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The Environmental Factors Influencing Cleft
– Literature Review

Czynniki środowiskowe wpływające na powstawanie rozszczepu
– przegląd piśmiennictwa

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Abstract
This paper presents a review on clefts to understand etiology and environmental influences towards this anomaly. Clefts are the most common craniofacial abnormalities resulting from the incomplete development of the lip and/or palate in the first trimester of pregnancy (4th to 12th week of pregnancy). The etiology is multifactoral, with a very strong genetic component. The family occurrence of clefts have been proved. The fusion between the lateral palatine processes is very complicated and correlated process. Fetal development may be disturbed by many environmental factors and the exposure of the pregnant woman to them. The crucial ones are: drinking alcohol, smoking, radiation, diseases of mother, working in harmful environment, use of drugs and medicaments. Clefts have been growing in numbers because of advanced age of pregnant women and increased exposure to environmental risk factors. As fusion of the cleft occurs early in the pregnancy, the prevalence is very difficult, since most women are unaware of pregnancy in its early stage (Dent. Med. Probl. 2011, 48, 2, 261–266).

Key words: clefts, etiology.

Streszczenie

Słowa kluczowe: rozszczepy, etiologia.

Clefts are the most common craniofacial abnormalities resulting from the incomplete development of the lip and/or palate in the first trimester of pregnancy. There are many factors involved in the formation of the clefts, in this article the authors discuss the etiology, epidemiology and causes concerning clefts.

Etiology of Clefts
In the early weeks of pregnancy the face is being formed, starting from the top and the two lateral sides of the maxillary bone. They develop at the same time and grow towards each other, finally fusing in the middle [1].
Palate formation begins at the end of the fifth week of gestation. At the beginning, the palate consists of two parts, one is the anterior (primary) palate and the second one is the posterior (secondary) palate. The intermaxillary segment is formed by the medial nasal prominences, and it is composed by the primary palate and incisors. The primary palate continues posteriorly to the incisive foramen [2].

The secondary palate is formed by the lateral palatal processes. It begins at the incisive foramen and encloses two sections, one bony and one muscular. The lateral palatine processes arise at about the sixth week of development and they are composed of the deep portions of the maxillary prominence that form two horizontal structures or palatal shelves. These two structures are derivatives of the first branchial arch and they are originally on either side of the tongue. When the tongue starts to move downward during the seventh week of pregnancy, the lateral processes grow medially. The fusion in the hard palate initiates anteriorly and persists posteriorly during the eighth week of gestation.

The fusion between the lateral palatine processes is very complicated and correlated with several different procedures. Programmed cell death at the free borders and production of an adhesive layer of glycoproteins and desmosomes determine an ideal bonding surface interface. The left side has the tendency to lag behind the right side, causing a bigger percentage of the left-sided clefts. The nasal septum is concluded between the 9th and 12th weeks of gestation consequently of the growth downward into the newly formed palate.

The bone originates from the anterior palate thereafter spreads out posteriorly. The soft palate and the uvula, which compose the posterior segment of the secondary palate, evolve during the eighth week of gestation. The tensor veli palatini advance, followed by the musculus uvula, inducing the formation around the seventeenth week of gestation [2].

The etiology of clefts is thought to be multifactorial, with both major and minor genetic influences with variable interactions from environmental factors. In recent years, a number of advancement have occurred with respect to the genetics of these conditions, in particular, characterization of the underlying gene defects correlated with various relevant clefting syndromes. The most important identification of mutations a re in the interferon regulatory factor-6 (IRF6) gene as the cause of van der Woude syndrome and the poivivirus receptor related-1 (PVRL1) gene as being responsible for an autosomal recessive ectodermal dysplasia syndrome correlated with clefting. While non-specific disease-causing gene mutations have been associated in non-syndromic clefting, a number of candidate genes have been isolated through both linkage and connected research [3, 4].

