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Designing Strategies for Cleft Lip and Palate Care

Edited by Mazen Ahmad Almasri

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Contributors

Donald R Laub Jr., Mustafa Chopan, Lorasb Sayadi, An-Suey Shiao, Chin-Lung Kuo, Enio Moura, Cláudia Pimpão, Norifumi Nakamura, Masahiro Tezuka, Aram Keteyian, Yuji Mishina, Letizia Perillo, Abdolreza Jamilian, Sara Eslami, Fabrizia D'Apuzzo, Mairaj K. Ahmed, Emanuela Taioli, Anthony Bui, Yunfeng Xue, Ayisha Ayub

Notice

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Meet the editor

Dr. Mazen Ahmad Almasri is an assistant professor of Oral and Maxillofacial Surgery at the Faculty of Dentistry, King Abdulaziz University (KAU), in Jeddah City that is located on the Red Sea at the glamorous Western Region of Saudi Arabia.

He graduated from KAU with an honor degree back in 2002 and went to McGill University (Montreal, Quebec, Canada) in 2005 for the training and education in the field of Oral Maxillofacial Surgery, Reconstruction, and Dental Implantology, where he completed his residency training program, fellowship, and masters of dental science degrees. Thereafter, Dr. Almasri succeeded to become an active fellow of the Royal College of Dentists of Canada since 2009 and a diplomate of the American Board of Oral and Maxillofacial Surgery since 2011. Dr. Almasri's passion toward advancing the clinical care and education has continued as a surgeon at KAU health center, an office practice, a researcher, and an educator to undergraduate and postgraduate Oral and Maxillofacial Surgery programs.

Contents

Preface

Back in the 1990s in the beautiful city of Jeddah, under the umbrella of the unique Faculty of Dentistry at King Abdulaziz University, I started spending some elective time in different hospitals in the city as a dental student trying to understand the difficult subject, oral and maxillofacial surgery. At that time, none of the internet programs were available in order to help a dental student to watch the meaning of cleft surgery, orthognathics, facial trauma, or dental implant by a simple click at any of the video media available nowadays. This made me very confused and yet curious to understand those topics and worried about the idea of entering the operating room (OR) to watch all the scary scenes that our former amazing teachers used to show us in the lecture halls. I did not imagine that only a couple of years later we had the chance to go through the experience at some of the popular health-care centers in the city. However, I was still confused about that specialty, and hence I had to take the decision of traveling to the USA to go through the experience again during summer vacation, hoping to get more answers to what I was looking for. Thereafter, a big part of the picture was uncovered, and I learned my valuable lesson; the medical service is like a four-dish meal that can only be designed by a chef. And that's where I fell in love with the field; I could always be the chef tailoring what is best to be served.

The field of cleft lip and palate is one of the areas in the medical practice that can show variable regimes according to different factors such as the general society understanding, access to specialized health care, manpower, resources, expertise, patient and parent compliance about oral hygiene, cleft grafting techniques, research evidence, and genetic advancement. One or more of the former can change the *recipe*.

During the process of exploring the recipe between Jeddah, Abha, and Montreal (Canada), I was lucky to meet a lot of amazing mentors in the field of oral and maxillofacial surgery : Dr. Edward Ellis III, Dr. Johan Ryneke, and Dr. Eric Dierks at international conference in Riyadh, Saudi Arabia. At that time, I was already involved deeply in a busy multidisciplinary practice. However, meeting those famous teachers took us into an amazing talk we enjoyed having over dinner about the concept of designing care. The impressive part was that each one of those amazing surgeons was practicing in a different region including the USA, South Africa, and Canada. And, I guess by the time we reached desert, we agreed about the general concept of health care, "being a chef is the key of success."

In "Designing Strategies for Cleft Lip and Palate Care" it was aimed to link the epidemiology from different areas in the world with the interspecialty surgical care and the future genetic research projects. The objective is to concisely discuss the methodology of interspecialty care and stimulate future ideas for prophylactically managing or preventing such deformities. I am confident that one day the surgical interventions that bombard the

patients from the day of newborn delivery and throughout the years of youth should be significantly decreased based on the genetic prophylactic intervention, probably.

I hope that the book can reach out easily to students, residents, practitioners, and researchers in the field to give them a different prospect of understating cleft lip and palate deformities and stimulating novel ideas to manage the patients all over the world. And hereby, I as an editor to the book acknowledge all the contributors' effort that was provided to put this work together.

Acknowledgment

I am very grateful to **Professor Abdulrahman Bin Obaid Alyoubi**, the respectful president of King Abdulaziz University in Jeddah City, Saudi Arabia, for his extraordinary support to science, manpower, and the society.

A special gratitude to the administration at the Faculty of Dentistry, Dean, Professor Abdulghani Mira, and the respectful vice deans for their continuous help toward education, clinical care, and research: Dr. Moath Attar, Dr. Rayan Kayyal, Dr. Ayman Darrab, and Dr. Sahar Bukhari.

A warm appreciation to my colleagues and friends Dr. Ahmad Saeed Jan, head of the Oral Maxillofacial Surgery Department, and Dr. Abeer Abdulrahman Alnuwaiser, head of the Internship Training Program, for their ongoing support to accomplish this project among others in King Abdulaziz University.

I can never thank enough all my family members, my father Ahmad Jawad Almasri, mother Fatima Abduljawad, friends, colleagues, nurses, and the secretarial office members. You all are the power of life, thank you!

Dr. Mazen Ahmad Almasri, BDS, MSc, FRCD(c), Dipl ABOMS
Consultant/Assistant Professor of Oral and Maxillofacial Surgery
Faculty of Dentistry, King Abdulaziz University
Jeddah City, Saudi Arabia

Section 1

Epidemiology of Cleft Lip and Palate Care

Chapter 1

Epidemiology of Cleft Lip and Palate

Mairaj K. Ahmed, Anthony H. Bui and
Emanuela Taioli

Additional information is available at the end of the chapter

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Abstract

Orofacial cleft (OFC) anomalies are amongst the most common congenital anomalies and the most common craniofacial anomalies. Despite their poorly characterized etiologies, cases of OFC are usually grouped by epidemiological studies as cleft lip, with or without cleft palate (CL/P), and cleft palate alone (CPO). Incidence of CL/P and CPO differs according to gender and ancestry and may vary widely across studies. Cases of OFC are characterized as either "syndromic" or "nonsyndromic," with further classification of nonsyndromic cases into isolated cases and cases that present with additional malformations. The genetic bases for many syndromic cases of OFC have been previously elucidated. Genetic associations have been described for nonsyndromic OFC as well. Importantly, etiology of OFC is known to involve interaction between genetic and environmental factors, including maternal nutrition and exposure to teratogenic agents. Furthermore, evidence points toward epigenetic as well as genetic factors influencing OFC etiology. Recent studies have begun to explore the association between CL/P and cancer. These studies report higher incidence of cancer among patients with CL/P and their family members as well as identification of common genetic markers mediating this increased risk, although much remains unknown about this link.

Keywords: cleft, epidemiology, etiology, genetics, epigenetics, environmental risk factors, cancer

1. Introduction

Orofacial cleft (OFC) anomalies may be unilateral or bilateral and involve the lip, the palate, or both. Due to similar phenotypic overlap and resulting health care needs of these patients, epidemiological studies usually group cleft lip, with or without cleft palate (CL/P), and cleft

palate alone (CPO) even though the etiology of each may be unique. Whether or not CL/P and CPO have distinct etiology and should be combined in investigations is under debate.

It is often found in epidemiological studies that CL/P and CPO is considered underneath the umbrella of either "syndromic" or "nonsyndromic." Furthermore, "nonsyndromic" CL/P and CPO cases can be subgrouped into those that are isolated or those that have additional malformations that do not form a recognizable syndrome. Relatively, the etiology of nonsyndromic cases of CL/P and CPO is lesser known compared to those found identified with a syndrome. Due to the poorly characterized etiology of CL/P and CPO, in general, there is still debate for the best method of grouping CL/P and CPO in epidemiological studies, but the most common current classifications are used to help determine associations and thus help the clinician with their diagnosis and subsequent treatment.

The genetic basis for many syndromic cases of CL/P and CPO are well-described. Evidence for genetic factors underlying nonsyndromic CL/P and CPO has begun to materialize as well. While less well-described, it is also known that epigenetic modifications can play a role in the development of CL/P and CPO. Recently, the association between OFC and cancer has been explored, with evidence suggesting existence of a link between the presence of OFC in patients and risk of cancer in these patients and/or their families.

2. Descriptive epidemiology

2.1. Prevalence

The overall prevalence of OFC is estimated to be approximately 1 in 700 live births, accounting for nearly one half of all craniofacial anomalies [1, 2]. As reported by the World Health Organization (WHO), the prevalence at birth of OFC varies worldwide, ranging 3.4–22.9 per 10,000 births for CL/P, and 1.3–25.3 per 10,000 births for CPO [3]. The incidence of CL/P and CPO can vary greatly between studies. The inclusion criteria, case definition, data sources, and selection bias contribute to the varying incidence estimates. Even though there are many different variables regarding the inclusion or exclusion criteria of in studies, the majority report a higher incidence of CL/P compared to CPO.

Prevalence has been found to vary based on ancestry, with the highest incidence rates observed amongst Asian populations (0.82–4.04 per 1000 live births), intermediate rates amongst Caucasians (0.9–2.69 per 1000 live births), and the lowest rates amongst African populations (0.18–1.67 per 1000 live births) [1, 4]. Prevalence has also been found to vary further by subgroup, for example, with one study reporting lower rates of OFC amongst Far East Asians compared to Filipinos [5].

2.2. Gender ratio

Prevalence of OFC additionally varies according to gender and cleft pattern. Male predominance has been consistently identified in CLP, with a male/female sex ratio of 1.81 (CI 95%:

1.75–1.86). For CP, the opposite has been shown, with a reported sex ratio of 0.93 (CI 95%: 0.89–0.96) [3]; however, this may be due in part to sampling bias, as one Danish study could not find a significant predominance of females in individuals with CP after combining both surgically treated and nonsurgically treated cases [6].

2.3. Laterality

OFC may be unilateral or bilateral. According to the International Perinatal Database of Typical Orofacial Clefts (IPDTOC) working group, the proportion of bilateral cases is 10.3% for cleft lip without palate (CL) and 30.2% for cleft lip with palate (CLP). Amongst unilateral cases, 36.9% of CL and 41.1% of CLP occur on the right side, suggesting that unilateral cases of CL/P occur more frequently on the left [7].

3. Classification

It is often found in epidemiological studies that CL/P and CPO are classified as either "syndromic" or "nonsyndromic." Cases of "nonsyndromic" CL/P and CPO are further categorized as isolated—those without an underlying syndrome or additional, nonsecondary malformations—or multiple—those that have additional malformations that do not form a recognizable syndrome. These distinctions are important epidemiologically, for identifying homogenous subgroups of cases, and clinically, for informing prognosis, recurrence risk, diagnosis, and treatment plan.

3.1. Syndromic

Individuals with "syndromic" CL/P or CP present with patterns of malformations and/or symptomatology that form a recognizable syndrome of known or unknown origin; hence, the CL/P or CP is part of a syndrome. Recognition of these syndromes is essential for assessing the risks faced by the child, providing the necessary treatment, and counseling the parents. Because the prevalence of associated anomalies varies across different populations of individuals with OFC, better understanding of the epidemiology of these anomalies could aid in the proper identification and characterization of the syndrome, leading to better care for the individual. Syndromes associated with OFC for which the underlying cause is known include chromosomal abnormalities, such as trisomy 13 or 18, Mendelian disorders such as Van der Woude Syndrome and teratogenic exposure.

A guideline for identifying syndromes in individuals with CL/P or CP is outlined by Venkatesh as follows [8]:

- Thorough clinical examination, preferably by geneticist or dysmorphologist.
- Comprehensive medical history: description of the cleft, antenatal history, birth history, developmental history, and family history.

- Physical examination: measurement of weight, length or height, and occipitofrontal circumference, identification of anomalies of eyes, ears, heart, extremities, and also to look for associated preauricular tags, lip pits, and epicanthal folds.
- Documentation by photographs of all affected individuals and first-degree relatives.
- Necessary laboratory and radiological evaluations.

3.2. Multiple

The multiple subset of CL/P and CPO includes those cases that are not a part of a recognizable syndrome and have major other malformations which may involve, but are not limited to, the eye, ear, head, neck, respiratory tract, gastrointestinal tract, and musculoskeletal system [5, 9]. Cases of "multiple nonsyndromic" CL/P and CPO may be classified as such simply by virtue of unrecognized syndromes or undocumented teratogenic exposures. Furthermore, wide variation exists in the classification of associated anomalies in cases of OFC [10].

3.3. Isolated

Cases of CL/P and CPO that are classified as "isolated" do not have an underlying syndrome or other secondary malformations. Most epidemiological studies of CL/P and CPO focus on those cases that are isolated in hopes to further gain insight into associations.

4. Etiology

Development of the head and face represents one of the most intricate events during embryonic development, synchronized by a network of transcription factors and signaling molecules together with proteins conferring cell polarity and cell-cell interactions. In mammals, the facial region develops from the facial primordia, which consists of the lateral and medial nasal prominences arising from the frontonasal process and the maxillary and mandibular processes arising from the first branchial arch. As demonstrated in **Figure 1**, fusion of medial nasal and maxillary prominences gives rise to the lip and primary palate, while fusion of separate palatal processes arising from the maxillary prominence gives rise to the secondary palate and occurs later during embryogenesis. These processes are known to be dependent, in part, on the migration and differentiation of neural crest cells from the neuroectoderm into the branchial arches [11].

Disturbance of this closely controlled cascade can result in a facial cleft where these facial primordia ultimately fail to meet and fuse or form the proper structures. Historically, OFCs have been classified as either CL/P or CPO [13, 14]. This broad subdivision is consistent with both the distinct developmental origins of the lip/primary palate and the secondary palate and the distinct cellular and genetic etiologies described for CL/P and CPO; cleft palate may occur secondary to or independently from cleft lip. However, there is some epidemiologic

evidence suggesting that cleft lip only has distinct etiologic features from cleft lip with palate and should be classified accordingly [15, 16].

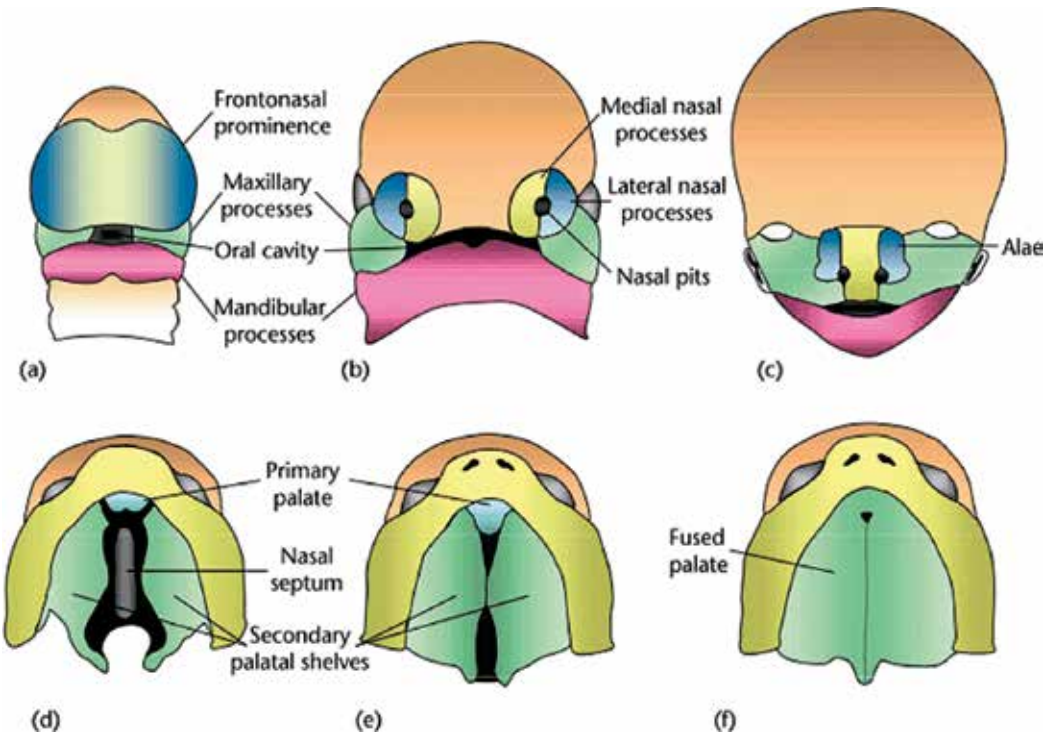

Figure 1. Schematic diagrams depicting human craniofacial development and formation of the secondary palate [12]. (a) By the fourth week of embryonic development, neural crest cells have migrated into the craniofacial region to form the frontonasal prominence, paired maxillary processes and the paired mandibular processes. (b) Formation of the nasal pits by the fifth week of embryogenesis divides the frontonasal prominence into paired medial and lateral nasal processes. (c) By the end of the sixth week of embryonic development, the medial nasal processes have merged with one another and with the maxillary processes to form the upper lip and primary palate, whereas the lateral nasal processes form the alae of the nose. The mandibular processes fuse together to form the lower jaw. (d) The secondary palate develops from the maxillary processes as bilateral outgrowths which grow vertically down the side of the tongue during the sixth week of embryogenesis. (e) During the seventh week of embryonic development, the palatal shelves elevate to a horizontal position above the tongue, make contact with one another and begin to fuse. (f) Fusion of the secondary palatal shelves with one another and with the primary palate and nasal septum is completed by the tenth week of embryogenesis. Figure is adapted from [12] © (2009) John Wiley and Sons Ltd.

5. Genetics

Both genetic and environmental factors have been shown to influence the risk of CL/P and CPO. Approximately 70% of all cases of CL/P and 50% of cases of CPO are designated as nonsyndromic [17], with the rest comprised of a wide range of malformation syndromes with known genetic and/or cellular etiologies. A summary of syndromic forms of CL/O and CPO in which the underlying genetic mutation has been elucidated is provided by Dixon et al. (**Table 1**; see original article for references) [18].

