:192430), which was first described in 1981, is one of the most common human congenital multiple malformation syndromes with cleft palate in the clinical presentation [1]. The prevalence of the syndrome is estimated at 1 in 2000 – 1 in 4000 live births. The actual incidence is likely to be higher as in some of the patients the diagnosis of the syndrome is missed due to the incomplete expression of VCFS clinical traits. The inheritance pattern is autosomal dominant and the syndrome is caused by the interstitial deletion of 1.5-3 Mb at the q11.2 region of the long arm of the the chromosome 22 and resulting lack or abnormal function of 40 genes located in that region [2, 3]. 22q11.2 microdeletion syndrome is a specific "umbrella" term for a number of diseases with a very similar spectrum of clinical symptoms, hence multiple names have been given to that molecular defect in medical terminology. Historically, apart from Shprintzen syndrome/VCFS, the expression spectrum of 22q11.2 microdeletion also includes CATCH22 syndrome (the no longer used acronym listing the symptoms: **C**ardiac defects, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, **H**ypocalcemia from parathyroid aplasia, microdeletion of chromosome **22**), as well as DiGeorge syndrome (OMIM 188400), Takao syndrome, Sedlackova syndrome and Conotruncal face syndrome [3, 4, 5].

Most patients have a typical deletion of 3Mb, whereas only ca. 7% of the subjects have smaller deletion of 1.5Mb. In other cases the deletion may be even shorter, yet the size of it does not have an impact on the expression of the typical clinical features [6]. Molecular pathogenesis and the role of individual genes from the 22q11.2 deletion have not been fully recognised yet, however, it is known that their inactivity disturbs the early morphogenesis of the branchial arches, throat, heart, blood vessels, skeleton and brain. There is no unanimous opinion on the role of the gene of transcription the *TBX1* factor in expression of VCFS. The outcomes of the studies published by Friedman et al. in 2011, conducted in a group of 360 subjects with VCFS, do not confirm that *the TBX1* gene is the only factor responsible for the occurrence of heart and aortic arch anomalies, as well as cleft palate in humans, which had earlier been indicated by the research animals studies[7].

In view of the latest data published in medical literature, it seems that the dysfunction of the *TBX1* gene caused by its deletion, is subject to a complex regulation by various epigenetic factors, modifying genes and polymorphic changes in other locations in the genome [6]. The fact that in ca. 25% cases of VCFS no structural cardiac defect is observed despite 22q11.2 deletion involving the *TBX1* gene, may confirm that hypothesis.

The complex molecular pathology of VCFS is reflected by a very wide spectrum of symptoms affecting multiple organs and systems. The clinical findings of 22q11.2 microdeletion encompass ca. 180 symptoms, none of which is obligatory in the clinical diagnosis of the syndrome. The phenotypic expression is highly variable in individual subjects, differing from almost asymptomatic or mildly symptomatic to a more comprehensive spectrum of disorder, affecting multiple systems.

In infancy and childhood the following facial features are noticeable: long face, maxillary flatness, hypertelorism, epicanthal folds, "tubular" nose, bulbous nasal tip, small mouth, asymmetrical facial grimace while crying. In adulthood the face is oval, the nose is long with a flattened tip and slight aurical anomalies may be detected. In 74% of the patients cardiac anomalies are identified, especially conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, VSD, truncus arteriosus). Palatal malformations, in particular velopharyngeal incompetence, hypernasal speech, submucosal cleft palate, hard palate cleft, bifid uvula and laryngeal anomalies are observed in ca. 69% of the affected subjects. Additionally, other frequent findings include: feeding problems with nasal regurgitation in the neonatal period, , gastroesophageal reflux, immunological defects (defects of humoral and cellular immunity), recurrent infections of the upper respiratory tract including acute otitis media, endocrinological problems (hypoparathyroidism, hypothyroidism, growth hormone deficiency), urinary tract malformations (renal defects). Enamel hypoplasia and advanced dental caries are also relatively frequent symptoms in childhood. Learning difficulties and problems with forming social bonds are identified in 70%-90% of the affected subjects, whereas symptoms from the autism and ADHD spectrum are observed in ca. 20% of the child patients [3, 8].

A wide and different spectrum of 22q11.2 microdeletion symptoms expression causes the VCFS diagnosis difficult even for experienced dysmorphologists and clinical geneticists. An accurate diagnosis often requires multi-specialist diagnostics including results of genetic tests, which are the basis to verification of the clinical suspicion of VCFS.

