

CLEFT PALATE IN THE DOMESTIC DOG *CANIS LUPUS FAMILIARIS* – ETIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS, PREVENTION AND TREATMENT

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Abstract. Cleft palate is one of the most common congenital defects in the domestic dog associated with abnormal craniofacial development. Brachycephalic breeds seem to be most predilected. This anatomical and functional disorder is characterized by the presence of the fissure connecting the oral and nasal cavities. There are clefts of primary and/or secondary palate. Despite developing diagnostic and therapeutic methods, clinical examination and surgery are still the basis for the diagnosis and possible treatment of the malformation. In most cases euthanasia of the animal is performed. The eliminatin of affected individuals from the breeding is strongly recommended. The defect has probably a heterogeneous etiology, both genetic and environmental factors contributing to its formation. However, its genetic etiology has not yet been clearly explained.

Key words: *Canis lupus familiaris*, cleft palate, congenital defect

INTRODUCTION

Cleft palate (CP) is one of the most commonly reported congenital anomalies both in humans and in domestic animals. It has been observed in horses

[Semevolos and Ducharme 1998, Semevolos and Ducharme 2002], cattle [Shupe et al. 1968, Smolec et al. 2010], sheep, goats, dogs and cats [Prescott 1972], especially Siamese and Persians [Mulvihill et al. 1980, Nelson 2003]. Single cases have also been reported in domestic pigs, wild felines [Loevy and Fenyes 1968] and gorillas [Siebert et al. 1998]. Animals with cleft palate living in the wild have no chance to survive [Shupe et al. 1968].

It has been found that cleft palate is more common in purebred dogs rather than mongrels. It is believed to be one of those congenital abnormalities that are responsible for an increased mortality of puppies within the first days of life [Löhr 2011]. Most frequently, CP occurs in the following breeds of dogs: Beagle, Cocker Spaniel, Dachshund, Labrador Retriever, Miniature Schnauzer, Shetland Sheepdog, German Shepherd Dog, West Highland White Terrier, Cairn Terrier, English Toy Terrier, Collie, Chihuahua [Jurkiewicz and Bryant 1968, Richtsmier et al. 1984, Nelson 2003, Grellet 2008, Fossum 2009, Ackerman 2011]. There have also been cases of cleft palate in the following breeds: Bernese Mountain Dog, Bullmastiff, Bull Terrier, Golden Retriever, Norwegian Elkhound, Staffordshire Bull Terrier, Toy Poodle, Wirehaired Fox Terrier. Brachycephalic dog breeds, which include Boston Terrier, Pekingese, Boxer, English Bulldog, French Bulldog and Cavalier King Charles Spaniel, are in fact predisposed to CP [Nelson 2003, Grellet 2008, Gough and Thomas 2010, Moura et al. 2012]. Cleft palate has been recognized as one of factors leading to death within the first three days of life of puppies belonging to four large dog breeds: Irish Wolfhound, Leonberger, Labrador Retriever, and Newfoundland [Indrebø et al. 2007].

Information on the incidence of cleft palate in dogs is far from complete, which makes any estimates unreliable, since dog owners or breeders often fail to report death cases resulting from CP [Max et al. 2012, Bar-Am 2013, Max et al. 2014].

The origin and types of cleft palate

Orofacial clefts may emerge during the embryonic or fetal life as a result of incomplete fusion of the anatomical structures associated with the craniofacial development. In dogs, these defects usually occur between day 25 and 33 of prenatal development [Nelson 2003, Krzyżewska and Max 2008, Dyce et al. 2009, Fossum 2009, Van den Berghe et al. 2010, Bar-Am 2013]. The upper lip and the incisive bone constitute the primary palate, whereas the hard palate (the palatine process of the maxilla and the palatine bone) and soft palate represent the secondary palate [Warzee et al. 2001, Nelson 2003, Dyce et al. 2009, Van den Berghe et al. 2010]. Hence, cleft palate is defined as a congenital oronasal fistula caused by incorrect fusion of the structures separating the oral and nasal cavities, which

involves the soft palate, hard palate, incisive bone, and lips [Krzyżewska and Max 2008, Fossum 2009].

Cleft disorders include cleft lip (cheiloschisis), a failure of the fusing of the maxillary prominence and the medial nasal process [Bar-Am 2013], and cleft palate. The latter (palatoschisis) can be either a primary or a secondary palate defect. Cleft of the primary palate affects the incisive bone and is caused by the failure of the medial nasal processes fusion. Cleft of the secondary palate, on the other hand, occurs when malformations involve the palatine process of the maxilla and palatine bone, which constitute the hard palate, and results from a lack of fusion between these two structures. Primary CP may be accompanied by median cleft lip; however, far more frequent is secondary CP, which may involve the hard and/or soft palate. Both defects may occur simultaneously with a varied severity, from unilateral incomplete to bilateral complete [Warzee et al. 2001, Cywińska et al. 2007, Van den Berghe et al. 2010, Krzyżewska and Max 2008, Bar-Am 2013].