Cleft type	Syndrome	Gene
Cleft lip +/− cleft palate	Autosomal dominant developmental malformations, deafness, and dystonia	*ACTB*
	Familial gastric cancer and CLP	*CDH1*
	Craniofrontonasal	*EFNB1*
	Roberts	*ESCO2*
	Holoprosencephaly	*GLI2*
	"Oro-facial-digital"	*GLI3*
	Hydrolethalus	*HYLS1*
	Van der Woude/popliteal pterygium	*IRF6*
	X-linked mental retardation and CL/P	*PHF8*
	Gorlin	*PTCH1*
	CLP—ectodermal dysplasia	*PVRL1*
	Holoprosencephaly	*SHH*
	Holoprosencephaly	*SIX3*
	Branchio-oculo-facial	*TFAP2A*
	Holoprosencephaly	*TGIF*
	Ectrodactyly-ectodermal dysplasia-clefting	*TP73L*
	Ankyloblepharon-ectodermal dysplasia-clefting	*TP73L*
	Tetra-amelia with CLP	*WNT3*
Cleft palate only	Oculofaciocardiodental	*BCOR*
	CHARGE	*CHD7*
	Lethal and Escobar multiple pterygium	*CHRNG*
	Stickler type 1	*COL2A1*
	Stickler type 2	*COL11A1*
	Stickler type 3	*COL11A2*
	Desmosterolosis	*DHCR24*
	Smith-Lemli-Opitz	*DHCR7*
	Miller	*DHODH*
	Craniofrontonasal	*EFNB1*
	Kallmann	*FGFR1*
	Crouzon	*FGFR2*
	Apert	*FGFR2*
	Otopalatodigital types 1 and 2	*FLNA*
	Larsen syndrome; atelosteogenesis	*FLNB*
	Hereditary lymphedema-distichiasis	*FOXC2*

Cleft type	Syndrome	Gene
	Bamforth-Lazarus	*FOXE1*
	"Oro-facial-digital"	*GLI3*
	Van der Woude/popliteal pterygium	*IRF6*
	Andersen	*KCNJ2*
	Kabuki	*MLL2*
	Cornelia de Lange	*NIPBL*
	X-linked mental retardation	*PQBP1*
	Isolated cleft palate	*SATB2*
	Diastrophic dysplasia	*SLC26A2*
	Campomelic dysplasia	*SOX9*
	Pierre Robin	*SOX9*
	DiGeorge	*TBX1*
	X-linked cleft palate and ankyloglossia	*TBX22*
	Treacher Collins	*TCOF1*
	Loeys-Dietz	*TGFBR1*
	Loeys-Dietz	*TGFBR2*
	Saethre-Chotzen	*TWIST1*
Midline cleft lip	Opitz G/BBB	*MID1*
	Oro-facial-digital type I	*OFD1*

Table 1. Clefting syndromes in which the mutated gene has been identified. Adapted from Ref. [18].

In contrast, nonsyndromic CL/P is complex and multifactorial in origin. Both genetic and environmental risk factors have been shown to influence the probability of occurrence. Furthermore, there is evidence that the presence of environmental factors—in particular, maternal smoking—modulates the risk conferred by genetic factors and vice-versa, complicating the genetic analysis of nonsyndromic forms of CLP [19]. As such, multifactorial models of inheritance which allow for the evaluation of these risk factors both independently and in interaction with each other are preferred.

Association studies such as candidate gene studies, which test correlation between a phenotype and prespecified genes of interest, and genome-wide association studies (GWAS), which identify genetic variations across entire genomes that are associated with a phenotype, have been used to evaluate a variety of genetic polymorphisms associated with nonsyndromic OFC. Genes that have been examined through these studies for associations with nonsyndromic OFC exhibit a range of functions, including growth, DNA transcription, nutrient metabolism, immunity, and oncogenesis. A few such genes are described here.

5.1. Growth factors

Transforming growth factor alpha (TGF-α) is a growth factor encoded by the *TGFA* gene that serves as a ligand for the epidermal growth factor receptor, which is involved in cell proliferation, differentiation, and development [20]. The first association study of genes associated with CL/P found an association with *TFGA* [21]; however, evidence of this linkage since then has been mixed [22, 23]. *TGFA* is currently viewed as a modifier, rather than a necessary or sufficient determinant, of risk for OFC.

Proteins in the transforming growth factor beta (TGF-β) family bind various TGF-β receptors leading to recruitment and activation of the SMAD family of transcription factors. TGF-β is involved in processes including apoptosis, modulation of immune cell function, and wound healing; disruption of TGF-β has been implicated in cancer, Loeys-Dietz syndrome, and other conditions [20]. Knockout experiences in mice have shown the *TGFB3* gene to be associated with OFC [24, 25], and subsequent association studies have identified these results in humans [26].

5.2. Transcription factors

The *MSX1* gene, which is a part of the homeobox gene family, codes for a protein that is involved in transcriptional regulation during embryogenesis as well as limb pattern formation, craniofacial development (in particular odontogenesis), and tumor growth inhibition [20]. This gene has been implicated in the development of cleft in several candidate gene studies, and may even account for 1–2% of all isolated cases of OFC [27].

Interferon regulatory factor 6 (IRF6) is a transcription factor protein that is involved in early development, especially of tissue in the head and face [20]. Mutations of the *IRF6* gene at 1q32 causes Van der Woude syndrome, a Mendelian-inherited disorder which induces CL/P or CPO and accounts for about 2% of all CL/P cases [28, 29]. The overlap between phenotypic presentation of Van der Woude syndrome and isolated CL/P motivated further study into the role of *IRF6* in development of OFC. Variation at *IRF6* has been found to be strongly associated with CL/P and may account for up to 12% of the genetic contribution to CL/P at the population level [30–32]. Furthermore, the discovery of *ILF6* as a risk factor for CL/P served as an important example of elucidating genetic variants associated with cases of nonsyndromic OFC, which are often excluded from genetic analyses [33].

5.3. Nutrient metabolism

Deficient maternal folate intake has long been implicated in risk of OFC in children, leading to suggestions that mutations of the enzyme 5,10-methyltetranhydrofolate reductase (MTHFR), which catalyzes the synthesis of 5-methylenetetrahydrofolate, play a role in the etiology of cases of nonsyndromic CL/P [34]. However, results from several association studies evaluating the role of *MTHFR* mutations in CL/P have been conflicting [35–37].

Retinoic acid plays an important role during development. Its functions, mediated by retinoic acid receptor alpha (RAR-α), include regulation of development, differentiation, apoptosis, granulopoeisis, as well as transcription of genes involved in the circadian

rhythm [20]. Transgenic and knockout mice studies have additionally proposed a role in facial development [38]. Mutations of the *RARA* gene have been associated with development of OFC [39].

6. Epigenetics

Due to the relative lack of success in identifying causal genetic factors involved in OFC despite the numerous association studies that have been performed, recent attention has been directed toward the role of epigenetic programming, or modifications that do not involve DNA sequencing. Commonly studied epigenetic events include histone modification, chromatin remodeling, posttranscriptional gene alteration via noncoding MicroRNAs, and DNA methylation. MicroRNAs and DNA methylation, in particular, have begun to demonstrate distinct roles in etiologies of OFC.

6.1. MicroRNAs

While protein-coding genes make up only about 1.2% of the human genome, recent estimates suggest that up to 93% of the human genome codes for RNA transcripts. MicroRNAs (miRNAs) represent the largest family of such noncoding RNAs in the human genome. They are involved in gene silencing and play important roles in cell and tissue differentiation, including development of the secondary palate [40–43]. miRNAs have been shown to orchestrate many of the processes that are central to palatal morphogenesis, including epithelial-mesenchymal transformation, platelet-derived growth factor (PDGF) and TGF-β signaling, cell migration and proliferation, and collagen synthesis [44–48]. As such, further analysis of miRNA expression and gene networks will be key to elucidating mechanisms of palatal development as well as etiologies of OFC.

6.2. DNA methylation

DNA methylation, one of the most important epigenetic modifications in mammalian cells, is a process by which methyl groups are added to DNA in order to regulate gene expression. Methylation generally occurs at cytosines within the context of symmetrical CpG dinucleotide sequences, which are often concentrated in regions known as *CpG islands* and found in both gene bodies and promoter regions [49, 50]. Classically, methylation of *CpG islands* at gene promoters is thought to induce silencing of gene transcription; however, *positive* correlation between gene body methylation and gene expression has been observed [51, 52].

DNA methylation was first identified as a potential mediator of palatal development after a series of studies in which DNA demethylating agents were used to induce cleft palate in mice [53–55]. Since then, failures in DNA methylation demonstrated involvement in craniofacial malformations including cleft palate [56, 57]. Despite the current lack of knowledge regarding the epigenetic mechanisms mediating palatal development, evidence strongly indicates that DNA methylation plays a central role in regulating this process, and may perhaps serve as future risk assessment and therapeutic targets for patients with OFC.

7. Risk factors

The role of environmental factors in the etiology of OFC has been extensively studied. Known and suspected risk factors for CL/P and CP include family history, maternal nutrition, and exposure to teratogenic agents. The upper lip and palate are developed by 7 and 9 weeks after conception, respectively. Therefore, risk factors must be present before these times to influence the risk of CL/P and CPO.

7.1. Heredity

Family history is one of the strongest risk factors for both CL/P and CP. The risk of CL/P and CP has been reported to be increased in the first-, second-, and third-degree relatives and the identical twins of individuals with CL/P and CP, with even nonsyndromic cases of CL/P exhibiting evidence of genetic components [58–61]. However, few cases demonstrate true Mendelian inheritance patterns [62]. Moreover, CL/P and CP are known to be influenced by environmental risk factors. Specifically, there is growing evidence of gene-environment interactions that may influence the risk of these conditions.

7.2. Maternal drug use

Maternal drug use seems to play only a small role for the origin of orofacial clefts, but studies have shown that maternal use of folate antagonists (valproic acid and carbamazepine), dihydrofolate reductase inhibitors (trimethoprim, triamterene, and sulfasalazine), benzodiazepines, nonsteroidal anti-inflammatory drugs, retinoids, and corticosteroids is associated with a marked increase of cleft lip and palate [63–67].

7.3. Maternal diseases

The increased risk of having a child with CL/P or CP in women with nongestational diabetes or maternal hyperthermia is well-characterized [68, 69]. Additionally, a study conducted in Hungary found an increased risk of CL/P for children born to mothers with influenza, common cold, orofacial herpes, and gastroenteritis during pregnancy, posterior CP in mothers with influenza, sinusitis, and bronchitis, and OFC in mothers with epilepsy or angina pectoris [70].

7.4. Nutrition

The role of maternal nutrient intake in the development of congenital malformations in the child has long been studied with the aim of elucidating the etiologies of specific birth defects and informing effective prevention strategies. Evidence indicates that maternal nutrient intake affects the risk of giving birth to a child with CL/P or CP. In particular, a lack of vitamin B9, more commonly known as folate (or its synthetic form, folic acid), in the mother's diet has long been linked to the risk of congenital malformations. An association between maternal

folate intake and reduced risk of having a child with CL/P or CP has previously been demonstrated [71]. However, studies have not consistently linked folic acid with OFC as they have with neural tube defects [72, 73].

Previous reports have shown maternal intake of vitamins other than folate, such as other B vitamins (e.g. riboflavin), iron, zinc, and the amino acids choline, methionine, and cysteine, to be associated with reduced risk of having a child with CL/P or CP [72, 74, 75].

Vitamin A is known to play a crucial role in fetal development. Deficient and excessive intakes of vitamin A increase the risk of birth defects, including OFC, in animals as well as humans [76–79], but exact daily intake numbers have not been established [80].

7.5. Maternal exogenous exposures

Most of the CL/P and CPO epidemiologic studies support a role for environmental factors in the etiology of clefting. The most common risk factors reported were maternal exposure to tobacco products [81, 82], alcohols [83], some viral infections [70], pesticides [84], and teratogens in the workplace or at home in early pregnancy [85–87]. Recognized teratogens included rare exposures such as phenytoin, valproic acid, thalidomide, and herbicides such as dioxin. As mentioned previously, risk of CL/P or CPO conferred by these exposures—in particular tobacco—may be modulated by the presence or absence of certain genetic factors [19, 88, 89].

8. Cleft palate and cancer

Several studies from different countries (USA, Latvia, Denmark, and Brazil) have identified an association between cleft palate and cancer [90–95]. The first epidemiological studies addressed the presence of cancer in cleft lip/palate subjects and their families. Parents of kids with sporadic CL/P have a higher risk of developing cancer than control families [96], and increased risk of cancer in adulthood can be seen in a Danish population-based cohort of CL/P subjects [97]. Such studies suggested that the association was most frequent for breast cancer but also colorectal, gastric, prostate, and uterus cancers. In a large study, 313 families segregating cases of isolated CL/P, including information of 13,879 individuals, were analyzed by Vieira [93]. The study brings further evidence that individuals born with CL/P and their family members have a higher prevalence of cancer than the general population. This risk is three times higher in first- and second-degree relatives and decreases to 1.5 times in third-degree relatives.

A possible genetic link was identified in two families with mutations in the E-cadherin gene CDH1 with CL/P and hereditary diffuse gastric cancer [98]. CDH1 is highly expressed in the palate. Vogelaar et al. also identified germline mutations multiple families with gastric cancer and orofacial clefts [99]. One concern in interpreting these studies is that cleft lip/palate patients tend to have a higher prevalence of behavioral risk factors, such as smoking and drinking because of their limited social interactions as adolescents, thus

are at higher risk of tobacco and alcohol-related cancers independently from their initial malformation.

What is lacking is a study of cancer cases and the risk of cleft palate in their family members. Such studies are limited by the fact that the genetic defect is still a rare event, and the number of cancer cases necessary to address the problem would be extremely large. A study conducted on family members of cancer patients (Taioli et al. [95]) involved an epidemiological questionnaire including family history of cancer and congenital oral cleft malformations that was administered to 168 cancer survivors and a population-based sample of 170 healthy subjects. In the control group, 1.2% reported a family member with CL/P; among cancer survivors, the figure was 4.2% (odds ratio: 3.7; 95% confidence interval: 0.75–17.8; $p = .07$). Among cancer survivors with a family member with CL/P, there was an apparent excess of testicular cancer and melanoma in comparison with the cancer survivors with no family history of CL/P. These preliminary results suggest a common etiologic background for cancer and CL/P.

Taken all together, the data suggest that there are shared environmental and genetic factors in families that predispose to both cleft palate and cancer.

9. Conclusion

OFCs are the most common craniofacial anomalies, and one of the most common congenital anomalies worldwide. OFCs have historically been grouped as CL/P or CPO. However, existing evidence suggests that separate etiologies may exist for cleft lip alone versus cleft lip with palate. CL/P and CPO are classified as syndromic or nonsyndromic; nonsyndromic cases are further subclassified as multiple or isolated.

Both genetic and environmental factors have been implicated in the etiology of OFC. The genes underlying a number of known syndromes associated with OFC have been identified. Furthermore, environmental factors such as alcohol and tobacco have been shown to modulate the risk of OFC conferred by certain genetic factors.

Although nonsyndromic OFCs are not traditionally the subject of genetic analysis, a number of genomic association studies have evaluated the link between genetic variants and nonsyndromic OFC. Examples of genes that have been examined in such studies include those that code for growth factors, transcription factors, and nutrient metabolism proteins. In addition to genetic factors, studies have recently begun to explore the role of epigenetic modifications in palatal ontogeny and etiology of OFC.

A number of environmental and maternal factors that influence the risk of having a child with OFC are well-described. In particular, family history, maternal drug use, nutrition, and exogenous exposures demonstrate strong links with development of OFC in the child.

Several studies have shown a higher incidence of cancer amongst patients with CL/P and their families. Additionally, studies have begun to identify higher rates of CL/P in the families of patients with cancer, although less is known about this. Combined, these suggest that CL/P and cancer may be mediated by shared environmental and genetic etiologies.

Author details

Mairaj K. Ahmed[1]*, Anthony H. Bui[2] and Emanuela Taioli[3]

*Address all correspondence to: mairaj.ahmed@mountsinai.org

1 Cleft/Craniofacial Center, Icahn School of Medicine at Mount Sinai, NY, NY, USA

2 Icahn School of Medicine at Mount Sinai, NY, NY, USA

3 Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, NY, NY, USA

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Chapter 2

Cleft Lip and Palate Patients: Diagnosis and Treatment

Letizia Perillo, Fabrizia d'Apuzzo, Sara Eslami and Abdolreza Jamilian

Additional information is available at the end of the chapter

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Abstract

Cleft lip or palate is one of the most common types of craniomaxillofacial birth anomalies. Midface deficiency is a common feature of cleft lip and palate patients due to scar tissue of the lip and palate closure. Cleft lip and palate patients should be carefully evaluated by the craniofacial team in order to detect potentially serious deformities. Craniofacial team is involved with diagnosis of facial morphology, feeding problems, guidance of the growth and development of the face, occlusion, dentition, hearing and speech problems, and psychosocial issues and jaw discrepancy of the patients with cleft lip and palate or craniofacial syndromes. Treatment for cleft children requires a multidisciplinary approach including facial surgery in the first months of life, preventive and interceptive treatment in primary dentition, speech therapy, orthodontics in the mixed dentition phase, oromaxillofacial surgery, and implant and prosthetics in adults. Treatment plan from orthodontic perspective can be divided into the following stages based on the dentition stages: (1) presurgical orthopedics, (2) primary dentition, (3) mixed dentition, and (4) permanent dentition. The aim of this chapter is to assess a rational team work approach in the management of the patient with cleft lip and/or palate from birth to adulthood.

Keywords: cleft lip, cleft palate, diagnosis, treatment, maxillary deficiency

1. Introduction

Cleft lip or palate is one of the most common types of cranio-maxillofacial birth anomalies. It accounts for 65% of all head and neck deformities [1]. Maxillary deficiency is a common feature of cleft lip and palate patients due to scar tissue of the lip and palate closure. For treatment of maxillary deficiency, various devices, such as facemask [2], protraction headgear [3], orthopedic mask [4], reverse chin cup [5], tongue appliance [6], tongue plate [7], surgically assisted orthopedic protraction, and distraction osteogenesis have been introduced [8]. Treatment of

cleft lip and palate in patients should be started after birth and continues to adulthood. Lip closure and palatal closure are performed at 3 months and around 12 months of age, respectively, as well as secondary alveolar bone graft is done between 9 and 12 years of age [9]. However, orthodontic intervention usually begins during the mixed dentition. Orthodontic treatment in patients with cleft lip and palate are focused on maxillary arch expansion, correction of upper incisor misalignments, gross rotations of incisors, and crossbites and correction of Class III skeletal growth pattern. Patients with cleft lip and/or palate should be treated by teamwork. The team conception allows a systematic treatment plan to be developed and allows the team members to work together properly to identify problems. Orthodontic treatment plan can be divided into the following stages based on the dentition stages: (1) presurgical orthopedics, (2) primary dentition, (3) mixed dentition, and (4) permanent dentition.

In the following sections about diagnosis, classification, and treatment options in different period of time are discussed. Therefore, the aim of this chapter is to assess a rational teamwork approach to the management of the patient with cleft lip and/or palate from birth to adulthood.

2. Diagnostic considerations

Ultrasonography serves as a noninvasive diagnostic tool, now regularly recommended as a routine component of prenatal consideration. This noninvasive diagnostic tool helps to determine gestational age, confirm fetal viability, check placental location, establish the growth and their number of fetuses, and examine fetal anatomy to detect any deformities [10].

3. Treatment planning for cleft lip and palate patients

The treatment of cleft lip and palate should be started right after birth. Treatment for cleft children requires a multidisciplinary approach including: facial surgery in the first months of life, preventive and interceptive treatment in primary dentition, speech therapy, orthodontics in the mixed dentition phase, oral and maxillofacial surgery, and implant and prosthetics in adults. So the treatment to achieve a proper occlusion and function often lasts from birth until adulthood. Patients with cleft lip and palate routinely require extensive and prolonged orthodontic treatment. Close cooperation between the orthodontist, surgeon, prosthodontist, and general dentist is required. Cleft lip and palate patients should be carefully evaluated by the craniofacial team in order to detect potentially serious deformities that can be associated with cleft lip and palate. The team conception allows a systematic treatment plan to be developed and allows the team members to work together properly to identify problems. Maxillary deficiency is a common developmental problem in cleft lip and palate patients. The treatment objectives are to correct the deficient maxillary arch, the anterior and posterior cross bites, correct misaligned maxillary incisors, and also obtain satisfactory overjet and overbite. The following general and local factors must be evaluated before planning any treatment.

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3.1. General factors

(a) Health of the patient includes physical, mental, and social.

(b) Family background and attitude.

3.2. Local factors

(a) Width of the cleft.

(b) Adequacy of tissue adjacent to the cleft.