Presence of the 22q11.2 microdeletion is detected using the FISH method (Fluorescence In Situ Hybridization), which requires the use of specific molecular probes (e.g. TUPLE1, N25), hybridising with the critical 22q11.2 region. Presently, the MLPA technique (Multiplex Ligation-dependent Probe Amplification) or the aCGH method (array Comparative Genome Hybridisation, also named as "molecular karyotype") are most commonly used as they enable identification of smaller deletions in the 22q11.2 region, which could be missed by FISH method. It should be underlined, that the result of routine karyotyping is correct in the majority of 22q11.2DS cases, including VCFS. Structural chromosomal aberrations (translocations) in the 22q11.2 region detectable by means of routine karyotyping are extremely rare (<1% cases) [8].

An interstitial deletion at q11.2 band of the long arm of the 22 chromosome is detected in over 95% subjects with clinical manifestations of VCFS. In ca. 93% the 22q11.2 deletion arises *de novo*, in the remaining 7% it is inherited from one of the parents. Therefore, if the deletion is identified in a child, it is recommended that its origin be analysed and parents tested (expression in parents may be very mild, e.g. it may be limited to nasal speech or psychiatric disorders). Detecting the deletion in one of the parents has serious implications for genetic counselling as the risk of passing on the mutation to offspring of either sex is 50% [8].

To date, there is little information about dental, facial and orthodontic problems of VCFS patients. This paper presents the case of a child with velo-cardio-facial syndrome, with particular focus on the diagnostic and therapeutic procedures applied in the case of craniofacial and oral anomalies.

CASE STUDY

The patient was born in the 39th week of gestation via spontaneous vaginal delivery, after normal pregnancy, weighing 3140g, and received the Apgar score of 9. In the first month of life the following defects were detected: congenital heart anomaly – atrial septal defect II (ASD II), cor triatriatum, anomalous pulmonary venous drainage, hypoplasia of the left ventricle and ventricular insufficiency. Cardiac surgical repair was performed in the 3rd month of life with the use of a patch closure of ASD and rerouting the blood from the right pulmonary veins to the left atrium. The appendix of testis was also removed surgically and the inguinal hernioplasty was performed. During the first months of life feeding problems and underweight were observed. During the visit to a GP practice, a partial cleft of the secondary palate, soft palate and 1/3 of the hard palate was diagnosed. The cleft repair (secondary palate) was performed at the age of 13 months. During the 1st year of life, the child required several hospitalizations due to intestinal obstruction, rotavirus-related diarrhoea and pneumonia.

Genetic tests performed in the 1st year of life with the use of the FISH technique confirmed microdeletion in the 22q11.2 region: nuc ish del (22)(q11.2q11.2)(TUPLE1-). Based on that result, anamnesis and clinical presentation, the diagnosis of VCFS was made. The FISH result in the parents was correct and did not reveal deletion in that region.

Presently, the patient has also been diagnosed with hypothyroidism, frequent infections of the upper respiratory tract, hearing impairment, speech disorders, immune disorders and food allergy (the child has been on a gluten-free and dairy-free diet).

Dental and orthodontic treatment

The heteroanamnesis indicated delayed teething as the 1st tooth, the mandibular central incisor, erupted at the age of 12 months. The patient began treatment in the Paediatric Dental Clinic at the age of 20 months. Rampant caries affecting the erupted deciduous teeth was diagnosed at that time, caused by gastroesophageal reflux and frequent vomiting. Impregnation with 10% silver nitrate and Lugol's solution was commenced and systematically repeated. Subsequently erupting teeth were quickly attacked by dental caries, which was treated by means of impregnation, removal of caries and filling in the cavities with glass ionomoer cement, as well as clearing and rinsing of canals due to *periodontitis chronica purulenta* (tooth 61) and *periodontitis chronica exacerbata* (tooth 73). Erupted permanent teeth were protected with fluoride treatment (Fluor Protector).