CP may occur separately [Moura and Pimpão 2012] or in combination with developmental abnormalities of other organs. About 8% of dogs suffering from cleft lip/palate are also affected by disorders occurring in other parts of the body [Shupe et al. 1968, Nelson 2003, Ingwersen 2012]. Mulvihill et al. [1980] reported that CP in dogs of various breeds (including Dachshund, Yorkshire Terrier, Chihuahua, Toy Poodle, Cocker Spaniel and others) as well as mixed-breed dogs may be accompanied by tumors and many other birth defects. The latter include hydrocephalus, distichiasis, epidermoid cyst, ventricular septal defect of the heart, microphthalmia or entropion, or rear limb malformation observed in Shin-Tzu dogs [Cooper and Mattern 1971]. Moura and Pimpão [2012] reported that cleft palate along with respiratory failure – resulting from retroglossoptosis caused in turn by micrognathism – may be accompanied by Pierre Robin sequence.

Palate development in mammals is considered to be evolutionarily highly conserved extending by a highly regulated phases: the growth of the palatal structures, ascending, adhesion, fusion and differentiation of cells [Van den Berghe et al. 2010, Bush and Jiang 2012, Wolf et al. 2014]. It seems that the formation of clefts may be significantly influenced by disturbances in the process of cell death [Zakeri and Lockshin 2009]. It should also be noted that in some animals like birds and most of reptiles, cleft palate normally occurs [Ferguson 1988].

Comprehensive studies and analysis of animal models of palate development revealed that its proper sequence is led by an extensive network of interactive transcription factors and signaling molecules involved in complex molecular pathways of various cell types [Bush and Jiang 2012]. Ding et al. [2004] demonstrated a role of the platelet-derived growth factor (PDGF) in the signaling, whereas Jiang et al. [2006] identified the components of several major signaling pathways, including Bmp, Fgf, Shh, and Wnt, which are crucial for the appropriate facial

morphogenesis and/or lip fusion. Due to the fact that palate is formed in a multistage process, and each phase undergoes strict regulation, any interference into proliferation, differentiation, or apoptosis of cells may lead in consequence to cleft palate [Van den Berghe et al. 2010].

Etiology and risk factors

Cleft palate is a condition with a complex etiology. There are both genetic (recessive or dominant with incomplete penetrance) and environmental factors (nutritional, chemical, toxicological, or infectious) involved in the occurrence and expression of the abnormality [Cywińska et al. 2007, Krzyżewska and Max 2008, Kemp et al. 2009]. In Shih-Tsu Dogs, as well as probably in Pointers, Bulldogs and Swiss Shepherd Dogs, congenital soft- and hard palate disorders may be inherited with incomplete penetrance [Ackerman 2011]. Richtsmier et al. [1984] observed that cleft palate in a population of Brittany Spaniel is inherited in an autosomal recessive pattern and only exceptionally is CP linked with cleft lip (CL). Kemp et al. [2009], on the other hand, confirmed in their studies and by a pedigree analysis that CP inheritance in a group of Pyrenean Shepherds was of autosomal recessive pattern, although they also suggested its monogenic character and excluded TGFb3, Msx1 and Fst as candidate genes.

Cleft palate has also proved to be the only abnormality observed in Boxer puppies. These studies, along with pedigree survey on the clinical phenotype, allowed drawing a similar conclusion that lip and palate cleft in affected dogs was in a nonsyndromic, isolated form (to distinguish from the same though the syndromic form, i.e. combined with other clinical disorders or congenital malformations) and monogenically determined and inherited autosomally recessively [Moura et al. 2012, Moura and Pimpão 2012].

Other experiments demonstrated that this trait is determined by the gene linked with the chromosome X or is a sex-linked dominantly inherited disease [Sponenberg and Bowling 1985]. Nevertheless, CP in West Highland White Terriers was recognized as a polygenic defect and it was never proved that inheritance could be determined by a single gene [Peterson and Kutzler 2011]. In triploid Alaskan Malamute puppies, on the other hand, cleft palate was diagnosed among the great number of birth defects [Johnston et al. 1989]. In studies on Nova Scotia Duck Tolling Retrievers (NSDTR), Karmi [2011] used GWAS (genome-wide association study), results of which suggested at least two independent CP-related loci; one locus was found in chromosome 14 (involving 5.8 Mb and 38 candidate genes), whereas the other one remains so far unidentified. Amongst many existing CP causes in NSDTR dogs, the most common form was referred to as Cleft Palate 1 (CP1). Subsequent studies led to identification of a large insertion in the gene as

the causative agent responsible for proper palatogenesis [Bannasch 2012, Warren 2012, Wolf et al. 2013]. Recently, however, an inactivating mutation in the gene essential for palatogenesis has been discovered, which causes another hereditary form of cleft lip and cleft palate called CLPS (Cleft Lip/Palate and Syndactyly, <https://secure.offa.org/dnatesting/clps.html> [Orthopedic Foundation for Animals 2010c]). In other breeds of dogs, neither of the mutations have been ever reported. It has been demonstrated that both CP1 and CLPS is inherited in a simple way and autosomally recessive pattern, which means that affected puppies inherit one of each mutated copy of the gene from each parent [Bannasch 2012, Warren 2012, Wolf et al. 2014].