(c) Length of soft palate in relation to nasopharynx.

(d) Configuration of nasopharynx.

(e) Functional activity of palate-pharyngeal muscles.

3.3. Interceptive treatment

Interceptive treatment is recommended because it can

- improve facial and dental esthetics,
- help overcome psychological issues,
- improve speech,
- reduce the risk of decay, and
- avoid the need for major surgery in the future.

3.4. Cleft lip repair

The aim of lip repair is to close the cleft to create esthetics of the face and to restore muscular anatomy of the upper lip. This procedure will serve to develop lip normally with minimal scar tissue. Closure of the lip is accomplished by the plastic or maxillofacial surgeon when the patient is approximately 3 months of age and weighs at least 10 pounds.

3.5. Cleft palate repair

The objective of cleft palate surgery is to close the palate to restore normal function to eating and drinking and to enhance the development of normal speech. The palate forms the floor of the nose and the roof of the oral cavity; thus, a cleft causes a free communication between these two cavities. Treatment of cleft lip and palatal patients is complex because of potential problems with middle ear infections, speech, feeding, occlusion, creating maxillary deficiency due to scar tissue from surgical procedure, and jaw abnormalities. Surgical procedure of the cleft palate is best performed before the child reaches 12 months of age. This procedure is called palatoplasty. Additional surgeries are often needed to achieve the best results [9].

3.6. Nursing care

The role of nursing in the care of patients and or families includes family education, case management, access to team care, assistance with infant feeding, consultation, research, and primary care.

3.7. Feeding problems

An infant with a cleft may have difficulty in feeding due to lack of suction. Cleft lip patients do not usually have feeding problems. But when the palate is involved, feeding can be a crucial challenge. Normally, the palate serves as a barrier to prevent food and liquids from entering the nose. A patient with cleft palate swallows a lot of air and regurgitates food into the nose. Cleft palate patients may need a special bottle and nipple to receive milk. Patients with feeding problems should be visited regularly by a specialist to make sure that they are gaining weight well.

3.8. Speech problems

Difficulty in speech is the number one issue for cleft patients after facial and dental esthetics. They have difficulty in speaking correctly, and treatment can help them to achieve a good tongue posture. Difficulty with speech articulation is common in cleft lip and palate patients. Many patients require speech therapy after surgery. Speech therapist will repeatedly evaluate speech development and will arrange for necessitate speech therapy.

3.9. Dental problems

Dental problems have an effect on chewing, facial esthetics, speech thus these patients frequently require orthodontic treatment. Prevalence of dental anomalies such as variations in tooth number, dislocation, missing, supernumerary, tooth shape, and reduced tooth dimensions has always been found to be higher in cleft lip and or palate patients when compared with general population [11]. Akcam et al. [12] reported that a significant amount (96.7%) of children with cleft had at least one dental irregularity. Shapira et al. [13] found that in the cleft area, most developmental dental anomalies are related to the maxillary lateral incisor, both in the primary and in the permanent dentitions. Shape anomalies, such as enamel hypoplasia and peg shaped, have also been frequently seen in cleft lip and/or palate patients [14]. Tooth agenesis, known as hypodontia or congenital absence of teeth, is the most commonly detected developmental abnormality of the human dentition. All types of clefts are often associated with congenitally missing teeth [15]. Jiroutova and Mullerova [16] studied the frequency of hypodontia in cleft lip and or palate patients and found that the maxillary dentition was affected more often in cleft lip and palate, the mandible was involved more frequently in isolated cleft palate. The dental bud of the upper lateral incisor was affected most commonly in cleft lip and in cleft lip and palate, whereas the second lower premolar was most frequently absent in an isolated cleft palate.

Paranaiba et al. studied prevalence of dental abnormalities in patients with nonsyndromic cleft lip and/or palate in Brazilian population and found that agenesis of the premolars and maxillary lateral incisors were significantly more frequent in patients with unilateral complete cleft lip and palate [17]. In various studies, lateral incisors were reported to be the most commonly missing teeth followed by second premolars [12, 18, 19]. While, in a another study Laatikainen and Ranta [20] found that the maxillary second premolar was the most frequently absent tooth, followed in order of frequency by the upper lateral incisor and the mandibular second premolar.

Polder et al. [21] did a meta-analysis of the prevalence of dental agenesis of permanent teeth of Caucasian populations in North America, Australia, and Europe and found that mandibular second premolar was the most affected tooth, followed by the upper lateral incisor and the upper second premolar. Shapira et al. [22] found a total of 47 missing second premolars in the upper arch and 23 missing in the mandible. In literature, Ranta [23] reported that the incidence of hypodontia rises strongly with the severity of cleft. Paranaiba et al. [17] also found that patients with unilateral cleft lip and palate were affected more significantly by dental anomalies than those with bilateral cleft lip and palate. It should be considered that ethnicity also plays an important role in prevalence of cleft and associated anomalies. Polder et al. reported that prevalence of dental agenesis in Europe and Australia was higher than in North America. In addition, they reported that the prevalence of dental agenesis in females is 1.37 times higher than in males for all three continents. Defects of enamel such as hypoplasia and opacities are common in the teeth adjacent to the cleft site. Decay is higher in these patients compared with the non-cleft populations. Therefore there is a higher incidence of caries in teeth with enamel defects, the issues of prevention and brushing are of great importance in cleft children [24].

3.10. Role of psychologist in cleft lip and palate patients

It is clear that attractive children are seen by others as happier, having more positive social behavior. Children with cleft may have a less attractive appearance and speech problems make it worst. Babies may face bullying and teasing because of their appearance. Parents may be more tolerant of misbehavior in their child and are more likely to spoil their child by being overprotective. Moreover, peer interaction also has an important role in maintaining psychosocial problems. Cleft lip and palate patients are at high risk for developing psychosocial problems especially those relating to self-concept, peer relationships, and appearance. Psychological problems affect development of children with cleft lip and palate. Therefore, these patients are treated by the interdisciplinary team to maximize positive outcome of treatment. Missing teeth, feeding difficulties, the infant's appearance, presence of misaligned teeth, and severe malocclusion can lead to social isolation. Moreover, frequent visits to the doctor and surgeries can be quite stressful. The psychologist provides treatment plan for developmental, emotional, learning, and adjustment abnormalities. They focused on the appearance, speech, patient's self-esteem, psychosocial problems, self-confidence, interpersonal relationships, and emotional handicapped problems [25].

3.11. Role of otolaryngologist in cleft lip and palate patients

Patients with cleft lip and palate have a higher incidence of hearing problems. They have more frequent problems with fluid, ear infections, and otitis media, which can be very painful. It is crucial that to have the infant's hearing tested during the first few months and it is also very important that cleft lip and palate patients have regular hearing tests to screen middle ear problems. This could adjust the development of normal hearing as well as speech. As the child gets older, the rate of ear infections seems to reduce. Any abnormality of the upper airway can affect the function of the Eustachian tube and enhance the possibility of persistent fluid in the middle ear, which is a major cause of repeated ear infections. Hearing loss can be a consequence of repeat ear infections and persistent middle ear fluid. Tubes can be inserted in the ear by an otolaryngologist to relieve fluid build-up and repair hearing. Cleft lip and palate patients are suffering from mouth breathing, feeding, hearing, speech problems, and jaw deformities. There are some areas of overlap with plastic surgery, oral and maxillofacial surgery, otolaryngology, and speech-language pathology. Oral and maxillofacial surgeon evaluates the skeletal discrepancies related to cleft and craniofacial abnormalities such as maxillary deficiency and other skeletal malocclusions. Surgeons work with other members of the group to ensure appropriate and harmonious facial form and dental arch.

3.12. Role of pedodontist in cleft lip and palate patients

The role of pediatric dentistry in treatment of cleft lip and palate cleft patients is the comprehensive preventative and therapeutic oral health care of children, counseling and caries control. These treatments include following steps:

(a) Growth and development monitoring.

(b) Caries prevention and oral hygiene guidance.

(c) Behavior modifications.

(d) Routine dental care.

(e) Preventive and interceptive dentistry.

(f) Interceptive orthodontics where appropriate.

(g) Restorative procedures.

(h) Removal of primary dentition in surgical site.

(i) Periodontal considerations.

3.13. Role of orthodontist in cleft lip and palate patients

In the management of cleft lip and palate patients the orthodontist has an important role in the cleft and craniofacial team. They are involved with diagnosis of facial morphology, guidance of the growth and development of the face, occlusion, dentition, and jaw discrepancy of the patients with cleft or craniofacial syndromes. They provide orthodontic and ortho-

pedic treatment and general expertise for consultation with all of the other members of the cleft team. Different phases of active treatment will be necessary from birth to adulthoods. Orthodontist should consider many factors in determining when to initiate orthodontic treatment. These factors include the ability of the patient to cooperate, the severity of the malocclusion, the amount of jaw discrepancy, type of dental anomalies, existence of missing, dental shape anomalies, supernumerary teeth, and the need for future orthodontic treatment in the early mixed or permanent dentitions.

Orthodontic treatment plan can be divided into following stages based on the time of treatment:

(1) Presurgical orthopedics

(2) During primary dentition

(3) During mixed dentition

(4) During permanent dentition

3.13.1. Presurgical orthopedics

Presurgical infant orthopedics is sometimes used to relocate the segments of the cleft in maxilla prior to lip repair. A custom-fitted orthodontic appliance is applied to bring the parts of the lips, upper jaw, and nose closer together. This is called Nasoalveolar Molding (NAM). These appliances can make lip closure easier.

Advantages of presurgical orthopedics:

(a) To facilitate feeding

(b) To help establish normal tongue

(c) To provide psychological boost to the patients

(d) To assist surgeon in the initial repair

(e) To stimulate palatal growth and orofacial functional matrix

(f) To help decrease the number of ear infections

(g) Improve esthetics

(h) Repositioning of premaxilla

Although the evidence does not support the neonatal maxillary orthopedics as an essential or desirable routine procedure; Nonetheless, the molding of the segments achieved by these appliances does make definitive lip repair easier for the surgeon, especially for patients with a severely protruding premaxilla caused by a bilateral cleft lip [26].

3.13.2. During primary dentition

Midfacial deficiency is a common feature of cleft lip and palate patients due to scar tissue of the lip and palate closure [25]. During deciduous dentition, no orthodontic and orthopedic

treatments are given because it has limited advantage. Orthodontic and orthopedic intervention starts in the mixed dentition.

3.13.3. During mixed dentition

Early orthopedic treatment in cleft palate children is essential because the maxillary bones and their component parts may be moved and altered in young children with relative ease and thereby creates a more functional dental arch. Orthodontic interventions in patients with cleft palate are focused at correction of Class III skeletal growth pattern, maxillary arch expansion, correction of upper incisor misalignments, gross rotations of incisors, and cross bite of buccal segments. Maxillary deficiency may be a reflection of the underlying skeletal abnormality for which growth modification and redirection may be indicated with a protraction headgear. Treatment approach to improve the midface deficiency was achieved by using the face mask [2, 27], tongue appliance [6], tongue plate [27], protraction head gear [3, 28], suborbital protraction appliances [4], ankylosed teeth [29], endosseous implants [30], and surgically assisted orthopedic protraction and distraction osteogenesis [8]. Jamilian et al. [6] evaluated the effectiveness of tongue appliance on deficient maxilla in growing cleft lip and palate patients. They showed that tongue appliance improved the deficient maxilla.

Tongue appliance has Adams clasp in first maxillary molars and C clasps in the upper incisors and deciduous teeth in order to increase the retention. A screw is mounted in midpalatal area to correct bilateral posterior crossbite. It was activated twice a week by the patient. Four separate tongue cribs were incorporated in the palatal area, behind the upper incisors. These cribs are long enough to cage the tongue and are adjusted in the clinic to avoid traumatizing the floor of the mouth. Tongue appliance is seen in **Figure 1**. **Figure 2** shows the profile of the patient before application of the tongue appliance and **Figure 3** shows the profile of the same patient after using the appliance. Extraoral appliances are not used suitably by the patients, whereas they prefer to apply small-sized and more convenient appliances. Besides to their large size of extraoral appliances, they need high compliance and many clinicians observe lack of cooperation by patients treated by big extraoral appliances. The philosophy of tongue appliance [31–33] is provided in the following two ways:

(1) The force of the tongue during each swallowing might be 5 pounds. Each patient might have 500–1200 times swallowing in 24 hours. The pressure from the tongue is transferred through the tongue appliance to the deficient maxilla.

(2) There is substantial continuous pressure of tongue. Because tongue is caged behind the cribs that is why this force is continuous in the rest position and centric occlusion. This force pushes the nasomaxillary complex into a forward position. In other words, functional activity and physiological position of tongue create these considerable forces that are conducted by tongue through the palatal cribs and finally transmitted to the deficient maxilla and nasomaxillary complex.

The more anterior the tongue, the greater pressure will be. The more posterior the crib, the greater pressure will be. Jamilian et al. [6] reported that the anterior part of maxillary plane moved superiorly (anteinclination) and posterior part of it relocated inferiorly. In other words, the maxillary posterior segment is extruded slightly and that is why the lower jaw

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rotated in a clockwise direction. These changes led to correction of the overjet and reducing of SNB and increasing of mandibular plane angle. Click wise rotation of the mandible is not favorable in long face patients.

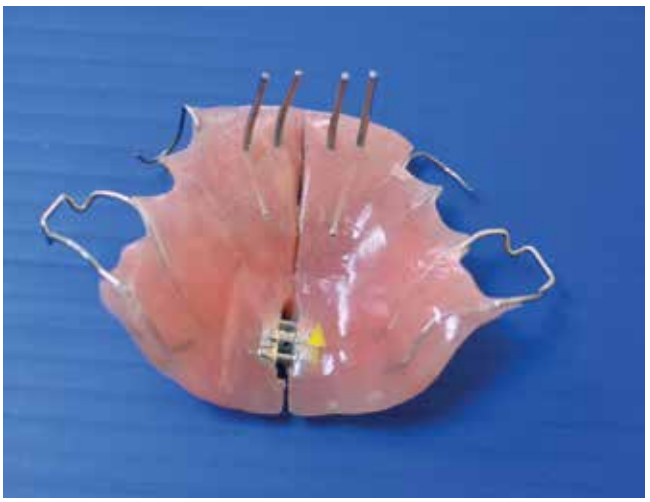

Figure 1. Tongue appliance with expansion screw.

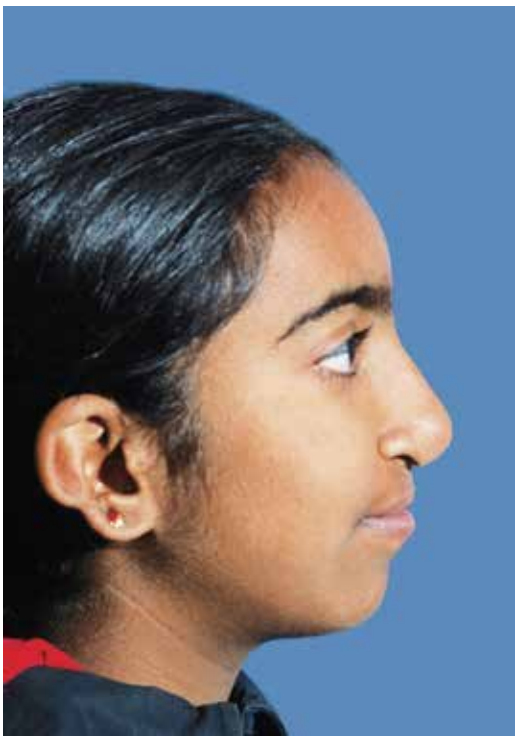

Figure 2. Profile view before treatment.

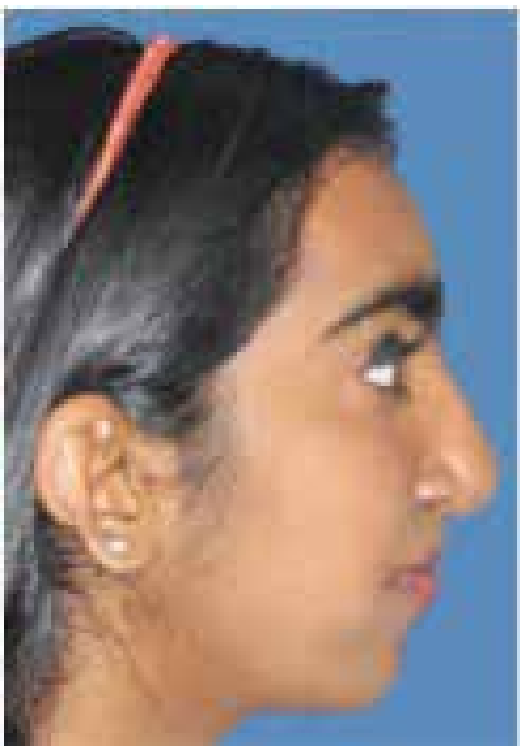

Figure 3. Profile view after treatment.

Tongue plate has been used for correction of maxillary deficiency [27]. Mechanism of tongue plate [7] is very similar to the tongue appliance. The pressure of tongue during rest position and swallowing is transmitted through the tongue plate to the deficient maxilla. The significant pressure of the tongue that is caged behind the acrylic plate transfers the nasomaxillary complex in a forward position. Some patients had some extent of irritation on the tongue from tongue appliance that is why tongue appliance was replaced by tongue plate. This has a smoothed area and these softened edges create it undamaging for the patient. Moreover, it is adjusted in a way to avoid traumatizing the floor of the mouth. Elimination of the cribs in tongue plate might offer a better psychological sense to the patients. Extra oral appliances such as facemask and reverse chin cup [5, 34] improve the deficient nasomaxillary complex but they have an unfavorable effect on the normal mandible. Extra oral appliances rotate the mandible in clockwise rotation and it is unfavorable in normal growth pattern and long face patients. Besides, the cup of facemask can create abrasion particularly in warm climates. Tongue appliance is an intraoral appliance and it is very comfortable and simple. It is constructed easily and it is not expensive. Tongue appliance and tongue plate will be accepted better than extraoral appliances due to less conspicuous of them. Children with cleft lip and palate have suffered from birth; tongue plate and tongue appliance are more comfortable as they create the least stress to patients in comparison with other big extraoral appliances. In spite of many advantages of them, tongue appliance and tongue plate have one disadvantage.

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Incisor mandibular angle is reduced due to removal of the pressure of tongue to the lower incisors and acting force of orbicularis oris to them. Tongue appliance and tongue plate have a screw to correct bilateral posterior crossbite. Expansion will lose all maxillary sutures like zygomaxillary, pterygomaxillary, thus, maxilla will transfer more easily in forward direction [35, 36]. On the other hand, upper jaw may be expanded in order to improve dental function, reliving crowding, align upper incisors, eliminate functional shifts, provide access for impacted teeth in the cleft site, provide restorative treatment to carious teeth, improve maxillary deficiency, and nasal airway in mixed dentition [6, 31]. Maxillary skeletal asymmetry in unilateral lip and palate patients may be reflected in a unilateral posterior cross bite, which may be corrected with a removable appliance with a screw or a quad helix type of appliance in the mixed dentition. A bonded or non-bonded hyrax expander are recommended along with extra oral traction, such as facial mask to stimulate maxillary protraction or chin cup to control mandibular growth (**Figures 4** and **5**). Patients with maxillary cleft do not have a midpalatal suture, which requires orthopedic forces to open. Instead there is a midpalatal cleft covered with scarred and repaired palatal tissues limiting the rate and amount of expansion. The slower rate of expansion and the lower force magnitude provided by a quad helix appliance allows the soft tissue of the palate to the increasing maxillary width, avoiding a breakdown of the scar tissue that can result in an oronasal fistula. As the permanent incisors erupt adjacent to the cleft site, maxillary incisors typically are rotated, misplaced, malformed, or hypo plastic. Removable appliance is used to correct upper incisor misalignment. Moreover, incisors may be absent or peg shaped and there may be one or some supernumerary teeth. Maxillary expansion appliances can be anchored on the permanent first molars and extended anteriorly to improve maxillary arch while correcting the cross bite. Usually expansion is followed by maxillary protraction using a traditional Delaire or other protraction appliances. After the expansion and protraction phase, full fixed appliances along with Class III elastics and sometimes extractions, if necessary, are usually needed to correct the malocclusion [33]. **Figures 6** and **7** show the intraoral photograph of a patient before and after orthodontic treatment, respectively. **Figures 8** and **9** show the frontal view of the same patient in pre- and postorthodontic treatment, respectively.