When the patient presented at the Clinic of the Maxillofacial Orthopaedics and Orthodontics, the following were identified: drooping mouth corners, hearing impairment, asymmetrical and posteriorly rotated auricles, correct swallowing, nasal breathing, with reduced intelligibility, hypernasal speech, laryngeal hoarseness, enlarged uvula deviating to the left and touching the left palatoglossal arch, enlarged right tonsil. In occlusion, habitual deviation of the mandible to the right by the width of 1.5 mandibular teeth was observed. Correct positioning of the mandible resulted in an open bite. During the examination, the patient was active and eager to play, yet uncooperative. A panoramic radiograph and photographic documentation were prepared (fig. 1-4). No missing tooth buds of permanent teeth were identified. The patient was referred for extraction of tooth 52, 53, 62, 63, 64 and 54 due to orthodontic reasons and the

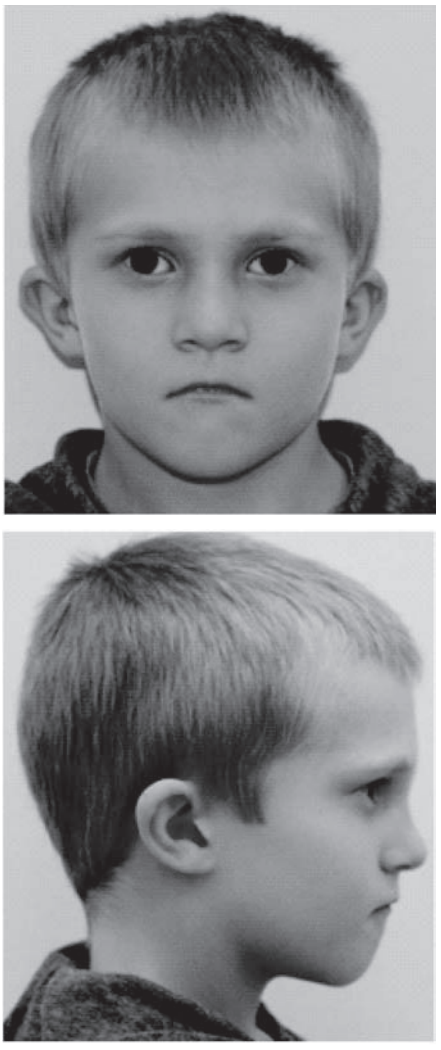

Fig. 1. The phenotype of the patient (R.T.) at the age of 7 Full-face photographic documentation and profile with a characteristic retruded mandible.

Ryc. 1. Fenotyp pacjenta R.T. w wieku 7 lat. Dokumentacja fotograficzna en face i profil z charakterystyczną cofniętą żuchwą.

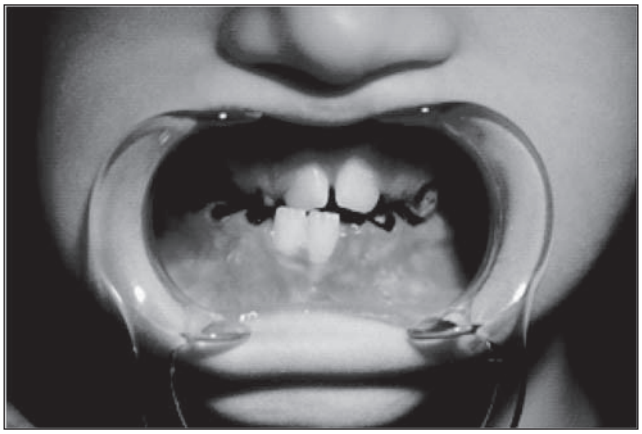

Fig. 2. The mandible deviates to the right by the width of 1 mandibular incisor.

Ryc. 2. Zbaczanie żuchwy w prawą stronę o szerokość około 1 zęba siecznego dolnego.

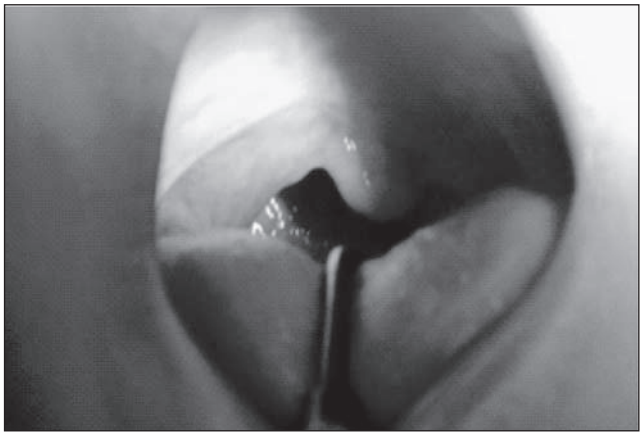

Fig. 3. The uvula deviated to the left and hyperdeveloped right palatoglossal arch.

Ryc. 3. Przesunięcie języczka w lewą stronę oraz przerośnięty prawy łuk podniebienno-językowy.