Performing GWAS on a group of 14 CP-affected and 72 healthy NSDTR dogs enabled the authors to identify a statistically significantly CP-associated region of canine chromosome 14 and a homozygous haplotype (5.1 Mb) common to twelve CP1 cases with a relative mandibular brachygnathia. Sequencing two candidate regions containing homeobox genes, DLX5 (distal-less homeobox 5) and DLX6 (distal-less homeobox 6), revealed a 2.1-kb LINE-1 insertion within DLX6 into CP1 of NSDTR. Based on an analysis of sequence and translation of approx. 1.2 kb of LINE-1 insertion, the authors additionally predicted that the insertion is responsible for introducing a premature stop codon associated with truncating 17 amino acids from the 60-amino acid long functional DNA-binding homeodomain. Also, a segregation analysis and allele frequency in NSDTR revealed that the LINE-1 insertion in DLX6 segregates both with the phenotype and with a complete penetrance, autosomal recessive mode of inheritance [Wolf et al. 2014].

There are a number of factors – other than genetic ones – which affect the pregnant female and may have a negative impact on the development of the palate of embryos. The wide head, typical for brachycephalic dog breeds, which may hamper the fusion of the palatine outgrowths [Warzee et al. 2001, Reiter 2011], probably make the puppies more prone to any other possible factors disturbing the normal craniofacial development [Van den Berghe et al. 2010]. Van den Berghe et al. [2010] emphasise that CP is an etiologically complex condition. It may result from disturbances during local cell proliferation, differentiation, and apoptosis, as well as from improper synthesis of mucopolysaccharides or disruptions during the process of active widening of the fetal neck. Presumably, cleft palate is a resultant of single- or complex-acting genetic factors, mechanic stimulæ, and/or environmental teratogens. It may occur in many breeds of dogs, often as a result of intrauterine fetal injury [Reiter, 2011]. Anabasine, alkaloid probably capable of interacting with nicotinic receptors, may also be responsible for CP [Weinzwieg et al. 2008]. Also, administration of acetylsalicylic acid (aspirin) to bitches at a dose of $400 \text{ mg} \cdot \text{kg}^{-1}$ per day between 23 and 30 days of gestation can result in many malformations, including cleft palate [Robertson et al. 1979]. Although

Jurkiewicz and Bryant [1968] did not detect anomalies in newborn puppies in response to chlorcyclizine hydrochloride administration, the authors confirmed the teratogenic character of 6-diazo-5-oxo-L-norleucine (DON) and its capability to cause CP in dogs.

Hypervitaminosis A may also be a causative agent of CP in puppies [Peterson and Kutzler 2011], as demonstrated by an oral administration of $125\,000\text{ IU} \cdot \text{kg}^{-1}$ BW to Beagle bitches at 17–22 days in gestation [National Research Council 1985]. According to Davies [2011], high dietary vitamin A content may be an etiologic factor in about 50% of CP cases. In contrast, studies on growing puppies (from 8 weeks to 12 months of age) generally showed no effect of vitamin A concentration on the potentially unwanted effects. Consequently, a safe retinol dose of $104.80\ \mu\text{mol}$ (100 000 IU vitamin A)/4184 kJ (1000 kcal) has been proposed for addition to animal growth-stimulating diets [Morris et al. 2012].

Cortisone and hydroxyurea may lead to the development of CP in the fetus. As in humans, the risk of CP in dogs is associated with the use of corticosteroids, as well as with exposure to cigarette smoke [Coile 2009].

Other factors that may contribute to cleft palate in the offspring include cytostatic drugs, antifungal agents, as well as impaired cholesterol metabolism in females, or certain viral infections [Max and Jurka 1994, Van den Berghe et al. 2010], traumas, stress, and hormonal factors during the crucial stage of development (25–28 days of pregnancy in dogs) [Reiter 2011]. Hormones that are involved in metabolism regulation, such as insulin and corticosteroids, are a particular group of factors. Pregnant bitches should not receive teratogenic compounds such as primidon, griseofulvin, or sulfonamides [Peterson and Kutzler 2011], also drugs such as metronidazole, corticosteroids [Ackerman 2011]. Certain toxins, such as those present in some lupines, may – at some stage of gestation – induce congenital defects in cattle (“crooked calf disease”) and the symptoms include cleft palate [Shupe et al. 1968, Rimbey 1969]. Ingestion of Tree Tobacco (*Nicotiana glauca*) plant suspension, which contains piperidine (anabasine, a teratogenic alkaloid) also may lead to this birth defect [Weinzweig et al. 1999]. Cleft palate can also be acquired as a result of recurrent infections (e.g. severe periodontal disease), traumas (e.g. dog bite), cancers, surgery, or radiotherapy [Reiter 2011]. Palatal defects can also be acquired as a consequence of a physical head injury, either caused by an impact or resulting from other forces, such as electrical burns, foreign body penetration, a necrotic factor, or a gunshot wound [Marretta 2012b]. Experimental studies have shown that teratogenic effects of particular substances depend on the affected animal species, dose, duration of the impact, and the developmental stage of the embryo [Verstraete 1999].

It has been found that folic acid can prevent cleft palate in dogs. Namely, its supplementation (5 mg per day) resulted in a drop (by 76%) of CP incidence in

a population of Boston Terriers, from 9/51 (17.6%) down to 8/191 (4%) [Elwood and Colquhoun 1997]. Such results, as well as the positive effects of folic acid in the first stages of gestation, have been confirmed by Guilloteau et al. [2006], who studied a group of French Bulldogs; the authors evidenced a significant reduction (by 48.54%) of CP risk, as compared to control (8.57% vs 4.41%) [Guilloteau et al. 2006, Grellet 2008]. However, folic acid supplementation does not prevent all cleft palate cases; in both studies, cleft palate was observed in approximately 4% of puppies [Coile 2009].