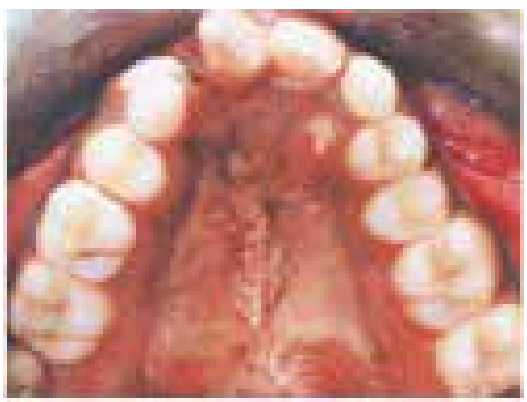

Figure 4. Upper arch before expansion.

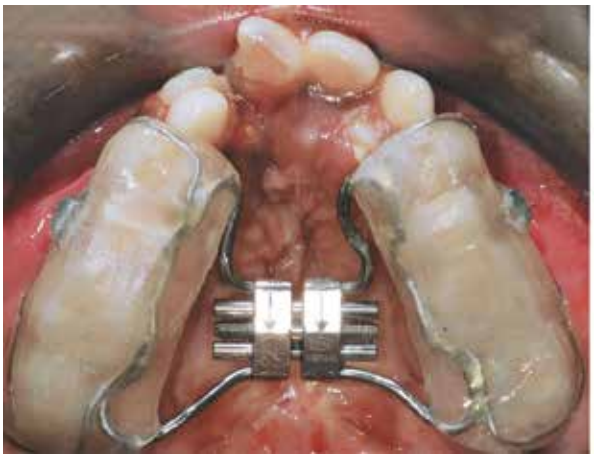

Figure 5. Upper arch during expansion with bonded hyrax.

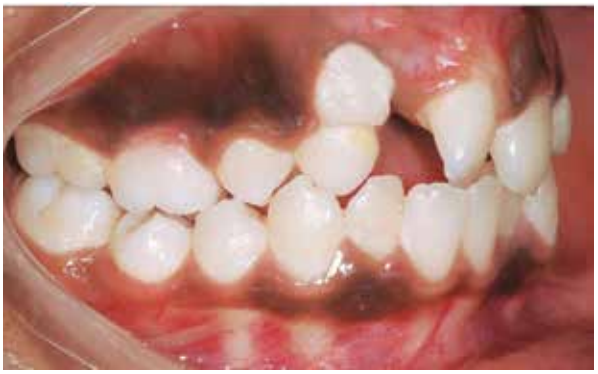

Figure 6. Intraoral view before orthodontic treatment.

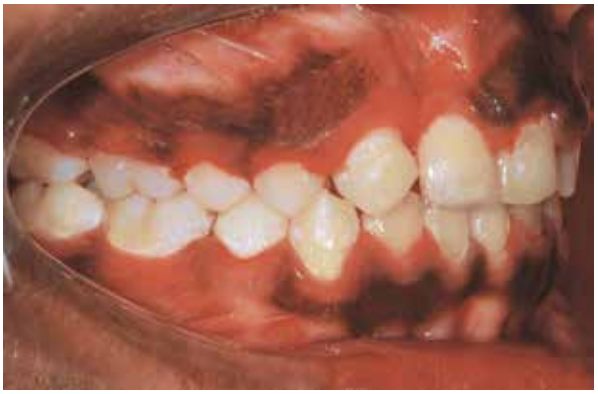

Figure 7. Intraoral view after orthodontic treatment.

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Figure 8. Frontal view before treatment.

Figure 9. Frontal view after treatment.

3.13.4. Permanent dentition

Comprehensive fixed appliance therapy usually occurs in the permanent dentition with the aim of preparing for alveolar bone graft that can be done by an oral surgeon. This phase usually involves aligning of malposed maxillary incisors. Reverse pull headgear or face mask therapy, expansion of maxillary arch may be continued during this time period. Final alignment of teeth is carried over with or without extraction. Orthodontic management is limited after eruption of permanent dentition. The established malocclusion and discrepancy between the upper and lower arch often require orthognathic surgery.

3.14. Role of oromaxillofacial surgeon in cleft lip and palate patients

Orthognathic procedure may be designated if a malocclusion develops due to abnormal growth of the maxilla. Treatment for adults may involve surgical in severe or camouflage in mild to moderate patients. Orthognathic surgery is performed to patients with deformities of the jaws to improve facial esthetics as well as to correct dental occlusion. Presurgical orthodontics are usually necessary to align the teeth, correct any compensations, decrowding, eliminate any dental midline discrepancy, coordinate arches, and localize space for prosthetic or implant replacement of the teeth. Ideally, the patient is referred to the surgeon after presurgical orthodontics. The postsurgical phase of orthodontics is required for creating perfect occlusion and better interdigitation after surgery.

3.14.1. Pharyngeal flap

Failure to achieve a seal between the posterior pharyngeal wall and soft palate lets leakage of air through the nose and causes cleft palate speech. This has proved not to be a problem in patients with a normal velopharyngeal mechanism. If a patient has speech problems a surgical procedure to create a pharyngeal flap probably will be required. To correct hyper nasality, this procedure contains raising a flap of tissue from the posterior pharyngeal wall and incorporating it into the soft palate. Pharyngeal flap is used when the muscles do not function appropriately or the repaired palate is too short. For adults with speech problems, pharyngeal flap, combined with an intensive schedule of speech therapy, can produce noticeable improvements.

3.14.2. Distraction osteogenesis

Distraction osteogenesis has become a new method for correction of maxillary deficiency [8, 37]. Distraction osteogenesis for maxillary advancement started in 1993 and is now broadly used in cases with skeletal Class III deformity due to maxillary deficiency [38]. Figueroa and Polley [39] reported that distraction osteogenesis was successfully used to advance the maxilla in children with cleft lip and palate. According to them the main advantages of distraction osteogenesis compared with conventional methods of craniofacial reconstruction were reduced time of surgery and cost and the ability to generate new bone. Many advantages and disadvantages of distraction devices have been detailed. For a large advancement in a patient with a cleft lip or palate, distraction osteogenesis may be advantageous. Figueroa and Polley [39] assessed the cephalometric landmarks on 14 patients with cleft palate who

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were treated with a rigid external distraction technique. Distraction osteogenesis provides less physical and psychological invasion in comparison to conventional LeFort osteotomy: that is, reduced operating time, less blood loss, less postoperative pain, and shorter hospitalization. Also, when intra-arch distraction is applied to lengthen the mandible or maxilla, orthodontic alignment of upper and lower arches are not necessary before the procedure [40]. Intraoral distraction osteogenesis devices are divided into two types namely bone borne or tooth borne. Advantages of these are their smaller size and better patient acceptance; however, the bone attached one has the disadvantage of the need for second intervention to remove the device [41].

Hyrax screw incorporated in an acrylic plate has been applied for treatment of maxillary deficient in cleft lip and palate patients. After creating horizontal cuts similar to LeFort 1 and vertical cuts between the premolars on both sides, a bonded hyrax screw was mounted on an acrylic plate for the slow sagittal expansion of upper arch. The distraction procedure can be initiated after 5 days of latency period.

The expansion is performed by activating the hyrax screw 0.8 mm per day after the latency period (**Figure 10**). Expansion was discontinued after achieving satisfactory overjet and occlusion (**Figure 11**). If open bite occurs during expansion period vertical elastics will be used to correct open bite. Consolidation period lasts 8 weeks and after this period hyrax screw is removed. One of the advantages of anterior maxillary distraction is that velopharyngeal area will be intact. Anterior distraction is used for skeletal deformity and fixed appliance is applied for correction of dental problems [8].

Some researchers suggested that distraction orthogenesis does not seem to have any advantages over surgery. Additionally, the occlusion at the end of distraction is much less defined than what is seen with conventional orthognathic surgery [42].

Figure 10. Hyrax screw incorporated in an acrylic plate.

Figure 11. Hyrax screw after activation.

4. Retention

The retention protocol for clefts follows the same principles of orthodontic treatment in Class III malocclusion without clefts. The upper and lower arches should have been coordinated throughout orthodontic and orthopedic intervention. Positive overjet and overbite with adequate intercuspation are necessary for retention. Hawley retainer in the maxillary and mandibular arch is used for retention. Hawley appliance often includes prosthetic teeth that will be displaced later with dental implants or prostheses. Patients are instructed to wear the Hawley appliance for 12 months continuously. After that, if the occlusion is stable, the Hawley retainer is used at night-time for additional six months.

Retention in cleft palate cases is longer than for noncleft patients. The reasons are due to:

(a) lack of bony stability,

(b) contracture of stretched or scar tissues, and

(c) missing teeth.

5. Recommendation

Treatment approach depends on the age and severity of the patients. Growth modification is the best treatment plan when the patient is still growing. We can take advantages of a child's growing years by guiding proper jaw bone formation with small intraoral appliances such as tongue plate and tongue appliance [6, 27]. These small intraoral appliances are recommended

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in cleft lip and palate patients who suffering from psychological and social problems associated with their malocclusion in early mixed children. Once the patient is an adult, camouflage may be an option for correcting mild deformities and surgery would be proper treatment plan for severe cases.

6. Conclusion

Cleft is the most common craniofacial malformation that an orthodontist may encounter. The orthodontist's role in the cleft lip and palate team requires close relationship with the other team members. Cleft lip and palate patients become more maxillary deficient and mandibular prognathic in their appearance. The most common specialties involved in the care of a child with a cleft are: oromaxillofacial surgeon, plastic surgeon, psychologist, orthodontist, general dentist, otolaryngologist, speech therapist, pediatrician, and prosthodontist.

Treatment plan from orthodontic perspective can be divided into the following stages based on the dentition stages: (1) presurgical orthopedics, (2) primary dentition, (3) mixed dentition, and (4) permanent dentition.

Author details

Letizia Perillo[1], Fabrizia d'Apuzzo[1], Sara Eslami[2] and Abdolreza Jamilian[2]*

*Address all correspondence to: info@jamilian.net

1 Multidisciplinary Department of Medical-Surgical and Dental Specialties, Second University of Naples, Naples, Italy

2 Department of Orthodontics, Cranio Maxillofacial Research Center, Tehran Dental Branch, Islamic Azad University, Tehran, Iran

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Chapter 3

Strategies to Optimize Global Cleft Care

Mairaj Ahmed, Yunfeng Xue and Ayisha Ayub

Additional information is available at the end of the chapter

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Abstract

Orofacial clefts represent the most common congenital craniofacial anomaly worldwide. This condition is best managed by an interdisciplinary team of specialists, often with gratifying results for both the patient and the care providers. Despite recent advances in the management, it remains a challenge today to provide cleft care in low- and middle-income countries (LMIC) due to the lack of basic health care infrastructure and long-term follow-up. International cleft mission trips have traditionally been successful in providing reconstructive plastic surgery to communities with limited resources. More recently, there has been a global effort in the cleft care community to facilitate development of sustainable local cleft care centers that are capable of providing longitudinal, comprehensive care to the indigenous population. This chapter focuses on the elements that are necessary for running a successful international cleft mission and a local cleft care facility, which include the essential personnel, operational protocols, equipment, logistics, patient selection, and follow-up. The challenges and future directions of providing cleft care in LMIC are also discussed.

Keywords: cleft, craniofacial, global health care, international missions, sustainable health care models

1. Introduction

Orofacial clefts represent the most common congenital craniofacial anomaly, with an estimated prevalence of 1.2 per 1000 people worldwide [1, 2]. Although the treatment of orofacial clefts and other craniofacial anomalies has improved dramatically in developed countries, this is not true for most low- and middle-income countries (LMIC), where the capacity of cleft treatment facilities is lacking and the overall care remains insufficient [3, 4]. More than 160,000 new patients with orofacial clefts are born globally each year [5], placing a significant

economic and psychosocial burden on the individual and the families involved. The burden of care for children with orofacial clefts in LMIC is disproportionally immense due to the severely limited access to basic care. People in these resource-limited regions regularly live with untreated clefts their entire lives, battling with prejudice and social ostracism [6]. A large number of humanitarian cleft care missions have provided corrective treatments to patients in LMIC who would not otherwise have had access to such care. However, it remains difficult to provide global care to these patients due to a number of obstacles, including security issues, logistical obstruction, lack of reliable social service facilities, unsustainable or short-lived local cleft care centers, less qualified local personnel, and long-term follow-up [7].

Until recently, there had not been a set of commonly accepted standards for cleft care in less developed countries. Aiming to fill this gap, in 2006, the Volunteers in Plastic Surgery Committee of the American Society of Plastic Surgeons/Plastic Surgery Educational Foundation undertook the project of creating universal guidelines to improve quality and safety for providing reconstructive plastic surgeries in developing countries. Experienced international cleft surgeons along with representatives from Society for Pediatric Anesthesia created and published a set of guidelines, and the final document has been reviewed and approved by the boards of both organizations [8]. During the same year, Operation Smile, the largest American international cleft organization, independently convened its own conference of experts from each specialty around the world to ensure that every child receives the same first world standard of care in an international mission. The product of the conference was "Operation Smile's Global Standards of Care," which was adopted by over 60 member countries within Operation Smile network [9]. Both documents included comprehensive outlines for each aspect of cleft treatment, including site preparation, team make up, equipment, logistics and traveling, and safety standards so that every cleft child and their family can expect the same level of quality care no matter where they live [8, 9]. They have also provided foundation to the new paradigm of international cleft care, which is the creation of free-standing, sustainable cleft centers around the world, staffed, and operated year-round by both local and international personnel [10–13].

This chapter will briefly focus on the strategies that can help optimize global standards for cleft care, which should be followed when planning a cleft mission or building a self-sufficient cleft care facility to provide optimal and longitudinal care to patients with craniofacial anomalies.

2. Multidisciplinary team building

A multidisciplinary team of qualified healthcare professionals is the foundation to achieve proper cleft care anywhere in the world, as the management of orofacial cleft requires expertise from providers in various fields of medicine and dentistry.

Given the complexity and life-threatening risks inherent in performing surgical procedures, it is crucial that all team members be highly skilled and well trained in the patient care of cleft anomalies. The educational and experience requirements of each specialist on the cleft team

are determined by individual specialty board, various professional associations, state licensing board, etc. These requirements change over time. The professional members should be encouraged to stay updated on all the current teachings in their respective fields by actively participating in continuing educational activities and attending professional meetings. This not only ensures that they possess appropriate and current credentials but also have the requisite experience in evaluation and treatment of patients with craniofacial anomalies [1, 7, 10].

For this purpose, large and fully articulated cleft care teams must be designed to deliver an entire range of care to the patients. This is essential in building long-term, sustainable, and self-sufficient cleft care centers. Such a team should include the following members [6, 7, 14–16]:

1. Pediatrician
2. Cleft/craniofacial surgeon
3. Cleft/craniofacial orthodontist
4. Anesthesiologist
5. Nursing staff
6. Speech pathologist
7. Psychologist
8. Medical record specialist/research coordinator
9. Other surgical specialties

If a cleft care center recruits international professionals once or twice a year during special cleft surgery camps and cleft missions, the presence of a skilled translator also becomes important because language barrier can hinder full team performance and potential. Therefore, qualified interpreters should be provided to ensure proper verbal and written communication among the team members, patients, and families. The team needs to work in a coordinated manner to provide appropriate care to any patient that comes with a cleft anomaly [10, 17].

Some cleft care centers are not able to provide all types of examinations and services required by the patients. The team in such facilities should have a mechanism for referral to the required professionals, who will be able to provide the necessary service to the patient [11].

Lastly, it is important that all members of the team are monitored regularly and their performance reviews are maintained, so that the quality of care provided to the patients is not compromised.

3. Protocols

Generally, competent surgeons, anesthesiologists, craniofacial orthodontists, and nursing staff each have their own particular way of doing things. This is especially true for professionals who work in different parts of the world. This presents a unique challenge when the

team is composed of healthcare providers with diverse backgrounds. In these circumstances, setting priorities and following protocols during different phases of care can help focus the personnel into a more coherent group. Protocols also ensure consistency and decrease the margin of error in most circumstances. For instance, operative protocols could recommend certain procedures to be used by all surgeons for patients with cleft lip and palate (e.g., assuming acceptable blood reports, primary lip repair at age 10 weeks, followed by Furlow double opposing Z-plasty at the age of 10 months). Nasoalveolar molding, craniofacial orthodontic, and dentofacial orthopedic protocols could be standardized in terms of biomechanics and timing of treatment. The anesthesiologists might suggest protocols on intra- and post-operative pain management. The nursing team might recommend certain staff to patient ratio in the post-operative recovery ward. Compliance with these protocols is imperative to the success of a mission trip or permanent craniofacial care facility, and should be well articulated to each team member from the start. However, it is important to keep in mind that changes in the protocol are permissible under circumstances where it does not apply properly.

4. Equipment

In general, the equipment and supplies needed in a developing world hospital are not different from the ones needed in a modern hospital. Acquisition, preparation, shipping (in case of cleft mission), deployment, and maintenance of equipment are a big challenge for both permanent craniofacial care centers and organizations that aim to provide cleft missions. At minimum, complete surgical trays, sutures and dressings, reliable anesthesia equipment, resuscitation packs, perioperative monitors, and sterile materials are necessary for the cleft repair operations regardless of the practice setting. Care should be taken when using medications and instruments purchased in the host countries, especially if the instructions are not in English or if they are unfamiliar pharmaceutical formulations. A partial list of recommended supplies and equipment for orofacial cleft care centers are listed in **Table 1**.

Screening and assessment	• Vital sign monitors
	• Camera
	• Lights, tongue blades, and other examination material
	• Medical records
	• Lab facility for blood tests
Anesthesia	• Anesthesia machine
	• Resuscitation boxes with updated, unexpired drugs and dosage schedules
	• Airway equipment including masks, endotracheal tubes, airways, laryngoscopes, positive pressure ventilation systems, suction devices, non-invasive monitors, difficult airway management items, anesthetic agent

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	• Blood supply
	• Defibrillator and other appropriate emergency equipment
	• Intravenous fluids and fluid administration sets
	• Equipment and soaking solutions for the sterilization of non-disposable anesthesia equipment
Post-anesthesia care	• Full resuscitation medications of appropriate doses
	• Arrangements for glucose level measurement
	• Oxygen and suction equipment at each bedside
	• Vital sign monitors with pulse oximetry
	• Suction equipment
	• Documentation system
Nasoalveolar molding	• Slow speed dental hand piece
	• Hard acrylic
	• Soft acrylic
	• Water bath
	• Boley gauge
	• Orthodontic spatula
	• Utility wax
	• Three-prong plier
	• Light wire plier
	• College plier
	• Scalpel
	• Orthodontic wire
	• Dental impression material and cast
Surgery	• Surgical instrument trays
	• Appropriate suture material
	• Sterilization material
	• Illumination
	• Suction machine
	• Electrocautery capability
Post-operative intensive care	• An appropriate ICU facility and a plan for critical patient transfer when the ICU is not within the hospital facility
	• Electronic monitors
	• Respiratory ventilators

Post-operative ward	• 24 hour nursing staff
	• Appropriate dressing and cleaning materials
	• Medications for pain management, antisepsis, nausea, and other nursing needs
	• Vital sign monitoring equipment
	• Oxygen availability

Table 1. List of minimum supplies and equipment required for proper cleft care [8, 9].