Other situations, possibly due to microdeletions or isodisomy, were also found and could contribute to clefts as well. The analysis of the genes involved has indicated that point mutations in FOXE1, GLI2, JAG2, LHX8, MSX1, MSX2, SATB2, SKI, SPRY2, and TBX10 may be rare causes of isolated cleft lip with or without cleft palate, and the linkage disequilibrium data support a bigger and unspecified part for variants in or near MSX2, JAG2, and SKI [4, 5].

**Environmental Causes**

Genes take an important role in facial development, but the role of environmental influence on modulating genetic effects is just as critical. At least four major classes of environmental triggers have been studied. One of these is maternal smoking. It is known that smoking is harmful for both mother and fetus. It gives variety of problems in fetus, from breathing problems to causing cleft. Smoking cigarettes has been recognized as an important covariate in clefting [6]. Drugs taken during pregnancy should also be considered as a factor associated with clefts. During the first trimester, analgesic, chemotherapeutic and antineurotic drugs had all been more often used by the mothers of children with clefts, than by the control group. It has also been proved that drugs taken by mothers of children with cleft lip, with or without palate was more frequent than the same drugs taken by the mothers of children with isolated cleft palate [7]. In the group of these drugs, there are: anti-seizure/anticonvulsant medications, acne medications containing Accutane, and methotrexate – a drug commonly used for treating cancer, arthritis, and psoriasis [8, 9].

Smoking and alcohol are also involved. First-trimester of pregnancy smoking is clearly associated with risk of cleft lip. This effect modifies variants of genes related to detoxification of compounds of cigarette smoke. Maternal alcohol abuse during early pregnancy increases the risk of oral clefts, but little is known about how genetic variation in alcohol metabolism affects this association [6, 10].

Other factors that increase the risk of cleft lip and palate through maternal ingestion include pharmaceuticals. The problem with drugs is that they spread in body instead of just going where we want. It is that unintended spread that gives us the unwanted effect. Some drugs have been cor-
related to give cleft problems, such as the anticonvulsant phenytoin and benzodiazipines, or pesticides, such as dioxin [11]. Then both nutrients and cholesterol metabolism are also increasingly seen as being important in influencing embryonic development. Human body needs both vitamin, minerals, amino acid and fat to build cells, and if any of these is in low concentration or missing then the cells can form abnormally. Cells that are abnormal will also have altered role and function, which can lead to different problems. There are 4 main nutrients that play an immense role in closing of the lip and palate in fetus. It is crucial to have them in normal concentration in mother’s body at early stages of pregnancy so that fetus can develop in a normal way. Folic acid in particular is recognized as playing an important role in neural tube formation. The identification of folic acid supplementation can decline the risk of neural tube defects has lead to prevention of many potential clefts [12]. Edison and Muenke [13] provided data that suggested that early embryonic introduction to the cholesterol-lowering statin drugs might have presented a risk for a wide range of birth defects of the midline, including clefts of the lip and palate. It is crucial to underline the fact that not only a low level of some nutrient can affect clefts but also excessive amount of them can contribute to cleft problem. Also minimal dietary intake of B-complex vitamins, in addition to exposure to deficient or excessive amounts of vitamin A, has been linked to raise the risk of clefts development [14, 15]. Excessive alcohol consumption during pregnancy has also been connected with malformations in humans, called fetal alcohol syndrome [16, 17]. It is suggested that alcohol might exert some of its embryopathic effects by destructively affecting cranial neural crest cell activities [18, 19]. A causal relation between extreme alcohol intake and fetal alcohol syndrome is generally acknowledged, but there is a minor epidemiologic confirmation that alcohol causes other major malformations [20]. There have even been some studies that link high altitude with cleft problems [21]. There are many more environmental causes that have not yet been discovered.