Symptoms and pathophysiology

Congenital palatine defects are manifested as cleft lip or cleft palate. Primary CP is easily diagnosed at puppy's birth, whereas secondary CP – although more common and more severe – is rarely revealed and an external visual inspection may fail to allow its identification at first [Nelson 2003, Reiter 2011]. The defects in the oral cavity disturb an independent operation of the digestive and respiratory systems, which is particularly important in the neonatal period. Consequently, first observed signs are more or less severe difficulties in the normal feed intake (suction), though other symptoms – such as dysphagia (swallowing problems) – may also appear [Grandage 2003, Ingwersen 2012]. With a large cleft, the puppy is even unable to hold the nipple. The condition can lead to deposition of the food and contamination of the nasal cavity. The consequence of the problems with milk intake is malnutrition, growth slowdown or arrest, and even death from starvation. Common are various respiratory tract infections, mucosal inflammation in the nose [Bleicher et al. 1965, Fossum 2009], coughing, sneezing, choking, tonsillitis, or reflux [Reiter 2011]. Cleft palate can also cause dental problems (e.g. hypodontia, malocclusion, gaps and misalignment of teeth, deformations) or laryngological defects (e.g. nasal deformity) [Bar-Am 2013]. Other CP consequences may include hearing impairment, or vulnerability to an often asymptomatic middle ear disease, which can lead to deafness. Besides recurrent infections, secondary CP often leads to aspiration pneumonia and – in the most severe cases (approx. one in three cases) – may lead to death of the animal [Gregory 2000, Shaw and Ihle 2006, Coile 2009, White et al. 2009]. Studies on a group of Spanish Pointers also demonstrated that cleft palate impaired maxillofacial growth and formation and led to nasomaxillary hypoplasia [Paradas-Lara et al. 2013].

Individuals affected by the defect may suffer from other coexisting, additionally weakening abnormalities. Crooked calf disease, i.e. a strong arthrogryposis of the forelimbs that involve the skeletal system, is an exemplary disorder accompanied also by cleft palate [Shupe et al. 1968, Rimbey 1969]. Depending on the

development stage and the intensity of CP inducing causes, other physical disorders or neurological abnormalities may also be present [Reiter 2011].

Heterogeneity of symptoms and diagnosed variability are great enough to have a different range even within the same litter [Max et al. unpublished data 1). Animals affected by severe acquired palatine defects may exhibit similar clinical symptoms to those suffering from congenital secondary palate anomalies [Reiter 2011]. Consequently, considering the above, it must be stressed that a veterinary treatment should be provided in such cases, since it would help the puppy to survive and would ensure a good quality of life in the future. Bearing in mind that there is a high risk of anomalies that might coexist in other anatomical structures, it is recommended to perform a comprehensive examination in order to exclude possible birth defects. Early diagnosis is important because it may prevent secondary complications. Thorough inspection and complete examination of the puppies will allow diagnosing CP not detectable at the first sight. In dogs, especially of brachycephalic breeds, such a diagnosis is equivalent to excluding the individual from further breeding [Fox 1963, Semevolos and Ducharme 2002, Cywińska et al. 2007]. Due to its commonness, however, it is impossible to eradicate the defect from the entire population. Therefore, cleft palate diagnosis is particularly distressing for the breeder. Although a puppy affected with this defect may be big, strong and have a nice and bulky head, it is usually subjected to euthanasia. Also, the CP carriers can produce a few healthy litters before the genetic defect will emerge.

Diagnosis

All clinical actions and procedures (case history along with the pedigree, physical and specialistic examinations for external and internal defects, follow up tests), conforming to the adopted criteria, are an essential part of diagnostic process and are aimed to gather comprehensive information to get a full clinical picture of the case. This in turn is necessary to accurately diagnose the disease and possibly to choose an adequate therapy. Affected animals that have not survived should undergo detailed post-mortem examinations, which may provide information for a correct diagnosis and may contribute to development of new treatment strategies for the future [Moura and Pimpão 2012].

In veterinary practice, the diagnosis is usually made as a postnatal clinical examination, without genetic tests. Besides palpation, veterinarians may order additional examinations, such as imaging diagnostics [Max et al. unpublished data 1, Marretta 2012a]. Thorough physical examinations and comprehensive analysis sporadically enable detection of other congenital disorders that occur concurrently with congenital palate malformations (anotia, bifid tongue, polydactyly, otitis

media, cranioschisis, atresias, omphalocele, microphthalmia, hydrocephalus, kyphosis, limb deformities etc.) [Sherwood et al. 1971, Fossum 2009, Pavletic 2010, Marretta 2012a]. The observable phenotype may vary within the breed. In NSDTR puppies with two copies of the mutated CLPS gene the type of defect can be varied and can occur in different combinations: from cleft palate to cleft lip with cleft palate, and in each case the puppies can have syndactyly. In a single clinical case, a cleft nose together with syndactyly occurred.