5. Logistics and transportation

Transportation of the team and equipment is an important part of cleft care during international mission trips, and should not be overlooked. Travel to and from sites can be a costly endeavor, and the logistics must be planned out well before the trip for any hope of coordinated arrival and departure of equipment and personnel. A week-long trip may require months of meticulous planning, including arrangements of passports and visas, housing, meals, social events, and security. If the mission is planned by an international healthcare organization, it is beneficial to have local partnerships or contacts to help navigate the custom regulations when bringing equipment into the host country. The equipment should also be acquired and tested prior to shipping time. Drugs and expendables should be checked for expiration dates and evidence of mishandling or breach in packaging. To further ensure successful transportation, all items should be inventoried and documented.

6. Patient screening and assessment

One of the most crucial elements in cleft care is to determine surgical priority through proper patient screening and assessment. Children in LMIC are often undernourished, and many have concomitant medical illnesses and infectious diseases, all of which can lead to a lowered healing reserve compared to children normally encountered in developing countries. Therefore, when a cleft patient first contacts a healthcare facility for treatment, he/she needs to be properly assessed by a multidisciplinary team. Blood tests should be ordered to evaluate any metabolic abnormalities and the presence of anemia. Low hemoglobin level may be a marker for poor nutrition, and thus associated with high surgical risk. Traditionally, hemoglobin value of 10 g/dl is considered the lower limit of acceptable surgical candidate; however, the data to support this are lacking [8]. During the first phase of screening, risk factors such as poor nutrition, low hemoglobin, significant airway anomalies, and young age should be considered to disqualify a child as a potential candidate for surgery. A number of studies have identified age as a significant risk factor for surgery in children using death or cardiac arrest as primary end points. These studies suggest that neonates (0–30 days) are at a risk as high as 40 times compared to older children or adults, whereas infants (1–12 months) have a 4- to 5-fold increased risk compared to older children [18–20].

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For patients that have passed the initial screening phase, a final assessment and evaluation occurs before the operation, which consists of two parts. A team of surgeons first determine surgical priority of the procedure and its estimated duration. If there are any surgical contraindications to the operation, they are identified at this point and the patient will not be scheduled for surgery. Second, the pediatric anesthesiologist team determines the American Society of Anesthesiologists (ASA) patient classification and provides a second independent opinion on the suitability of patient for the surgery. Most importantly, the cardiac and respiratory status of the patient is carefully evaluated at this time [12]. A patient who has satisfied the criteria for each of these phases is selected for surgery. When indicated, a course of preoperative nasoalveolar molding therapy is advised.

Such a comprehensive and lengthy selection procedure is important to ensure patient safety, as well as to maximize the expected benefits from surgery and proper usage of time and resources. **Figure 1** shows an outline of the steps involved in patient selection.

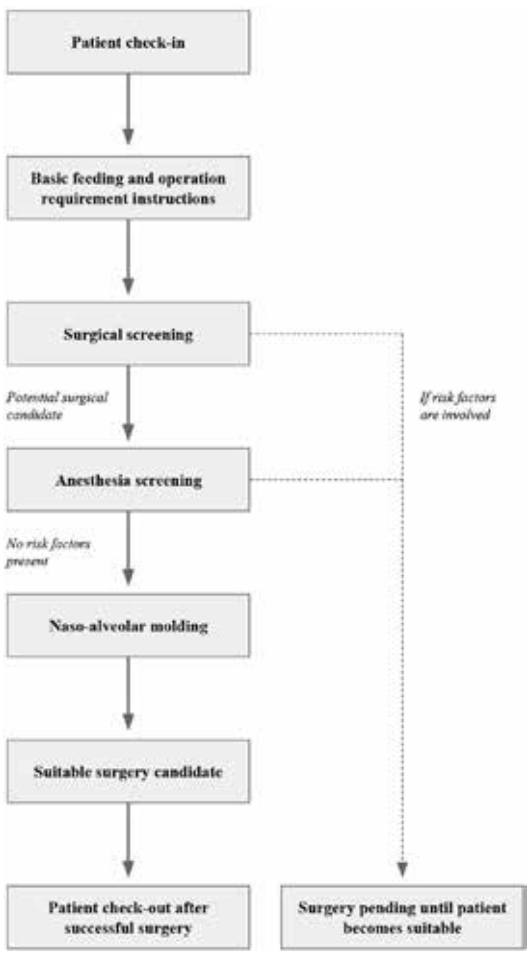

Figure 1. Steps involved in patient selection.

7. Documentation

As in all other endeavors, if it is not written it has not been done. Organizations offering optimal care ought to create detailed documentation and provide an accurate and secure record for the basis of ongoing care and outcome assessments. Documenting details of a patient at every stage makes developing the treatment plan easier for cleft patients. As shown in **Figure 2**, documentation can be divided into five vital areas.

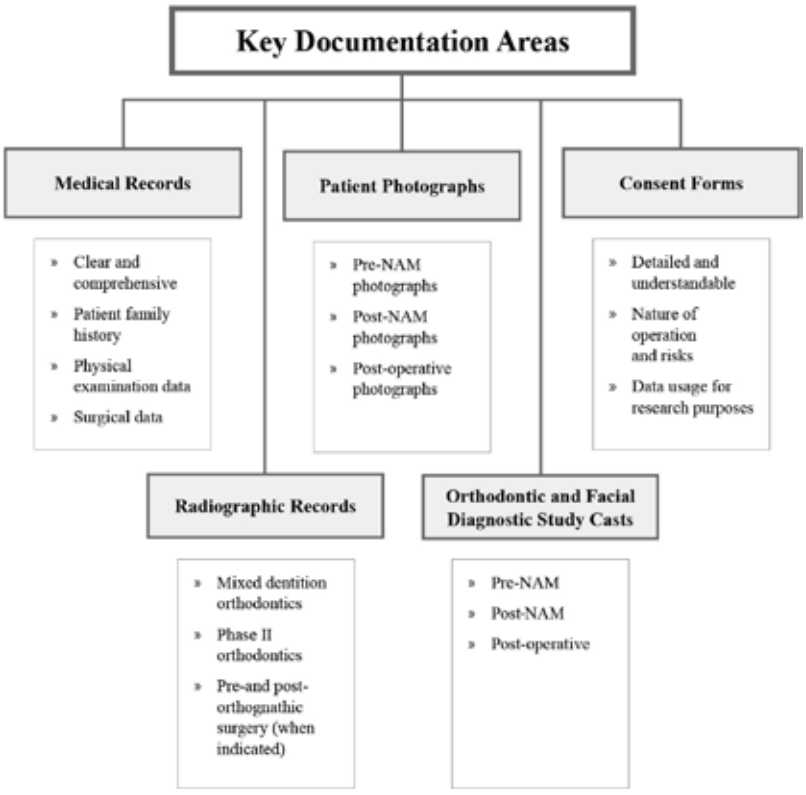

Figure 2. Key documentation areas.

- **Medical records**

These forms, whether written or electronic, should be identical throughout the organization. They should be comprehensive, explicit, and clear. The history section should include family background, demographic details, and previous history of cleft in the family. A complete record of physical examination and medical diagnosis of data must be entered. Multiple copies should be made for each file. This allows one copy to be left with patient's medical chart in the host country, and another copy to be used for tracking and future analysis.

- **Patient photographs**

Pre- and post-operative photographs of patients are also important as they are a key factor in analyzing results. These photographs can be further used for outcome assessment and research purposes.

- **Orthodontic and facial diagnostic study casts**

Pre-, progress, and post-nasoalveolar molding (NAM) facial and orthodontic diagnostic study casts are imperative for the fabrication of NAM appliances, orthodontic appliances, and orthopedic appliances. Additionally, they are required to evaluate treatment progress, outcomes assessment, and for research purposes.

- **Radiographic records**

Pre-, progress, and post-orthodontic and surgical imaging should be taken as indicated in order to aid in the diagnosis and treatment planning of craniofacial orthodontics, dentofacial orthopedics, and orthognathic surgery. Like photographs and diagnostic study cases, they are also useful for research purposes.

- **Consent forms**

Lastly, consent forms are an integral part of the documentation process. All patients and guardians must read and sign a consent form, which should be comprehensive and clear. The form must include the nature of the operation and its risks, use of anesthesia, potential blood transfusion, HIV, and hepatitis testing in the case of needle stick and permission for taking photographs. The families should also be informed, and oral or written consent should be taken if the data are to be used for research purposes. When language difference exists, professionals should utilize interpreters to assure informed consents are properly documented prior to delivery of care and surgery.

All members of the multidisciplinary cleft care team are responsible for documentation. The cleft care facility should work systematically to ensure that documentation tools are readily available to all health care providers, while at the same time respecting and maintaining patient confidentiality.

8. Sustainable cleft care facility

International organizations have long provided cleft care through surgical missions to selected areas in LMIC with shortage of resources and experienced personnel. The drawback of this practice model is that these health missions often provide short-term relief, making treatment available to limited amount of people for a short time period [3]. The mission trips are dependent on proper funding, grants, and resources. This model of intervention is ideal for urgent humanitarian response to disasters or epidemics, where a substantial amount of resources can be mobilized quickly for disease-specific use in LMIC. However, it is less effective for sustaining long-term care to the indigenous population and for conducting educational/preventive endeavors. This type of practice has been criticized for operating outside of the existing health

care systems and structures, doing little to strengthen the primary care systems in LMIC, and compromising countries' autonomy and participation in health care initiatives [6]. Finally, most of the mission trips are not designed to deal with the complex socioeconomic disease determinants many patients face, and lack the capacity to maintain prolonged post-operative follow-up and therapy.

It has become increasingly clear that one of the most important strategies that can help optimize and increase cleft care globally is to establish effectively run, high-volume, indigenous centers of excellence, capable of serving large and wide spread populations in the LMIC [6]. The ideal long-term goal for international groups should be to prepare local surgical teams to provide the same quality care for their population without outside medical assistance [8]. Once established and maintained, such local cleft care facilities not only provide services throughout the year to its region but can also contribute to the funding needs of much poorer sites in the future.

In order to offer effective surgical and orthodontic/orthopedic interventions, these facilities must develop and maintain an environment that meets world class minimums on proper workforce, access to supplies, instrumentation, infection control, and supporting infrastructure. See **Table 2** for a list of basic requirements.

Physical space	An adequate space should be present for patient screening, assessment, operating rooms, preoperative, and post-operative wards
Laboratory	A basic clinical laboratory to perform regular blood and electrolyte tests
Equipment	The minimum number of instruments required for patient examination, anesthesia, surgery, orthodontics, nasoalveolar molding, and ward care
Staff	Administrative, management, nursing, and permanent or visiting expert surgery staff to run the facility
Donors	Various funding agencies and/or private donors to run and maintain the cleft center as well as support patients that cannot afford the treatment otherwise
Quality control	A system that ensures that quality of cleft care provided is according to international standards, assures patient/family satisfaction, conducts staff performance reports, and develop guidelines to address the problems faced in the facility

Table 2. Basic requirements for a sustainable cleft care infrastructure/facility.

9. Patient follow-up

Whether it is a cleft mission or a permanent cleft care facility, arrangements for adequate follow-up are important to maximize treatment effectiveness, access the available options for future treatment, and monitor outcomes. As shown in **Figure 3**, a basic post-operative follow-up has two intervals.

However, such a simplified follow-up regimen is rarely adequate for most cleft patients. From birth throughout childhood and adolescence, a cleft patient requires coordinated care among surgeons, orthodontists, and other health care providers. Even after surgery, most cleft patients require regular ear examinations during infancy. Approximately 75% of cleft patients require two to three additional orthodontic/dentofacial orthopedic interventions and continued speech therapy throughout childhood and adolescence to achieve satisfactory growth, speech, and language competence. Coordination of various dental procedures is crucial from the period of mixed dentition through adolescence. Furthermore, overall health and the psychosocial impact of having a cleft also need to be monitored routinely [1, 12, 21].

To achieve such a prolonged follow-up plan, it is the responsibility of the cleft team to maintain communication with the patients and families, extensively educate them on the importance of follow-up and maintain appropriate documentation and record keeping.

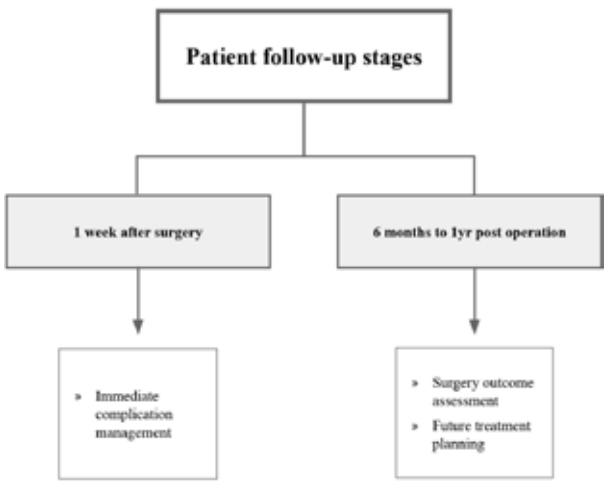

Figure 3. Patient follow-up stages.

10. Education and research

Finally, education and awareness regarding orofacial clefts are key factors in achieving better long-term global access to cleft care. Education in cleft care is conducted at two levels:

(a) Education of parents and caregivers

Educating the care givers of cleft patient is crucial in achieving proper care and satisfactory future outcomes. On the initial visit, caretakers of the children should be given instructions on feeding assistance, airway maintenance, and other basic cleft care information to help the patient prepare for surgical intervention. After the operation, families should be given strict instructions regarding the remainder of their post-operative care at home prior to discharge. Families must

be educated on the need for follow-up after operations and the importance of regular visits to the craniofacial orthodontist, pediatrician, speech therapist and feeding specialist for the long-term.

(b) Training and education of local professionals

It has long been the aim of global health care organizations to provide educational and training opportunities to health care professionals of LMIC, who can thereafter deliver high quality, team-based care in their local regions. A number of approaches have been outlined and proven to be effective in accomplishing this goal:

- **On-site education**

Delivering knowledge to local professionals on-site during cleft missions is effective in transmitting small, focused, and discrete areas of knowledge and experience. Although enormously enriching, such short-term programs provide a rather limited introduction to cleft care and surgery to local professionals present at the time [6].

- **Long-term education and training**

Long-term partnerships between local hospitals and academic institutions in wealthy countries help to provide proper, professional education, and experience. This can either be achieved by allowing fully credentialed visiting surgeons to stay with a host hospital and teach for an extended period of time or by bringing a limited number of host country participants to educational programs in regions with well-established craniofacial centers. More robust academic partnerships can also promote local academic leaders and would enhance training for health care providers in other fields, including speech pathology and surgical technicians. Such training programs aim to provide much needed local cleft care experts, who can contribute to the development of sustainable, self-sufficient cleft care centers.

(c) Clinical research

Collection of prospective, standardized data can yield high quality information that can be used to improve overall knowledge, cleft care processes, and outcomes. In addition to contributing to the field, research results can be presented to local health care professionals and the general population. Research can broadly be categorized as: epidemiological, genetic, prevention/risk factors, clinical presentation, outcomes assessment, and quality of life.

11. Conclusion

Orofacial clefts are a correctable condition with proper treatment resulting in a dramatic improvement of function and quality of life. Providing universal cleft care in LMIC still faces numerous challenges today due to a lack of basic health care infrastructures [22]. Traditionally, international health missions have been very successful in providing reconstructive plastic surgery to people in resource-limited regions. Largely due to the success of

cleft missions, the cleft care community is now in position to increase surgical capacity and promote development of sustainable local cleft care centers that are capable of providing comprehensive, longitudinal care to the indigenous population [6]. With the shift in global cleft care delivery, many organizations have started to incorporate efforts to expand local facility, increase human capital, and foster interdisciplinary quality health care by local providers [22]. As we move toward the future of accessible, sustainable cleft care in LMIC, it will continue to rely on concerted efforts from both international aid groups and local governments to invest in the local health care system.

Author details

Mairaj Ahmed[1]*, Yunfeng Xue[2] and Ayisha Ayub[3]

*Address all correspondence to: mairaj.ahmed@mountsinai.org

1 Cleft/Craniofacial Center, Icahn School of Medicine at Mount Sinai, New York City, NY, USA

2 University of Texas McGovern Medical School, Houston, TX, USA

3 Cleft Hospital, Gujrat, Pakistan

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Section 2

Surgical Strategies

Chapter 4

Surgical Strategy of Cleft Palate Repair and Nasometric Results

Norifumi Nakamura and Masahiro Tezuka

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67093

Abstract

The goal of cleft palate (CP) repair is to achieve normal speech. Despite the recent development of surgical repair of cleft palate, there is no standard procedure that ensures patients' speech to the same level as that in noncleft children. In this chapter, we describe our surgical strategy of cleft palate repair that approaches each anatomical and pathological abnormality of cleft palate and the postoperative speech outcomes using the subjective and objective manners. After palate repair based on our surgical strategy, patients' speech was significantly improved, and the nasalance scores were recovered to almost the same levels as those of Japanese children without cleft palate.

Keywords: cleft palate, palatal repair, nasometry, speech

1. Introduction

The surgical goals of primary repair for cleft palate (CP) include closure of the defect of the hard and soft palate and achievement of normal speech based on favorable velopharyngeal (VP) closure. Patients and family members always desire their speech in the same level as that of healthy children. However, it is said that approximately 40% of patients have a persistent, often lifelong, speech impairment in connected to CP [1]. Despite the recent development of surgical repair of cleft palate, there has been no standard procedure that can ensure complete VP closure (VPC) in patients with CP to date.

The Department of Oral and Maxillofacial Surgery, Kagoshima University Hospital, worked on cleft lip and palate repair for 30 years. We assessed their speech from 2000 to 2005 and revealed that more than 30% of patients had a moderate or poor VPC, and only 40% had achieved normal articulation. Therefore, to improve our speech results, the following countermeasures were carried out: First, we tried to standardize the surgical procedures for pala-

tal repair. Second, postoperative speech results were assessed objectively by speech language therapists (SLT). Third, these objective data were shared with all surgeons to provide feedback for the next operation.

In this chapter, we described our surgical strategy of cleft palate repair that approaches each anatomical and pathological abnormality of cleft palate and evaluated postoperative speech outcomes including presence/severity of hypernasality, nasal emission, and nasalance scores after standardize palatal repair. We then compared speech outcomes to ones using our previous palatal repair protocol without following surgical strategy. Furthermore, we also compared them to the nasalance scores of Japanese noncleft children.