### Epidemiology

Cleft lip and/or palate (CLP) make up for nearly one-third of all congenital malformations, thus making the most frequent incidence of this anomaly as 1.6 per 1000 live births. Roberts, Kallen and Harris [23] gather the data of five birth registries from California, Sweden and France to study the prevalence of CLP anomaly. Five million newborn were examined for craniofacial deformities and epidemiological characteristics and they found that a total of 8315 children were affected by this anomaly amongst the sample studied. Roberts, Kallen and Harris [23] gather the data of five birth registries from California, Sweden and France to study the prevalence of CLP anomaly. Five million newborn were examined for craniofacial deformities and epidemiological characteristics and they found that a total of 8315 children were affected by this anomaly amongst the sample studied. They calculated the incidence of CPL 1.57/1000, although the numbers are different in different countries. Despite the frequency of this abnormally the exact etiology of cleft lip and palate is vague because of its heterogeneous presentation. There are many factors contributing for CLP, some cases are sporadic while others are familiar.
Many children born with cleft lip and palate without any positive family history would have genetic predisposition, which may have been exacerbated in a phenotype cleft.

The inheritance pattern in CLP is higher in children where there is a positive family history of CLP. If either parent or siblings have CLP the risk of developing cleft lip and palate is approximately 0.1%. The risk of CLP passed on to the next generation differs depending on whether parent or sibling is affected. One could state that one parent or sibling with CLP would result in approximately 4% of recurrence, while one parent and one sibling with CLP showed 10% of recurrence. However, two siblings with CLP will give rise to 14% of recurrence. One parent and two siblings with CLP would double the recurrence with 25%; further investigation showed that if both parents and minimum one sibling gave numbers like 50% recurrence [24, 25].

Among the environmental causes, anti-abortificant drugs, anti-emetics, phenytoin, excessive alcohol and smoking have been linked to congenital defects including cleft lip and plate. Maternal alcohol abuse during early pregnancy increases the risk of oral clefts. The relationship between maternal tobacco and alcohol consumption during the first trimester of pregnancy increases the number of cases observed by analysing 161 infants with oral clefts and 1134 control infants. Several analyses also showed a higher risk of cleft lip with or without cleft palate associated with smoking (odds ratio [OR] = 1.79, 95% confidence interval [CI] = 1.07, 3.04) and an increased risk of cleft palate connected with alcohol consumption (OR= 2.28, 95% CI = 1.02, 5.09). The risk increased with the number of cigarettes smoked [26]. Passive smoking is also a very accurate subject to bring up in this matter. Maternal passive smoking and the risk of CLP among non-smoking women were examined in China. The odds ratio for exposure levels of 1–6 times per week and more than 6 times per week (at least 1 cigarette each time) were 1.6 (0.9–2.9) and 2.8 (1.5–5.2), respectively. The research concluded that maternal passive smoking during pregnancy was associated with an increased risk for CLP in offspring [27].

Nutrition seems to play a significant role as well. The role of folic acid used in prevention of CLP in high dose (3–9 mg/d) suggests a positive benefit to reduce occurrence of CLP abnormality [28, 29].

It is known that older age in mothers is clearly associated with CLP. Among the 1,489,014 live births in Denmark for 23 years (1973–1996), there were 1920 children with non-syndromic cleft lip with or without cleft palate and 956 children with non-syndromic cleft palate. The connection between mother and father's age was included in this analysis. Results showed that older age was connected with increased risk of both cleft lip with or without cleft palate and cleft palate only. Both maternal and paternal ages were associated with the risk of CLP, but the contribution of each was dependent on the age of the other parent. Both high maternal age and high paternal age were linked with CLP. Higher paternal age but not maternal age showed an increased in the risk of cleft palate only [30]. However, some studies showed the contrary about paternal age association with CLP. A study carried out in Brazil showed no increased risk connected with paternal age [31].

Conclusions

Clefts occur during the early weeks of pregnancy because of disturbance in the fusion process of the lateral palatine processes. This formation is easily disturbed by many different factors. It is hard to predict when a cleft will appear in a child, but we are aware of the risks of this abnormality. Some of the risks are linked with genetics, others are connected with environmental factors which could be avoided. Since this formation occurs so early in the embryonic development, the mother might not know that she is pregnant, and embryo can be exposed to risk factors such as tobacco smoking, alcohol and some categories of drugs. The number of clefts is increasing, due to the postponing pregnancy, the raised ratio of female smokers, the escalation in the use of drugs and the changes in our environment. Today more research is needed about how to detect and avoid CLP as early as possible.

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References


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