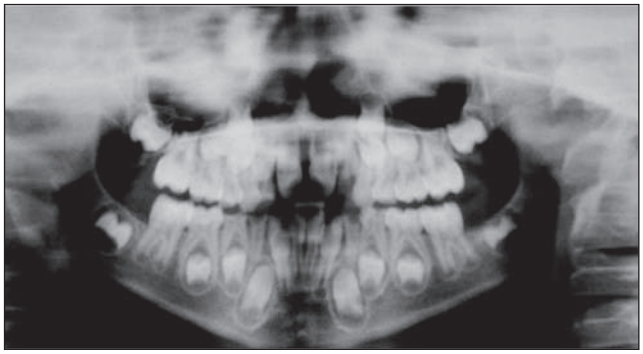

Fig. 4. Panoramic radiograph taken at the age of 7 years. The number of teeth is correct.

Ryc. 4. Zdjęcie pantomograficzne w wieku 7 lat. Liczba zębów prawidłowa.

treatment was commenced. The patient was provided with a functional appliance (trainer) and recommended to wear it at night and for 3-4 hours during the day. After 6 months, the deviation was reduced to the width of 1 mandibular tooth. 8 months after the commencement of the therapy, the patient was referred for further extractions (tooth 72 and 82) as tooth 32 and 42 started to erupt on the lingual side. An occlusal X-ray was taken and the therapy with the trainer was continued. One month later the sanation of the oral cavity was continued and the patient was referred for extraction of tooth 73, 74, 83 and 84.

Prognosis for orthodontic treatment

In cases of severe damage inflicted by caries and no option of conservative treatment, monitored extractions of deciduous teeth are justified prior to the commencement of the orthodontic therapy. They also improve the general health condition of the patient. In view of a shifted midline, arrested maxillary growth, micrognathism, retruded mandible and mesiocclusion, the prognosis for full correction of the occlusal defects is uncertain. A therapy with a fixed appliance for the upper and lower dental arch, upon complete sanation and eruption of the permanent teeth, entails a material risk of early caries, given poor oral hygiene due to the intellectual disability of the patient.

DISCUSSION

Publications providing a detailed account of skeletal and dental anomalies in patients with the VCFS diagnosis are scarce, therefore we find it worthwhile to mention some of them.

The studies on skull morphology conducted by Molsted et al. (2010) based on cephalometric analysis of lateral head radiographs of 33 patients with VCFS, revealed anomalies in the morphology of the sella tursica and increased angular values in the cranial base as compared to the control group [9].

Łuszyńska et al, while describing the laryngological and phoniatric problems in a 10-year-old child with Velo-Cardio-Facial syndrome, also focused on dental and occlusal anomalies: teeth crowding in the maxilla and mandible, partial mesiocclusion [10]. Da Silva Dalben et al. (2008) examined 26 patients with the VCFS and arrived at the conclusion that the main dental malformation was the underdevelopment of the lingual cusp in the first premolars. Anomalies in the teeth number were similar as in the control group, therefore the authors stated that tooth agenesis and supranumerary teeth were not characteristic for subjects with VCFS. A similar conclusion was reached regarding tooth rotation (observed in the case of 12 teeth) and ectopia (3 teeth). The correlation with VCFS was found only in the case of enamel opacity, as it was observed in 68% of the patients. Out of the 26 examined patients, the submucous cleft palate was identified in 11 subjects, cleft soft palate in 3 subjects, partial cleft palate affecting hard palate in 2 subjects, velopharyngeal incompetence without visible anatomical changes in 10 subjects [5].

Other frequent findings include: delayed eruption of deciduous teeth, closed bite, open bite, asymmetry of the perioral muscles during mouth opening, a high number of caries lesions, gingivitis, reduced saliva secretion and buffering capacity [11].

The majority of those traits were identified in the analysed case (tab. I). The first deciduous tooth erupted at the age

of 12 months, which confirms the delayed teething, and shortly after birth a characteristic secondary palate cleft was detected. The patient was also diagnosed with open bite, mandible deviation, lingual location of tooth 31 and 41, velopharyngeal incompetence and multiple caries lesions. No enamel hypoplasia or hypocalcification was observed and the underdevelopment of the lingual cusp in the first premolars cannot be assessed as they have not erupted yet.

In the treatment of congenital craniofacial abnormalities, interdisciplinary therapy is of great importance [12]. This is also the case in the velo-cardio-facial syndrome. Based on the data published in the literature and own

Table I. Clinical findings identified in the patient.