In a clinical examination of oral cavity, palate defects are quite readily detectable [Gawor 2004]. Although cleft palate may occur already in the embryonic life, it is also possible that the defect will not be detected in the puppy at birth. Therefore, in order to diagnose CP accurately, the veterinarian needs to thoroughly check all possible symptoms. In order to determine the clinical signs, a case history should be completed, followed by a physical examination. Detecting cleft lip is easier, while diagnosis of incomplete fusion of the incisive bone, hard palate or soft palate may involve a detailed examination of the oral cavity, or the use of general anesthesia [Fossum 2009]. Differential diagnosis includes congenital secondary CP, post-traumatic CP, oronasal fistula, and foreign objects wedged in the oral cavity [Warzee et al. 2001].

Typical symptoms of cleft palate include difficulties in food intake, choking, sneezing, coughing or nasal discharge [Shaw and Ihle 2006]. Peripheral blood cell counts and urinalysis results may be abnormal. If aspiration pneumonia develops in consequence of cleft palate, an initial blood test can help identify infection. So far, imaging diagnostics and laboratory tests have been recommended in some situations (e.g. in the case of aspiration pneumonia) [Fossum 2009, Marretta 2012a, Bar-Am 2013]. Max et al. [unpublished data 1] and Max et al. [unpublished data 2] presented a possible practical application of imaging diagnostics. Since standard tests (e.g. X-ray radiography) provide only a partial picture of the defect and there are numerous related health threats, a comprehensive diagnosis is necessary. Multislice computed tomography provides an opportunity to identify structure dysfunctions undetectable during clinical examination [Max et al. unpublished data 1].

A recognition of craniofacial disorders caused by foreign bodies requires both imaging diagnostics and rhinoscopy (endoscopy of the nasal cavity), as well as chest radiography and biopsy – in the cases of cancer [Marretta 2012b]. Cleft palate extent, severity, and occurrence of other defects or complications (i.e. pneumonia) are key prognostic determinants of a prospective CP treatment [Semevolos and Ducharme 2002]. Nevertheless, the best way to definitively diagnose cleft palate in puppies is to conduct a thorough inspection of the mouth under general anesthesia during which the veterinarian is able to carefully examine the hard and soft palate and assess the nature and extent of the defect.

In the face of phenotype-based exclusion of putatively sick animals and facing the reluctance of the breeders to cope with the difficulties of affected puppy care, Max et al. (unpublished data 2) emphasized the potential hidden in the application of computed tomography in the diagnostics of defect severity and possible comorbid disorders within the head. Early imaging diagnostics might support the decision of surgical treatment of affected puppies or – under poor prognosis – euthanasia.

The research team of the Bannasch Laboratory at the University of California, Davis, who identified the specific causative mutation of cleft palate 1 and cleft lip/palate and syndactyly in NSDTR dogs, have developed a genetic test to diagnose carriers of CP1 [Bannasch and Dziuk 2014] and CLPS (offered by the Orthopedic Foundation for Animals [2010a] at: <http://www.offa.org/dnatesting/>). The authors presented possible test results that allow identifying the genetic grounds of CP1 (<https://secure.offa.org/dnatesting/cp1.html> [Orthopedic Foundation for Animals 2010b]) and CLPS (<https://secure.offa.org/dnatesting/clps.html> [Orthopedic Foundation for Animals 2010c]), and also ensured that in order to maintain genetic variability within the breed and to select the carriers for other positive traits, dogs with one mutant gene copy (N/A carriers) are healthy and can be safely bred with CP1 non-carriers (N/N) [Bannasch 2012, Warren 2012]. Nonetheless, the information about the occurrence of clefts are incomplete or remain unpublished, and DNA tests have not been developed so far or are still hardly available, therefore, the diagnosis and elimination of hereditary diseases can be problematic. To prevent their expansion within the population of purebred dogs, other methods than DNA testing, which are at the disposal of genetic counseling, can still be used [Van Hagen et al. 2004]. In their studies, Van Hagen et al. [2004] computed the estimated breeding value (EBV) and transformed it into an odds ratio (OR), which is identified with a relative risk (RR) of the disease. Breeders, however, consider the diseases that occur later in puppy's life as more important, compared to those developing before it has been sold (such as cheiloschisis or palatoschisis).

Prophylaxis and treatment

Cleft palate, a possible pathological connection between the oral and nasal cavities, is a malformation that in dogs usually requires surgical treatment [Cywińska 2007]. The literature describes a number of correction methods in cleft lip/palate [Nelson 2003, Fossum 2009, Pavletic 2010, Marretta 2012a, Marretta 2012b, Bar-Am 2013]. In terms of acquired palatine defects, the source of the disorder must be eliminated before starting the reconstruction procedure and prior to treatment [Reiter 2011]. A secondary aspiration pneumonia can be treated by administration of appropriate liquids, oxygen, bronchodilators, agents thinning respiratory

secretions, and sometimes corticosteroids. In the cases of pneumonia and rhinitis, antibiotics are recommended [Fossum 2009]. It is also important to prevent infections of the airways, proper nutrition and energy intake [Bar-Am 2013]. On the other hand, folic acid dietary supplementation of the pregnant bitch is one of the preventive measures against cleft lip/palate in the offspring. The effect of folic acid in dogs is similar to that observed in humans. The addition of folic acid in dogs will not prevent all cases of cleft palate, since it is a polyetiological anomaly [Guilloteau et al. 2005].