2. Surgical strategy of palate repair approaching each anatomical and pathological abnormality

The concept of our strategy for CP repair was to approach each anatomical and pathological abnormality that may cause postoperative velopharyngeal incompetence (VPI): short palate, asymmetric palate, insufficient velar elevation, and a midline defect of the velum, to establish CP repair that can ensure VP closure (**Table 1**) [2]. The above factors were identified based on our experiences during the treatment of persistent VPI after CP repair. Therefore, our CP repair consisted of (1) presurgical orthopedics using Hotz's plate as much as possible to minimize the cleft space, (2) modified V-Y palatoplasty, allowing conservation of the periosteum in the anterior part of the maxilla, minimizing maxillary growth disturbance, (3) lengthening of the nasal mucosa using a large Z-plasty and a free mucosal graft, (4) muscular reconstruction producing a symmetrical levator sling and pharyngeal arch, and (5) two-layered suture of the palatal muscles.

Possible causes of VPI	Anatomical pathological abnormalities	Surgical procedures in palatal repair
Short palate	• Wide cleft palate. • Growth deficiency of the soft palate. • Insufficient retropositioning of the palatal muscles.	• Presurgical orthopedics for narrowing the cleft space using Hotz's plate, as much as possible. • Sufficient retropositioning of the palatal muscle.
Asymmetric velopharynx	• Antero-posterior discrepancy between the maxillary segments. • Discrepancy of the velar length between the segments. • Malpositioning of the palatal muscles.	• Presurgical orthopedics improving the positional gap using Hotz's plate, as much as possible. • Extension of the nasal mucosa by large Z-plasty with a free mucosal graft. • Symmetrical reconstruction of the palatal muscle referencing the anatomical landmarks.

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Possible causes of VPI	Anatomical pathological abnormalities	Surgical procedures in palatal repair
Insufficient velar elevation	• Insufficient releasing of the palatal muscles from the palatal bone. • Muscular pooling in the soft palate. • Wide scar in the soft palate.	• Freeing the palatal muscle in a single layer on the tensor aponeurosis. • Sufficient retropositioning of the palatal muscle. • Sufficient extension of the oral and nasal mucosa.
Midline defect of the velum	• Unsatisfactory repair or defect of musculus uvulae.	• Two-layer suture of the palatal muscles in the midline of the velum.

Table 1. Our surgical strategy for palatal repair approaching each anatomical and pathological abnormality and possible causes of VPI [2].

3. Surgical procedures for cleft palate repair

We adopt a modified V-Y palatoplasty for cleft palatal repair, although a large number of surgeons have developed surgical procedures for palatal repair [3–10]. The reason why we adopt a modified V-Y palatoplasty for cleft palatal repair is due to the following previous reports. Brothers et al. observed that the success rates for VP closure after Furlow palatoplasty and the modified Wardill-Kilner procedure were 64.0 and 70.0%, respectively, using pressure-flow testing, and they concluded that there was no difference between the two procedures [11]. Van Lierde et al. also compared Furlow palatoplasty and the Wardill-Kilner procedure using the nasometry and observed significantly better results in those treated with the Wardill-Kilner procedure [12].

The surgical procedures of a modified V-Y palatoplasty are shown in **Figure 1**. On designing the incision line, anatomical landmarks at the velopharynx were marked carefully (**Figure 1a**). The palatal flaps were elevated while preserving the periosteum in the anterior and lateral parts of the hard palate, and the palatal muscles were bluntly dissected along the surface of the tensor aponeurosis and nasal mucosa in a single layer. For extension of the nasal mucosa of the soft palate, large Z-plasty was performed in the nasal surface of the soft palate (**Figure 1b**). Mucosal incision for the large Z-plasty was extended until the surgeon could confirm contact between the soft palate and posterior pharyngeal wall without any tension. When the velar length became shorter on complete closure of the Z-plasty, the mucosal defect that remained on the nasal side was filled using a free mucosal graft donated from the buccal area (**Figure 1c**). Palatal muscles were then sutured in the midline of the soft palate by the two-layered suture (**Figure 1d**).

Palatal muscle was sutured carefully on producing a symmetrical levator sling and also the symmetrical palatopharyngeal and palatoglossal arches and uvula, while referencing five anatomical landmarks, as described above.

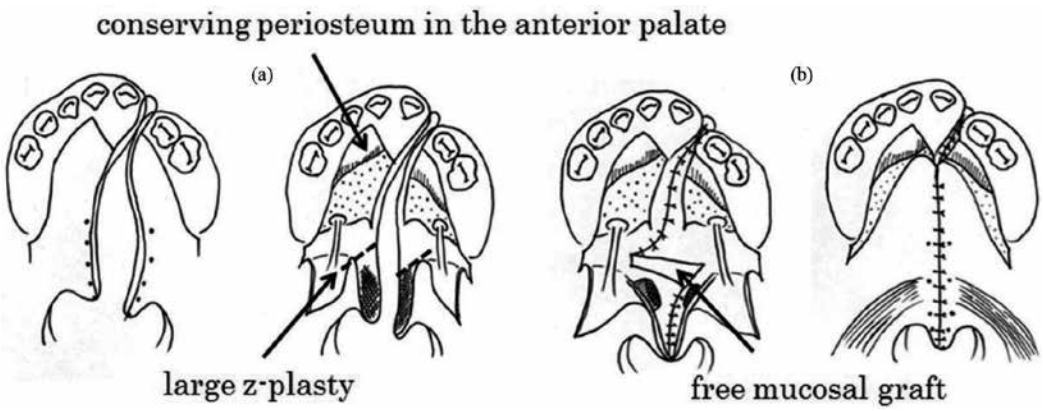

Figure 1. Surgical steps in palate repair for UCLP.

On designing the incision line, anatomical landmarks at the velopharynx were marked using 0.05% Toluidine blue solution (**Figure 2**). The marked points included the tip and base of the uvula (nos. 1 and 2), point in which the extension line of the palatoglossal arch crossed the cleft edge (no. 3), posterior edge of the hard palate (no. 4), and midpoint between nos. 3 and 4 (no. 5).

The palatal flaps were elevated while preserving the periosteum in the anterior and lateral parts of the hard palate, and the palatal muscles including the levator veli palatini muscle, palatopharyngeal muscle, and musculus uvulae, although these muscles were not clearly identified, were bluntly dissected along the surface of the tensor aponeurosis and nasal mucosa in a single layer. Muscles were sufficiently retropositioned as the direction was turned sideways. The hamular process was not fractured.

For extension of the nasal mucosa of the soft palate, a large Z-plasty was made in the nasal mucosa of the soft palate (**Figure 3a**). Mucosal incision for the large Z-plasty was extended until the soft palate contact to the posterior pharyngeal wall without any tension. The mucosal defect produced by a large Z-plasty was closed. However, when the velar length became shorter on complete closure of the Z-plasty, the mucosal defect that remained on the nasal side was filled using a free mucosal graft donated from the buccal area (**Figure 3b**). Because the shortened velar length due to complete closure of a Z-plasty might cause an asymmetric VP form and asymmetric closure motion.

Palatal muscles were then sutured in the midline of the soft palate by the two-layered suture (nasal and oral sides) using a nonabsorbable thread (5-0 Nylon; **Figure 3c**). Palatal muscle was sutured carefully on producing a symmetrical levator sling and also the symmetrical palatopharyngeal and palatoglossal arches and uvula, while referencing five anatomical landmarks, as described above. The raw area of the hard palate was dressed using a collagen-based artificial dermis and covered using an acrylic plate for 1 week.

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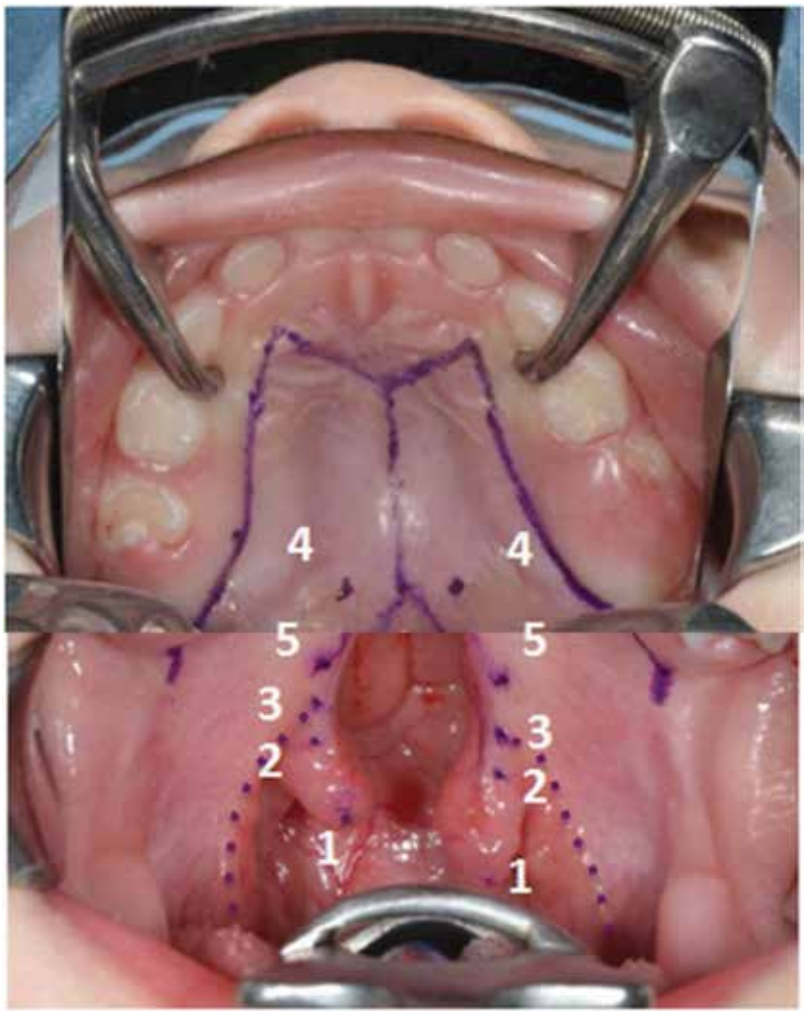

Figure 2. Surgical steps in palatal repair. The figure demonstrates anatomical landmarks and the incision line.

Figure 3. Surgical steps in palatal repair. The figure demonstrates elevation of the palatal flaps conserving the periosteum in the anterior and lateral parts of the hard palate and a large Z-plasty on the nasal side (dotted line) (a), a free mucosal graft on the nasal side (b), and symmetrical muscular reconstruction producing a levator sling while referring to the anatomical landmarks (c).

4. Speech assessment

Figure 4 shows our treatment schedule for speech in cleft palate patients. Speech management by a speech therapist starts just after birth, and the patient's motor development is facilitated. A check by an ENT doctor for the presence of otitis media is performed every 6 months. Palatal repair is then performed at 1.5 years. And after palatal repair, exercise facilitating VP closure is performed by a speech therapist. When the patient reaches the age of 4 years, VP closure (VPC) function is evaluated more precisely. If VPI remains, speech therapist starts training facilitating VPC. Our goal is to achieve a normal speech before entering elementary school.

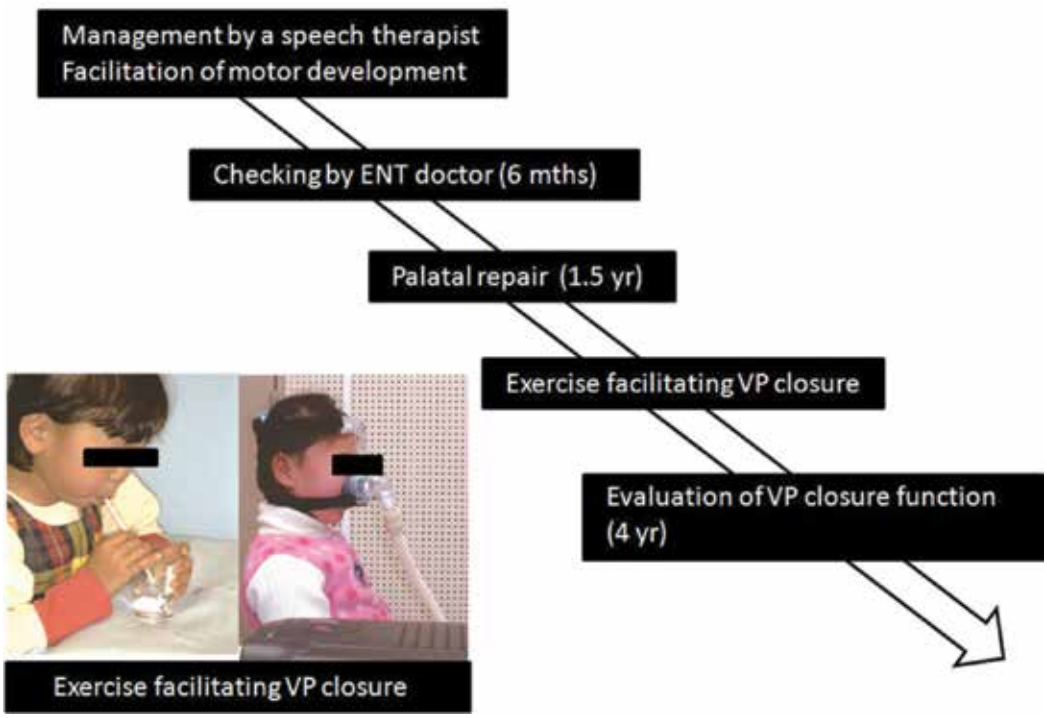

Figure 4. Treatment schedule for speech in cleft palate patients in Kagoshima University Hospital.

Postoperatively, patients were followed by 2 SLTs every 3 months until around 4 years. In this study, perceptual rating of hypernasality and nasal emission was carried out for all participants using the preserved sound sources by SLTs. In perceptual rating, hypernasality and nasal emission were classified into four categories: none, slight/mild, moderate, and severe. Articulation was also evaluated using the articulation test of the Japan Society of Logopedics and Phoniatrics and then converted to IPA 2005 phonetic symbols so that all abnormalities could be diagnosed and transcribed in IPA.

Nasometry scores were obtained for all patients using the Kay 6200 Nasometer II (Kay Elemetics, Lincoln Park, NJ, USA). For speech stimuli, the low-pressure vowel /i:/ and

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low-pressure sentence /yooi wa ooi/ and the high-pressure consonant-vowel syllable /tsu/ and high-pressure sentence /kitsutsuki ga kiwotsutsuku/ were used [13]. The reason, why we selected /i:/ extending the verbalization of /i/ among the all low-pressured vowels, was based on our previous study on the relationship between nasalance score and the perceptual rating of resonance in Japanese cleft and noncleft subjects [14]. In the previous study, we found that nasalance score during phonation of /i:/ was correlated with perceptual rating of resonance and cleft and noncelft subjects with normal resonance demonstrated the mean nasalance score less than 20% during phonation of /i:/.

5. Postoperative speech results comparing to the previously operated patients and noncleft controls

Postoperative speech results of 94 patients who underwent palate repair based on our surgical strategy during 2006–2012 (strategy group) and those of 109 patients who previously underwent palate repair without following strategy during 2000–2005 (previous group) were compared. As control group, speech data on 37 Japanese noncleft controls were used. For speech assessment, perceptual rating of hypernasality and nasal emission was classified into four categories: none, slight/mild, moderate, and severe, by one experienced speech language therapist for all participants. Articulation was also evaluated using the articulation test. For objective assessment, Nasometer test was performed for all patients. This study was approved by the Clinical Research Ethical Review Boards of Kagoshima University Hospital.

Comparison of the rate of achieving normal resonance in each cleft type is shown in **Figure 5**. Normal resonance was achieved in 35/37 (94.6%) in Unilateral cleft lip and palate (UCLP), 15/18 (83.3%) in Bilateral cleft lip and palate (BCLP), 24/27 (88.9%) in CP, and 8/12 (66.7%) in Submucous cleft palate (SMCP) in the strategy group. Severe hypernasality was observed in each one patient with BCLP and SMCP. On the other hand, normal resonance was achieved in 40/57 (70.2%) in UCLP, 16/25 (64.0%) in BCLP, and 19/27 (70.3%) in CP in the previous group. Successful achievement of normal resonance was obtained more reliably in all types of CP following palate repair based on our surgical strategy.

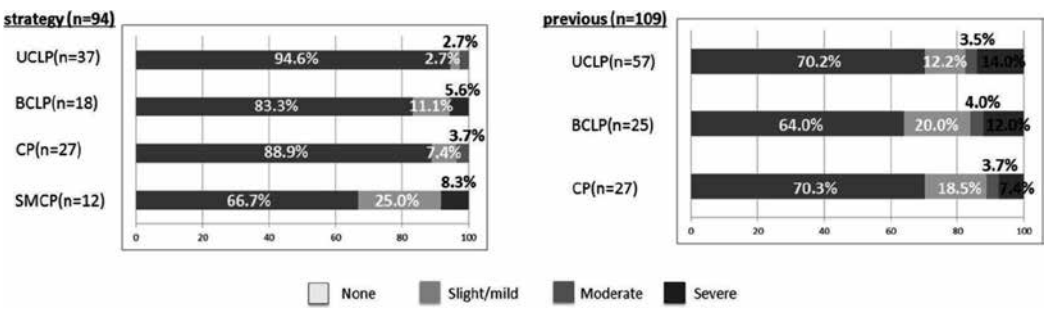

Figure 5. Postoperative hypernasality of each cleft type in the strategy and previous group.

The mean and SD of the nasalance scores of the strategy and previous groups and controls are shown in **Table 2**. The mean nasalance scores in the strategy group were less than 20% and were significantly lower than those of the previous group. When comparing the nasalance scores of control groups, those in the previous group were significantly higher on phonating /i:/ and the low-pressure sentence than in controls. On the other hand, there was no significant difference between the strategy and control groups. In other words, the nasalance scores representing hypernasality in the subjects of the strategy group recovered to almost the same levels as those of Japanese children without cleft palate.

Regarding articulation at 4 years of age, normal articulation was obtained in 68.4% in the strategy group, and this was better than that of the previous group (**Figure 6**).

	Nasalance score (%)				
	Strategy (n = 94)		**Previous (n = 109)**		**Controls (n = 37)**
/i/	20.3 ± 13.5	<0.01	33.6 ± 23.9	<0.01	22.7 ± 14.4
/tsu/	16.8 ± 13.5	<0.05	22.6 ± 19.3	<0.05	15.2 ± 8.5
/youihaooi/	19.7 ± 13.6	NS	24.2 ± 17.0	<0.01	13.0 ± 9.7
/kitsutsuki ga kiwo tsutsuku/	19.2 ± 12.7	NS	23.6 ± 18.3	NS	17.5 ± 9.8

Table 2. Mean ± SD of the nasalance score in the strategy, previous, and control groups.