Tabela I. Objawy kliniczne obecne u pacjenta.

Clinical findings ***Objawy kliniczne***	
Congenital cardiac anomalies ***Wrodzone anomalie serca***	Condition after the surgery performed due to the atrial septal defect (ASD II): cor triatriatum; anomalous pulmonary venous drainage; hypoplasia of the left ventricle *Stan po operacji z powodu ubytku międzyprzedsionkowego typu ASD II: serce trójprzedsionkowe; nieprawidłowy spływ żył płucnych; hipoplazja lewej komory serca*
Facial dysmorphy ***Dysmorfia twarzy***	Shape: oval *Kształt: podłużna*
	Eyes: slight hypertelorism *Oczy: nieznaczny hiperteloryzm*
	Ears: hearing impairment; auricles set low and posteriorly rotated *Uszy: niedosłuch; nisko osadzone, zrotowane ku tyłowi małżowiny uszne*
	Nose: flattened nasal tip, wide nasal bridge *Nos: spłaszczony wierzchołek nosa, szeroki grzbiet nosa*
	Mouth: small; thin vermillion; drooping mouth corners *Usta: małe; cienka czerwień wargowa; opadające kąciki ust*
	Mandible: small; retruded; deviated to the right *Żuchwa: mała; cofnięta ku tyłowi; zbaczająca w prawą stronę*
Thymus ***Grasica***	No thymic hypoplasia identified *Nie stwierdzono hipoplazji*
Hypocalcemia ***Hipokalcemia***	No hypocalcemia identified Nie stwierdzono
Genome anomaly ***Zaburzenia genomu***	Deletion 22q11.2 *Delecja 22q11.2*
Oral cavity **Jama ustna**	Palate: cleft affecting soft palate and 1/3 of hard palate, submucous, bilateral; enlarged right palatoglossal arch *Podniebienie: rozszczep podniebienia miękkiego i 1/3 twardego, podśluzówkowy, obustronny; powiększony prawy łuk podniebienno-językowy*
	Uvula: enlarged; deviated to the left; touching the left palatoglossal arch *Języczek: powiększony; zbaczający w lewą stronę; kontaktuje się z lewym łukiem podniebienno-językowym*
	Tonsils: the right tonsil enlarged; the left one normal *Migdałki podniebienne: prawy powiększony; lewy w normie*
Speech ***Mowa***	Velopharyngeal incompetence. Nasal speech, with reduced intelligibility, "laryngeal hoarseness", delayed onset (the first words at the age of 5.5 years) *Niewydolność podniebienno-gardłowa. Mowa nosowa, niewyraźna, „chrypka krtaniowa", opóźniona (pierwsze słowa w wieku 5 i pół roku)*
Thyroid ***Tarczyca***	Hypothyroidism *Niedoczynność*
Immune disorders ***Zaburzenia immunologiczne***	Identified *Obecne*

Table I. Cont.
Tabela I. Cd.

Muscles ***Mięśnie***	Normal; muscular hypotonia in the past *W normie; w przeszłości hipotonia mięśniowa*
Fingers/toes ***Palce rąk/stóp***	Normal *W normie*
Respiratory system ***Układ oddechowy***	Asthma (no symptoms since the age of 3 years) *Astma oskrzelowa (ale brak objawów od 3 r.ż.)*
Height ***Wysokość***	115cm (below the 3rd centile) *115 cm (poniżej 3 centyla)*
Weight ***Masa ciała***	22kg (10th centile) *22 kg (10 centyl)*
Intellectual development ***Rozwój intelektualny***	Mild intellectual disability *Opóźniony w stopniu lekkim*

observations, it can be stated that children with VCFS require multi-disciplinary medical care and, first of all, an early diagnosis [13]. A thorough clinical examination of new-borns, including the assessment of facial dysmorphic features, may allow early detection of anomalies potentially signifying congenital defects, such an early detection being a condition of a successful therapy. A tubular nose in an infant with conotruncal malformation and cleft palate should be an indication for including 22q11.2 microdeletion syndrome in the differential diagnostics.

Although we cannot cure a child with the Velo-Cardio-Facial syndrome, we can apply a life-saving treatment (cardiac defect) or improve the quality of life of such a patient. This requires knowledge, experience and cooperation of many specialists from different fields. It is also important to provide the parents with psychological assistance as the disease is incurable and requires their full commitment in taking care of the affected child. Referring the family to a genetic clinic should be a standard in providing medical care to families suspected of 22q11.2 microdeletion syndrome.

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