Congenital defects include clefts of the hard palate, lip, soft palate, alveolar process, as well as soft palate hypoplasia, in which a correction is carried out using various surgical techniques [Marretta 2012a]. Although the correction of cleft lip is mainly performed for cosmetic reasons, surgical treatment of secondary CP is necessary, also in order to prevent chronic respiratory infections and to facilitate food intake for the proper nutrition of the animal. Congenital clefts of both anterior and posterior parts of the palate are operated successfully using varied techniques. In addition, dogs require appropriate pre- and post-operative handling, that is the preparation the animal before the procedure and the care and convalescence afterwards.

Proper conduct of the operation is an important step, though complications may arise, especially if the fissures are large. To achieve the objective, that is separating the oral cavity from the nasal cavity and restoration of tissue continuity, while minimizing the risk of complications and dehiscence (appearing sooner or later), and consequently incomplete healing of the oronasal fistula, the key is to maintain the minimum tension at the point of closure along the suture. All the procedures are usually carried out in animals after completion of a certain stage of growth. Throughout that period, the dog owners should deal with their dogs very carefully, applying special diet consisting of creamy feeds, commercial or home-made, using a tube or through a stoma (esophagostomy or gastrostomy). Feeding in an upright position and systematic cleaning of food debris is important to improve the quality of life and allow the puppy to attain an appropriate age (approx. 3–4 months) for the patient to be eligible for corrective surgery.

Veterinary surgeons promote individualized care, carried out for a sufficient period of time, warn the breeders that there is a potential risk of transmission of the defect to offspring, and recommend castration of affected animals [Bleicher 1965, Gawor 2004, Shaw and Ihle 2006, Coile 2009, Fossum 2009, Pavletic 2010, Marretta 2012a, Bar-Am 2013]. The owners are required to show particular commitment, including reading and adhering to certain proposed guidelines, which needs both patience and meticulousness. Widely published instructions inform how to care of the pregnant bitch and how to handle with CP-affected puppies from the first day until eight weeks of age; the guidelines also include detailed

care instruction, i.e. how to feed the puppy, what to feed, how long, how to administer medications, and how to handle feeding problems or those arising from breathing difficulties.

Literature sources indicate that when the dog has reached the age of 6 months, small fissures may be closed spontaneously within some time, while larger ones, although reduced in size, never heal totally [Coile 2009]. Possible surgical treatment is recommended after eruption of permanent teeth [Wijdeveld et al. 1988, Wijdeveld et al. 1989] and at age older than 6–8 weeks [Nelson 2003, Shaw and Ihle 2006]; Pavletic [2010] proposed 4–5 months as the lower limit of age appropriate for corrective surgery. Gawor [2004] suggested the third month of life as the optimal age, since earlier the tissues are too fragile, while later the defect may grow unduly large. Plastic surgery of the palate is normally carried out between 8 and 12 weeks of age. The correction of the CP is supposed to reconstruct the bottom wall of the nasal cavity [Wijdeveld et al. 1988, Fossum 2009, Séguin 2011]. If the cleft affects both hard and soft palate, the hard palate should be closed first.

Bardach et al. [1993, 1994] demonstrated that closing the clefts sequentially, first cleft lip and then cleft palate, is a better solution, as it reduces the risk of injuries during subsequent stages of the maxillary complex development and possible disturbances are less severe, compared to a reversed operation sequence (cleft palate repair followed by cleft lip correction) or a repair carried out at the same time. The patient, especially with extensive lesions, may need more than one surgery to close the cleft successfully. Each additional operation, as well as each unsuccessful one, may be a recommendation for euthanasia of the animal [Bauer et al. 1988, Coile 2009]. Gawor [2004] claimed that a surgical treatment often requires follow-up corrections and repairs, and the animals should be later sterilized. Various surgical techniques were presented, although in the cases of extensive clefts, a prosthesis may be the best method of treatment [Gawliński et al. 2007]. Besides, not only before but also after the treatment it is necessary to support the puppy's nutrition. As medications in post-surgical pain relief, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended.

During the follow-up treatment one should prevent the growth inhibition in the dento-maxillary part of the facial skeleton, as limiting the potential for regeneration of the palate. It can pose one of the fundamental problems in the repair of cleft palate [Latham and Deaton 1975, Meijer and Prah 1978, Forbes et al. 1988]. Therefore, clinicians try to possibly delay, and thus facilitate any surgeries of CP. This is accomplished through the implementation of methods based on satisfying patient's needs and taking it under comprehensive care, which taking into account the feeding and watering until the puppy reaches the size of an adult [Davidson et al. 2012].

Spontaneous restoration of palatal continuity is a rare condition. Different surgical techniques are applied depending on the extent and location of the defect. With narrow CP it is sufficient to refresh the edges and join the mucous membranes; wider fissures, however, require the release incisions [Gawliński et al. 2007]. Nevertheless, in most cases, the treatment involves the techniques – mucosal bipedicle flaps from the palate and muco-periosteal flaps from the palate. Pharyngeal flaps can also be used. The repair of hard palate cleft is done by overlapping flaps, or by rotating one of the flaps by 180° and applying it onto another flap (“Sandwich”), by sliding two bipedilce flaps for closure (the von Lagenbeck palatoplasty), or using other techniques based on its modification, in order to correct the distortion of the maxillary part of the facial skeleton. On the other hand, such techniques as overlapping pf flaps, moving flaps from the hard or soft palate, or flaps from the nasal mucosa or nasopharynx, are mostly used in soft palate palatoplasty. In most cases, the correction consists in detaching mucosal flaps and placing them in the midline of the two– or three–layer closure.