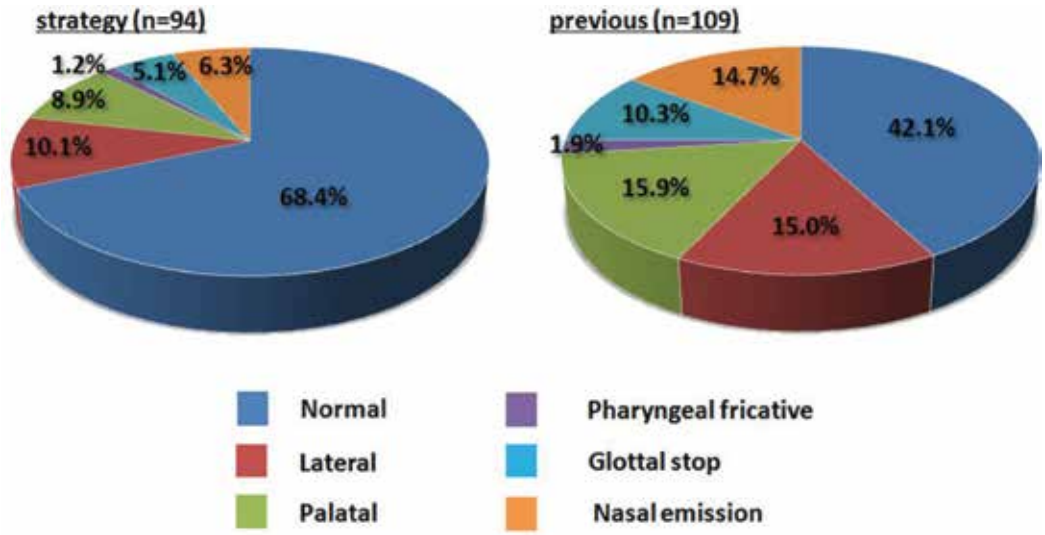

Figure 6. Postoperative articulation in the strategy and previous groups.

6. Discussion

When considering the postoperative VPI following CP repair, there are several main causes, including a wide cleft, short palate, deep pharynx, and unsatisfactory muscle reconstruction,

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when syndromic conditions, hearing loss, and mental retardation are excluded (**Figure 7a, b**). The preoperative portion between the velar length and pharyngeal depth bilaterally often differed, especially in subject with UCLP whose major and minor segments dislocated anteroposteriorly. During palatal repair, Z-plasty was usually used for adjusting the velar length; however, complete closure of the mucosal defect by large Z-plasty sometimes moved the uvula forward remaining asymmetry of the uvula position and pharyngeal arches (**Figure 7c**). The authors thought that these asymmetries in the velopharyngeal form may disturb the symmetrical muscular approximation and cause different sizes of the velopharyngeal orifice, resulting in persistent VPI following palatal repair [15, 16]. Therefore, it is thought to be useful to add a mucosal graft on the nasal side to fill the mucosal defect and to avoid an asymmetric VP form that may facilitate symmetrical velar motion in the VP closure mechanism.

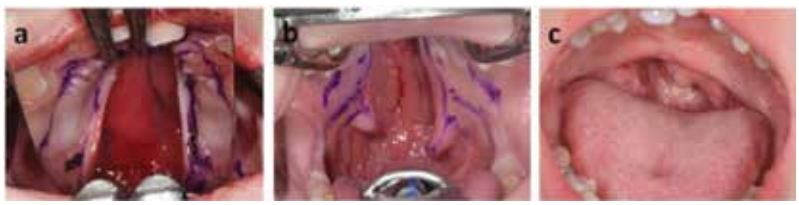

Figure 7. The reasons for postoperative VPI following CP repair: (a) the wide cleft, (b) short palate, (c) asymmetry of the uvula position and pharyngeal arch.

Furthermore, in the authors' experience during endoscopic examination of patients with persistent VPI, an asymmetric pharyngeal form or movement of the velopharynx and the midline defect of the velum were often observed, and they might be critical causes of VP closure dysfunction. Regarding the midline defect of the velum, Kuehn and Perry also reported that a midline defect suggested the presence of a deficiency or lack of musculus uvulae tissue or unsatisfactory surgical repair of this muscle (**Figure 8**) [17]. The anatomy and functional significance of the uvular muscle for VP closure was described by Kuehn et al. [18]. The uvular muscle courses posteriorly from its origin along the midline of the velum near the nasal surface of the velum. It is in its most cohesive form in the area overlying, and cradled by, the levator sling. The uvular muscle adds bulk to the dorsal aspect of the velum, thereby helping to fill the area between the velum and posterior pharyngeal wall. Without such bulk, the dorsal region would be concave, rather than convex, demonstrating a midline defect in the velum. In these cases, complete VP closure would not be achieved [17].

Considering the above, to ensure complete VP closure on CP repair, it is important to construct a symmetrical and functional velopharynx. Therefore, the authors have established a surgical strategy for palatal repair focusing on sufficient lengthening of the nasal mucosa, retropositioning the palatal muscles to produce a symmetrical levator sling, and unionizing the palatal muscles with a certain width in the midline of the velum. In the result, the surgical strategy for palatal repair facilitates successful speech outcomes in almost the same levels as those of Japanese children without cleft palate. There was no description about speech results of the CP patients based on the successful achievement of postoperative Velopharyngeal closure function equal to normal children.

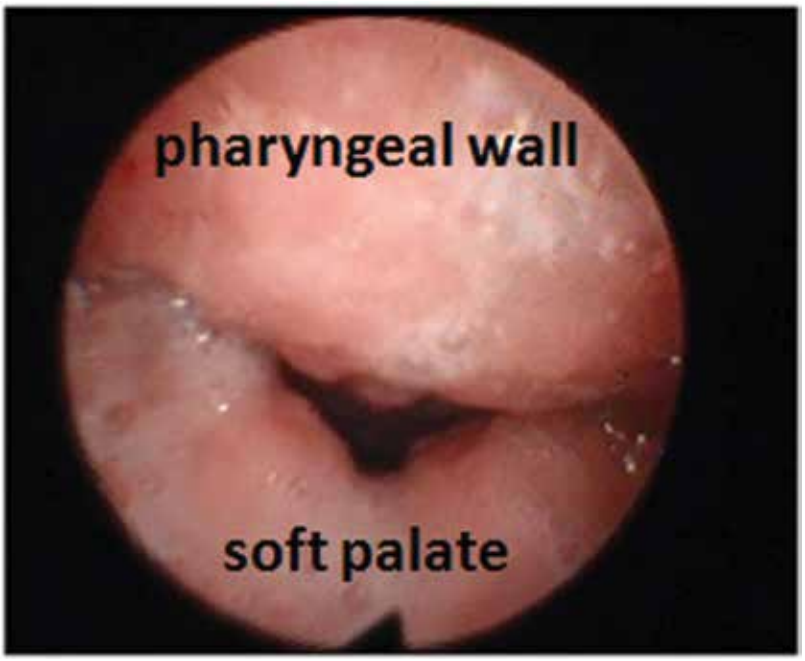

Figure 8. The midline defect of the velum of endoscopic examination might be a critical cause of VP closure dysfunction.

7. Conclusions

Cleft palate repair using a modified V-Y palatoplasty combining with a large Z-plasty and a mucosal graft on the nasal side of the velum for symmetrical muscular reconstruction based on the surgical strategy that approaches each anatomical and pathological abnormalities of cleft palate. Following palate repair based on our surgical strategy, patients' speech was significantly improved, and the nasalance scores were recovered to almost the same levels as those of Japanese children without cleft palate.

Author details

Norifumi Nakamura* and Masahiro Tezuka

*Address all correspondence to: nakamura@dent.kagoshima-u.ac.jp

Department of Oral and Maxillofacial Surgery, Field of Maxillofacial Rehabilitation, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

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Chapter 5

Surgical Techniques for Treatment of Unilateral Cleft Lip

Mustafa Chopan, Lohrasb Sayadi and
Donald R. Laub

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Abstract

A surgeon intending habilitation of a child with cleft lip should be familiar with the normal anatomy of the lip and nose, the distortions introduced by the cleft deformity, and the many techniques available to employ those best suited to correction of that child's deformity.

Keywords: surgical techniques, cleft lip, cleft surgery

1. Introduction

"Whatever is worth doing at all is worth doing well."

—Philip Stanhope, 4th Earl of Chesterfield

The treatment of children with cleft lip deformity has long challenged surgeons. Numerous surgical techniques have been developed to restore function, symmetry, and aesthetics. Early surgical techniques in treatment of cleft lip deformity involved straight-line repairs were limited in restoring symmetry to the lip of a child with unilateral cleft lip. LeMesurier and Tennyson developed the use of flaps that allowed reconstruction of the cupid's bow of the lip. Millard's technique of "rotation-advancement" brought about the modern era of cleft lip reconstruction. Later refinements by Salyer, Noordhoff, Cutting, and others have allowed the surgeon to more effectively restore function, symmetry, and aesthetics

2. Normal anatomy

"All cleft surgery is merely applied embryology."

—Victor Veau [1]

The pathologic origins of a cleft lip are traceable to distinct embryological events. The fusion failure during gestational weeks 4–7 of facial primordia: the central frontonasal prominence and two lateral maxillary prominences result in a typical cleft lip of a newborn. Advances in developmental science have promoted our knowledge and understanding of this phenomenon, helping to guide diagnosis and surgical reconstruction; however, craniofacial embryology is beyond the scope of this chapter.

It is important to note that cleft lip and palate is considered a distinct entity from isolated cleft palate, the difference chiefly characterized by the location of the cleft palate anterior or posterior to incisive foramen, respectively. Soft-tissue and bony deficiencies are variable with accompanying nasal distortion (**Figure 1**). Surgical management hinges upon the accurate identification of involved structures and methodical attention to detail in surgical techniques in reconstruction.

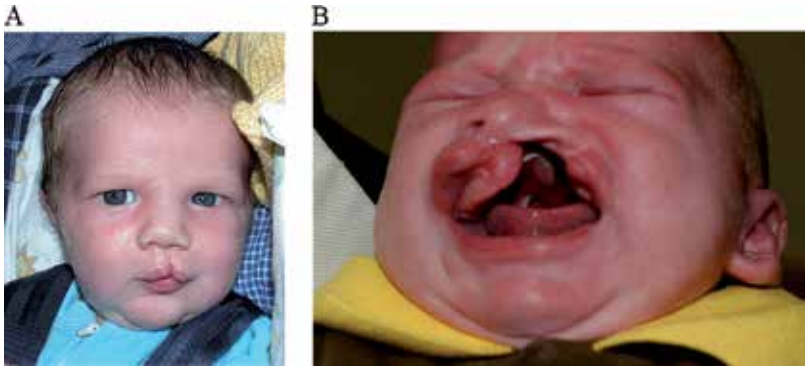

Figure 1. (A) A child with a microform or "forme fruste" cleft lip, demonstrating vermilion notching, scar-like depression. (B) A child with a complete unilateral cleft lip, demonstrating tissue hypoplasia and asymmetry.

2.1. Normal anatomy of the lip

The layers of the lip include the skin, a thin layer of subcutaneous tissue, orbicularis oris and other facial muscles, and mucosa. The vermillion is a unique tissue consisting of modified mucosa, and the white roll is a ridge at the junction of the vermillion and the lip skin. The lips are divided into four aesthetic subunits: the philtrum, two lateral wings (from the philtral columns to the nasolabial folds), and the entire lower lip.

Muscles of the upper lip include orbicularis oris, levator labii superioris alaeque nasi, zygomaticus major and minor, levator labii superioris, and nasalis. The orbicularis oris consists of superficial and deep layers. The deep fibers run circumferentially between modioli and function as the primary sphincter in feeding. The superficial fibers originate from the ipsilateral modiolus and run obliquely toward midline, interdigitating with the other muscles of facial expression and inserting into the dermis. The superficial fibers are further distinguished into either superior fibers (pars peripheralis) or inferior fibers (pars marginalis) of the upper lip. The pars marginalis courses along the vermillion border connect with the contralateral pars marginalis fibers at midline and inserts into the region of the vermilion tubercle. The pars peripheralis has a flat-fan shape diffusing out from each modiolus, and inserting into the skin of the contralateral philtral ridge [2]. Two other distinct fibers of the pars peripheralis have

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also been identified using micro-computed tomography [3]. One bundle terminates at the tissue below the ipsilateral anterior nasal spine, in continuation with depressor septi. The other bundle crosses midline and continues with the alar portion of nasalis muscle. The decussation of fibers creates the philtral columns, and lack of insertion at the midline creates the philtral depression.

Superficial layers of the levator labii superioris alaeque nasi, zygomaticus minor, and levator labii superioris cross the nasolabial groove and migrate toward the superficial orbicularis. The levator labii superioris alaeque nasi originates from the upper face, enters the upper lip superior and lateral to the ipsilateral philtral column, and descends on the medial side of the column. A bundle of fibers terminate in the dermis of the lateral aspect of the ipsilateral philtral column. Another bundle of short and long fibers terminates in the skin of the vermillion border; however, the long fibers interlock with the pars marginalis before their insertion. Thus the lip peak of the vermillion border, which creates cupid's bow, is due to a balance of muscular tension between the pars marginalis and levator labii superioris alaeque nasi.

Superficial reticular fibers of the levator labii superioris alaeque nasi, zygomaticus major and minor, levator labii superioris, and orbicularis oris insert into the medial philtrum ridge. The intersection of these fibers and the contralateral orbicularis oris forms the philtral column. The bulging appearance of the region lateral to the philtral column, however, results from a greater number of muscle insertions into the lateral skin than to the philtral dimple [4] (**Figure 2A**).

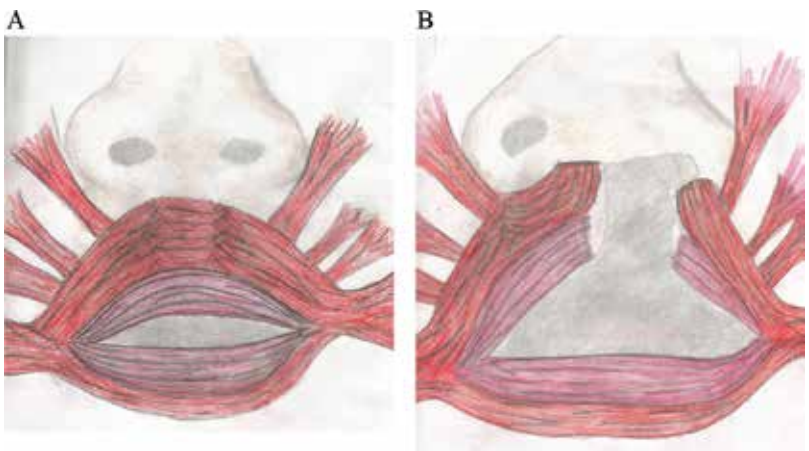

Figure 2. (A) A schematic representation of the orbicularis oris, demonstrating symmetry and continuity. (B) A schematic representation of the orbicularis oris affected by a cleft, demonstrating asymmetry and discontinuity.

2.2. Normal anatomy of the nose

The nose can be divided into anatomical thirds. The proximal third consists of the paired nasal bones and bony septum (vomer, perpendicular plate of ethmoid, nasal crest of maxilla and palatine bone). Upper lateral cartilages and cartilaginous septum comprise the middle third. Lower lateral cartilages, the tip, and caudal cartilaginous septum form the lower third of the nose. The lower lateral cartilages consist of the medial, middle, and lateral crura

(**Figure 3A**). The scroll area refers to the overlapping of lateral crura with the caudal edge of upper lateral cartilages. The nasalis muscle originates at the incisive fossa and inserts into four different regions. The transverse part courses past the alar base around the lateral side of the nose, and ascends medially to join procerus and the contralateral transverse fibers at midline. Fibers that course around the alar rim and above the lower lateral cartilages are the alar portion of nasalis. The columella and basal parts insert in the membranous septum, medial crura, and nostril sill skin. The columellar part of nasalis is synonymous with depressor septi.

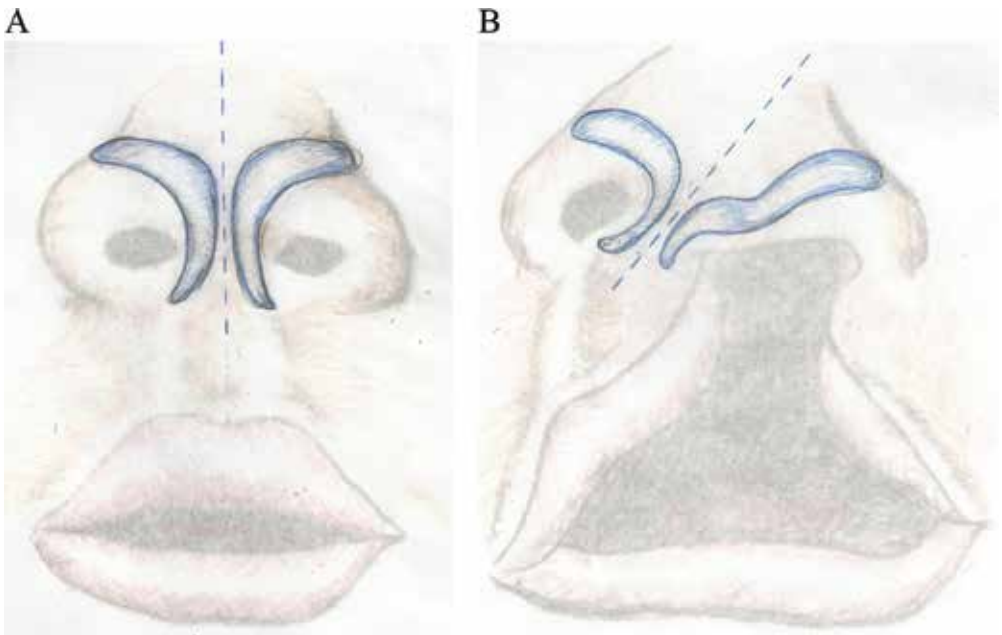

Figure 3. (A) A schematic representation of the lower lateral cartilages demonstrating symmetry. (B) A schematic representation of the lower lateral cartilages demonstrating asymmetry: a short medial crus, an obtuse genu, and a lateral crus that is longer and drawn into an S-shaped fold on the cleft side.

The facial artery is the main blood supply to the upper and lower lips. The facial artery travels through the cheek beneath zygomaticus major and superficial to buccinator muscles, giving rise to the inferior and superior labial arteries. Once the superior labial artery emerges from the zygomaticus major, it may dive into the substance of the orbicularis oris, giving rise to the ipsilateral columellar artery. After giving rise to the superior labial artery, the facial artery terminates as the angular artery. The lateral nasal artery is a branch of the angular artery.

3. Abnormal anatomy of unilateral cleft deformity: muscle imbalance, tissue hypoplasia, and skeletal asymmetry

"If you can articulate a problem, it is 98% solved."

—Edwin Land

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The severity of a unilateral cleft lip varies from the microform (**Figure 1A**) to a complete cleft extending into the nasal sill (**Figure 1B**). Varying degrees of nasal deformity and alveolar deficiency may also be present [5, 6]. There is varying degree of absence of central lip, philtral and nasal columella tissue [7].

The unilateral cleft typically results in a disruption of cupid's bow and the absence of one philtral column. The continuity of the orbicularis oris circumferentially is compromised, with abnormal insertions. In the lateral lip element, the upper part of cutaneous orbicularis (Pars Superficialis) inserts in the lateral aspect of the alar base and the nasolabial fold, while the lower part inserts into the nostril base periosteum of the pyriform rim. In the medial lip element, the cutaneous orbicularis (pars superficialis) inserts into the anterior nasal spine and columella. The deep orbicularis (pars marginalis) is simply interrupted by the cleft deficiency and results in a diminished vermillion-cutaneous ridge at the cleft margin (**Figure 2B**).

Anatomical characteristics of unilateral cleft lip include nasal deformities of the tip, columella, nostril, alar base, septum, and skeleton. The lower lateral cartilages on the cleft side have a short medial crus, an obtuse genu, and a lateral crus that is longer and drawn into an S-shaped fold (**Figure 3B**). The caudal septum is deviated toward the noncleft side. The nasal tip it typically directed toward the noncleft side [8]. In addition, the columella is shorter on the cleft side with deviation toward the noncleft side due to the unopposed action of the orbicularis oris. The alar base is more horizontal on the cleft side with deviation of the nasal septum toward the noncleft side. The alar base on the cleft side is positioned laterally, inferiorly, and posteriorly.