With lateral soft palate cleft repair, mucosal flaps of the oropharynx or nasopharynx are applied in accordance with the two-layer closure technique. Also, in order to reconstruct the primary CP, surgeons use mucosal flaps connecting a buccal or a gingival flap with the nasal mucosa; to ensure the generated separating layer, a nasal mucosal flap can be sutured to a flap derived from the oral cavity mucosa [Griffiths and Sullivan 2001, Warzee et al. 2001, Fossum 2009, Pavletic 2010, Marretta 2012a, Bar-Am 2013]. A technique based on the folded flap palatoplasty (FFP) has also been successfully applied for the correction of elongated soft palate (ESP), which is a birth defect accompanying the brachycephalic airway syndrome (BAS), typical for brachycephalic breeds of dogs [Findji and Dupré 2009]. Inevitably, these procedures leave injuries in the form of donor beds, which need time (approx. 3–4 weeks) to heal through granulation and epithelization [Nelson 2003, Fossum 2009, Marretta 2012a]. After conducting studies on an experimentally induced clefts of lip, alveolar process, and palate, Bardach et al. [1982] and Kelly and Bardach [1989] found that palatoplasty using two muco-periosteal flaps not only does allow closing the cleft, but also stimulates formation of new bone within the fissure, simultaneously preventing any malformations that might arise from the defect.

Depending on the causative factors, the extent of the defect, its location and severity, decision is reached as to the choice of the therapeutic method. Since the first surgical treatments are generally more successful, its is crucial to plan the procedure properly and to select the most adequate one. One can distinguish single-layer flap (using vestibular flaps, transposition flaps, advancement flaps, tongue flaps, split palatal U-flaps, and island palatal flaps) and two-layer flap (using vestibular flaps and reflected palatal flaps) surgical techniques [Marretta 2012b].

The aim of the scientific research is striving constantly to develop new and more effective treatments. Many authors, who proposed new treatment procedures, explained also how to deal with CP-affected animals and suggested the rehabilitation, emphasizing the role of latest proceedings in the field of surgery and orthodontics [Bleicher et al. 1965]. Most clefts, even when extensive, may be closed by means of local and/or axial flaps, whereas other, more advanced techniques, such as free tissue graft and prosthetic implants, are used less frequently [Sivacolundhu 2007]. Ishikawa et al. [1994] applied an osteochondral autograft transplantation in the treatment of a wide cleft palate in a six-month-old dog.

There are also reports on the use of fixing screws or silicone-coated acrylic plates [Gawliński et al. 2007]. Martínez-Sanz et al. [2011] recommended individualized therapy of dogs and other animals based on making feeding teats or palate prostheses using thermoplastic material or dental implants. This easy-to-use prosthesis performed very well in protecting the surgical wound, and its replacement could be done without anesthesia [Lee et al. 2006]. Prostheses made of plastic are attached to the teeth in order to protect the mucosal-submucosal flaps closing large cavities. Proper anchoring and stabilization, however, depends on the good dental condition. Gawliński et al. [2007] recommended the use of a durable, flexible, and non-resorbable titanium mesh coated with a barrier membrane, covered again with resorbable collagen membrane. It appears that in animals (as compared to humans) such membranes relatively quickly degrade in the mouth, but they can also foster partial regeneration of the soft tissue, which is sufficient to reduce significantly the defect (incomplete barrier between the mouth of the nose needs to be sealed).

Methods alternative to unreliable surgical operations, besides more reliable though relatively inaccessible in the animal treatment and rejection-prone prostheses [Thoday et al. 1975, Gawliński et al. 2007], include the use of buccal mucosa flaps in the correction of a significant bilateral soft palate defect [Sager and Nefen 1998]. The results of a comparative study by Wang et al. [2006] showed that autogenous bone grafting prior to the two-flap palatoplasty may help to reduce the distortion caused by maxillary growth and formation of the maxilla under complete CP. It does not exclude, however, some other maxillary malformations in this area [Shi et al. 1998]. Another, revolutionary approach consists in developing a flapless and minimally invasive palatoplasty technique. Compared to traditional methods, which impair the palatine bone growth, injection of hyaluronic acid-based hydrogel containing hydroxyapatite and BMP-2 was estimated to be both easier to carry out and faster in terms of recovery [Martínez-Álvarez et al. 2013].

Rapid suture expansion [Vardimon et al. 1998, Liu et al. 1999, Liu et al. 2000a, Nelson 2003] or distraction osteogenesis [Carls et al. 1997, Ascherman et al. 2000,

Liu et al. 2000b, Liang et al. 2002, Liang et al. 2003, Liang et al. 2005, Nelson 2003, Tibesar et al. 2005, Aoki et al. 2010] should be definitely considered as revolutionary surgical techniques of extension and permanent elongation of the hard palate; the methods also enable corrections of clefts or cavities in the soft palate and, moreover, they promote soft tissue development and do not impair the growth of the maxillary structures. Also Arzi and Verstraete [2011] described a technique which has successfully been applied in Springer Spaniel dogs. The authors suggested that their method should be chosen for correcting the bifid nose, which may occur in connection with primary CP, in order to overcome accompanying clinical symptoms.

Studies on the use of biodegradable materials in surgical procedures has been carried out intensively since it was proved that separation of the muco-periosteal area from the bone has a beneficial effect on the development of the dental alveolar process in the dog model. Amongst the films studied *in vivo* by Leenstra et al. [1995, 1998], PHB-co-HV 80/20 (a copolymer of poly hydroxybutyrate 80% – hydroxyvalerate 20%) was the most suitable for use in dogs; it also participated in wound closure after von Langenbeck palatal repair and prevented unwanted operation outcomes through limiting the process of bone scarring. It was suggested that integrating a matrix onto the wound allowed overcoming adverse effects of scar tissue formation and the complications associated with the operations of cleft lip and palate resulting from a deficit of tissue [Ophof et al. 2007]. Of the two tested substrates implanted by Ophof et al. [2004] in dogs, the substrate of cutaneous origin – not the one based on collagen – proved superior, although it was demonstrated that the implantation of a skin substitute after von Langenbeck palatoplasty did not improve the development of the dental-alveolar process [Ophof et al. 2010]. Roels et al. [2003], who tested different biomaterials in a dog model studies, selected the appropriate ones and found, which of them would probably be promising substitutes for autologous bone grafts and could be used in patients with cleft palate. Autologous substitutes of oral cavity mucosa also seemed promising candidates as possible graft material. It turned out, however, that they did not contribute to the improvement of palatal wound healing process, which could indicate a too slow revascularization of the region; it is considered crucial to maintain the stability and integration of substitutes used [Ophof et al. 2008]. It is suggested that mesenchymal stem cells (MCSs) express vascular endothelial growth factor (VEGF), which is beneficial for bone regeneration due to induced vascularization. X-ray and histological studies on induced cleft palate in Beagle dogs may suggest that MCSs transplantation with carbonated hydroxyapatite (CAP) particles become a new treatment of cleft lip and palate patients [Yoshioka et al. 2012].

Despite the rise of so many new technical solutions and adaptation to the requirements in each of the projects, abnormal growth and development of the maxillofacial part may occasionally occur, what can lead to distortion of the maxilla and, in consequence, occlusion problems [Fossum 2009, Séguin 2011]. While the priority in human medicine is to find new therapeutic solutions to improve the compensating for or correcting clefts, animals suffering from CP are usually euthanized, also for financial reasons (e.g. due to expensive operations) and/or for other practical reasons. In addition, each of the dogs, that have undergone surgical CP correction is automatically disqualified from the full participation in the Dog Show, while at the same time it might seem that the consciousness of animal welfare and social mentality indeed change. It has been repeatedly emphasized that each identified case of CP is different, and the defect – thought a challenge for the breeder or the owner of the dog – is certainly not a death sentence. The meaning of dysmorphology in the observed congenital defect requires a specific approach and intervention of the veterinary surgeon, emphasizing how much one can make instead of simply resorting to euthanasia of the animal [Moura and Pimpão 2012]. This can be supported by the fact that many owners of CP-affected dogs claim that their dogs have lived a long time in good health despite the diagnosis, regardless of whether they had been operated upon or not [Coile 2009]. Nevertheless, due to humanitarian reasons, affected puppies are put down immediately after birth.

Breeders recognize the importance of genetic counseling and the DNA test results play an important role in the selection of a stud dog, especially if it is possible to reduce the risk of a disease that might by life-threaten to puppies. Despite the constantly innovating, faster and more efficient methods of research involved in pursuit for mutations and polymorphisms in the genes potentially responsible for the development of diseases and defects, no candidate gene or group of genes responsible for cleft palate in dogs of different breeds has been identified so far. Researchers put a priority both to the quest for cleft palate causes and to define the mechanism underlying its inheritance.

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ROZSZCZEP PODNIEBIENIA U PSA DOMOWEGO *CANIS LUPUS FAMILIARIS* – ETIOLOGIA, PATOFIZJOLOGIA, DIAGNOSTYKA, ZAPOBIEGANIE I LECZENIE

Streszczenie. Rozszczep podniebienia jest jedną z najczęściej występujących wad wrodzonych u psów, związaną z nieprawidłowym rozwojem twarzoczaszki. Największą predylekcję wydają się wykazywać rasy brachycefaliczne. To anatomiczne i czynnościowe zaburzenie charakteryzuje się obecnością szczeliny łączącej jamę ustną z jamą nosową. Rozszczep może dotyczyć podniebienia pierwotnego lub wtórnego. Mimo rozwoju w zakresie diagnostyki i metod terapeutycznych, badanie kliniczne i postępowanie chirurgiczne nadal stanowią podstawę rozpoznania i ewentualnego leczenia tej wady. W większości przypadków przeprowadza się eutanazję zwierzęcia. Wskazana jest eliminacja z hodowli osobników dotkniętych wadą. Defekt ten prawdopodobnie ma złożoną etiologię, oprócz czynników genetycznych, czynniki środowiskowe również przyczyniają się do jej powstania. Jednakże podłoże genetyczne wady nie zostało jeszcze jednoznacznie wyjaśnione.

Słowa kluczowe: *Canis lupus familiaris*, rozszczep podniebienia, wada wrodzona

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