Nasal deformities in a unilateral cleft lip-nose arise from this cartilage deformity, muscle imbalance, and skeletal hypoplasia [5]. The various deformities are listed here:

1. Alar base displacement posteriorly and inferiorly, causing a flattening of the dome
2. Lateral crus of the alar cartilage and underlying skin is drawn to an S-shaped fold
3. Short medial crus of the alar cartilage on the cleft side
4. Columellar deviation toward the noncleft side and shortening on the cleft side
5. Nasal tip displacement and asymmetry
6. Caudal septum and anterior nasal spine displacement toward the noncleft side, with deviation to the cleft-side airway causing obstruction
7. Inferior turbinate hypertrophy of the cleft side
8. Hypoplastic maxillary segment and displacement on the cleft side
9. Nasal floor is lowered or absent
10. Nasal pyramid asymmetry

4. Goals of surgical repair

"If you know what you value, then making a decision is easy."

—Walt Disney

The goals of unilateral cleft lip repair are both functional and aesthetic. In order to address these goals, one must understand the anatomical characteristics of unilateral cleft lip. Aesthetically the goals of surgical intervention include formation of lip continuity, establishing symmetry of the cupid's bow and the nose in a manner that places scars in less discernable areas. Recreation of the orbicularis muscle to circumferentially surround the opening of the oral cavity is important for long-lasting cosmetic outcomes and lip and mouth function. Patients with isolated cleft lip rarely have feeding problems, unlike those with cleft palate. However, enrolling the child in a multidisciplinary clinic is advised to address the needs of each patient and family.

5. Preoperative tissue mobilization

"Success depends on preparation, and without preparation, there is failure."

—Confucius

The goal of preoperative tissue mobilization is to lessen the soft tissue and bony cleft and accompanying deformities prior to definitive surgical treatment. Preoperative improvement facilitates surgical repair and results in better outcomes.

5.1. Adhesive tape

Pool and Farnworth advocated the use of adhesive tape for soft tissue mobilization prior to surgical repair of unilateral and bilateral clefts Long strips were applied from cheek to cheek for 6 weeks prior to surgery (**Figure 4**). They found a 53% average reduction in alveolar gaps, and lip segment narrowing from 40% to complete apposition [9].

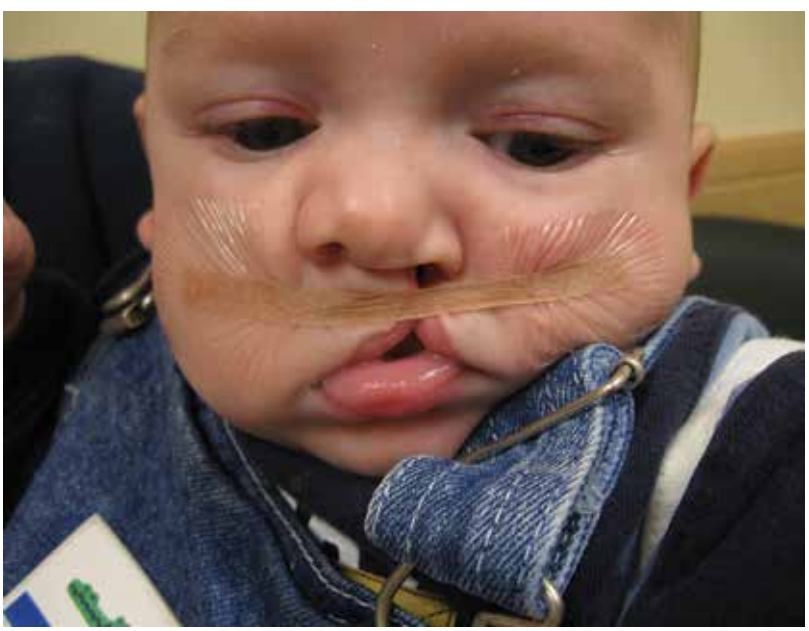

Figure 4. A child with a complete unilateral cleft lip, with adhesive tape therapy in place. This is the same child in **Figure 1B**. Note the mobilization of soft tissue.

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5.2. Nasoalveolar molding

Alveolar molding is performed with an intraoral appliance to align the maxillary alveolar segments and narrow the cleft. Latham developed an active orthopedic device consisting of methyl methacrylate bases attached to the palatine bone with metal pins, and connected by a screw [10, 11]. Turning of the screw exerts an anterior force on the cleft-side segment, narrowing the gap.

Grayson and the NYU group employ presurgical molding, using the nasoalveolar molding (NAM), a passive orthodontic appliance [12, 13]. An acrylic orthodontic plate is fitted to cover the entire maxillary arch, with two buttons placed at 45° angle to the occlusal plane. Circular elastics are attached from the buttons and to steristrips on the face bilaterally (**Figure 5**). Every 1–2 weeks the orthodontist adjusts the device small amounts by removing and adding acrylic. Once the alveolar gap measures less than 5 mm, a nasal stent is added to the appliance by wire extending from the plate. The stent is positioned under the soft triangle, and periodically augmented by adding soft acrylic. This tissue-expansion effect molds the alar cartilage and lengthens the columella with the goal of increasing tip projection.

Figure 5. A child with a complete bilateral cleft lip, with an NAM device in place.

5.3. Surgical lip adhesion

Lip adhesion is a first surgical stage in a two-stage reconstruction developed by Randall [14]. A lip after adhesion not only molds the alveolar segments, but also improves nasal contour and vertical lip height of both medial and lateral segments. The disadvantages of a two-stage surgical repair include an additional procedure and scarring, possibly making dissection more difficult during the second, definitive surgery. Randall made incisions on the vermillion of the medial and lateral lip elements. On the lateral lip element, supraperiosteal dissection is performed through a buccal incision. Subcutaneous dissection is performed on the medial segment to the nasal tip, allowing for mobilization of the cleft-side lower lateral cartilage independent from rest of the nose. Mattress sutures are passed through the medial cleft margin incision, through the orbicularis oris and buccal mucosa. The mucosal flaps are then closed in layered fashion.

6. Surgical techniques of unilateral cleft lip repair

"Things done well, and with a care, exempt themselves from fear."

—William Shakespeare

In unilateral cleft repairs, regardless of the name assigned, except for straight-line techniques, have an oblique medial incision to correct the nasal malposition and drop the cupid's bow into a horizontal posture [15]. If the lateral segment is contoured to interpolate a congruent tissue flap, the repair can be conceptualized as a Z-plasty. We have categorized lip repairs in this chapter by the level at which in the tissue is interpolated.

6.1. Straight-line repairs

6.1.1. Early repairs [16, 17]

Ambroise Paré described a straight-line repair for cleft lip in 1575. He excised the skin margins of the cleft with a razor, freeing the lip elements from the upper jaw and joining them together by transfixing the edges of the cleft with a needle and securing the needle with thread in a figure of eight pattern. In 1570 Gaspar Tagliacozzi of Bologna described excoriating the cleft edges and using interrupted sutures to close the cleft.

6.1.2. Rose-Thompson (et al.) principle

Some of the earliest changes in cleft lip repair were based on modifications to the straight line repair to increase the vertical length of the lip. In 1879, William Rose developed a design for cleft lip closure using curved incisions mutually concave from nostril to vermilion at a 60° angle [18]. This method was significant as it lengthened the union of the two cleft margins (**Figure 6**).

Later, James E. Thompson who aspired to reproduce a natural cupid's bow designed his paring procedure in a shape of a diamond excision. He emphasized the need for accurate markings for precise matching of the cleft sides when brought together [19]. In addition, when the vermilion thickness varied, Thompson altered the angle of his incisions to balance

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the vermilion closure [20]. Victor Veau performed a modified straight-line closure, where on the noncleft side he excised the mucosa just distal to the mucocutaneous junction line to achieve a normal length [1]. He was successful in approximation of the muscular elements but rarely achieved a symmetric cupid's bow. The British surgeon Thomas Kilner described a technique of straight-line closure combining methods used by Rose, Thompson, and Veau. Kilner's technique, known for its simplicity, lengthened the lip, and reapproximated the muscle. Kilner believed that a superior cosmetic result could be achieved by secondary surgery to perfect the initial repair. Nakajima and others utilized curved incisions on the noncleft side and but straight incisions on the cleft side to equalize the length and allow a straight line repair [21].

Straight-line repairs have grouped together as the "Rose-Thompson principle." While these techniques have the advantage of simplicity and speed, they often result in an asymmetric cupid's bow, a prominent scar and retrusion of the maxilla.

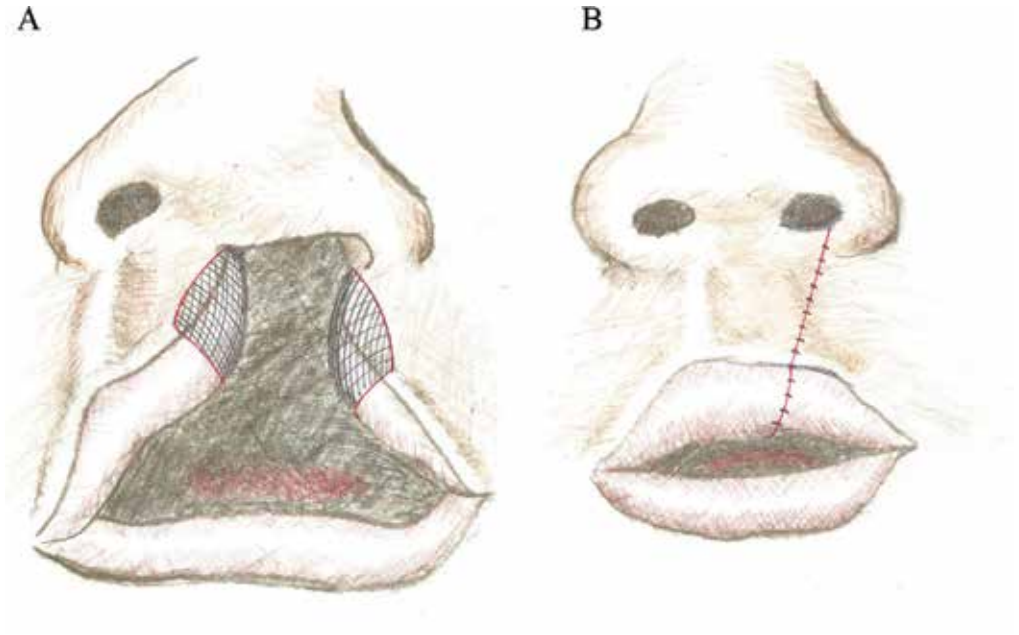

Figure 6. (A) Schematic representation of the incisions for a Rose repair. (B) Schematic representation of the closure of a Rose repair.

6.2. Upper lip flaps

6.2.1. Millard technique

Millard conceptualized his rotation-advancement technique while serving in Korea and first published in 1957 [22]. His technique is the most widely used by cleft surgeons, but has been modified since its inception. Its principles serve as the foundation of many unilateral repairs today.

Millard preserved anatomical landmarks: the cupid's bow and the philtral column. Downward rotation of the medial lip element restores vertical lip height and advancement of the lateral lip element repositions the alar base.

Millard marked the nadir and peaks of cupid's bow on both the lateral and medial lip with methylene blue. The distance from the alar base and the point selected for cupid's peak on the lateral segment should equal that of the noncleft side. His medial segment incision extends from the lateral cupid's peak of the medial element through the columellar-labial junction to the philtral column of the noncleft side. The lateral advancement flap extends from the nasal sill around the alar base. The medial segment with cupid's bow is rotated downward, and the lateral segment flap is advanced into the defect created.

Millard felt that markings served as a guide only, with the actual repair being "cut-as-you-go" individualized surgery (**Figure 7**).

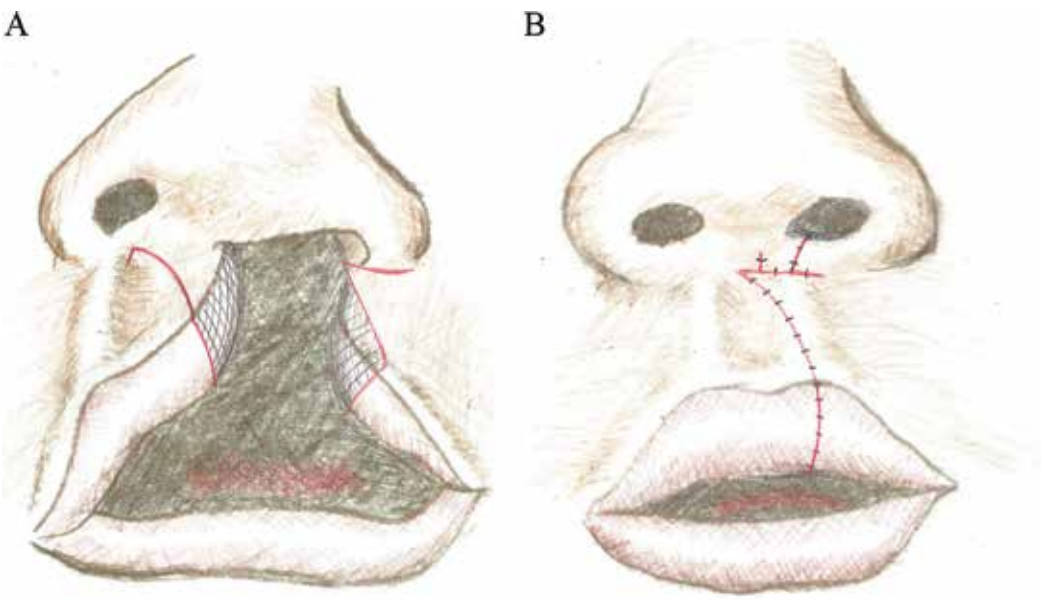

Figure 7. (A) Schematic representation of the incisions for a Millard repair. (B) Schematic representation of the closure of a Millard repair.

6.2.2. Salyer's modification

Salyer modified the rotation advancement with many improvements, most notably by making the transverse incision of the lateral segment B-flap not below the alar rim, but instead intranasally [23].

6.2.3. Mohler technique

Whereas the scar runs obliquely across the philtral column in Millard's repair, Mohler modified the technique to create a "mirror image" of the philtral column on the noncleft side [24]. He accomplished a straight-line closure of the lip by moving the rotation flap up into the

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columella. His technique used a back-cut that terminated at the midpoint of the philtral depression. The defect created by the downward rotation was filled by tissue from the lateral element.

6.2.4. Cutting technique ("Extended Mohler")

Mohler's technique was modified by Cutting who moved the upper end of the incision to just beyond the midline of the columella (about 4/7th of the width on the noncleft side), and extended the back-cut down to the noncleft philtral column [25]. This left a enough columellar tissue to fill in the defect created by downward rotation. A straight-line closure symmetric to the noncleft side philtral ridge is the result. There is then abundant lateral segment tissue that may be used to provide nasal lining, as shown in **Figure 8A** and **B**.

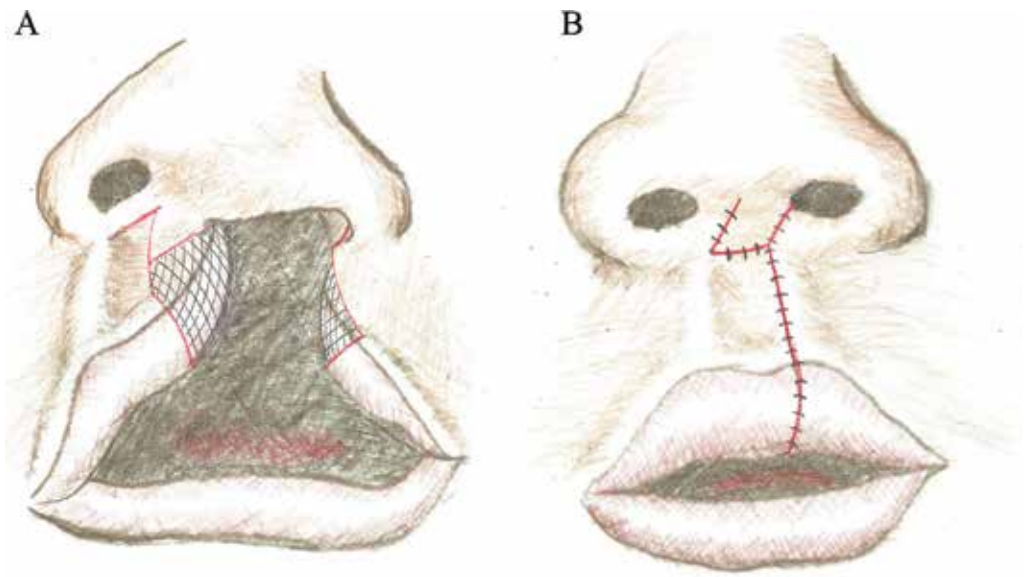

Figure 8. (A) Schematic representation of the incisions for a Cutting repair. (B) Schematic representation of the closure of a Cutting repair.

6.3. Middle lip flaps

6.3.1. LeMesurier technique

In the LeMesurier technique, a quadrilateral shape flap is created on the lateral side of the cleft lip which is rotated to the medial side where a notch is formed by a back cut, as shown in **Figure 9A** and **B** [26].

In addition to creating fullness in the lower lip, an advantage of this technique includes the placement of the suture line down the center of the lip. Thus, the cupid's bow can be made symmetrical. The scar that develops from the LeMesurier technique is a "step line" scar which is unlike most scars associated with cleft lip repair. This may overcome the characteristic appearance of a cleft lip repair and can look like an accidental wound to the observer [27].

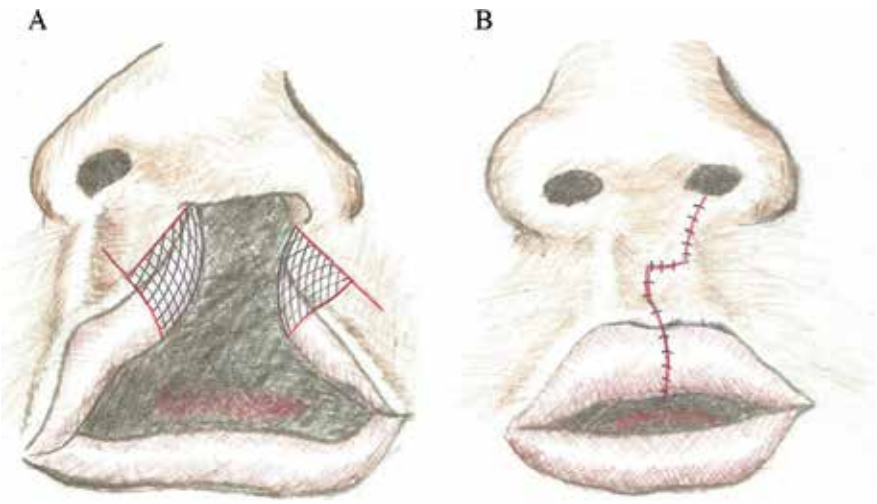

Figure 9. (A) Schematic representation of the incisions for a LeMesurier repair. (B) Schematic representation of the closure of a LeMesurier repair.

6.3.2. Pool repair

Pool placed the transverse limb of his Z-plasty repair of the lip approximately 3–4 mm below the alar bases [28]. He found that positioning the incision of the medial segment allowed for complete caudal rotation and proper horizontal positioning of the cupid's bow without the need for back-cuts or secondary flaps, see **Figure 10A** and **B**. He also found that this

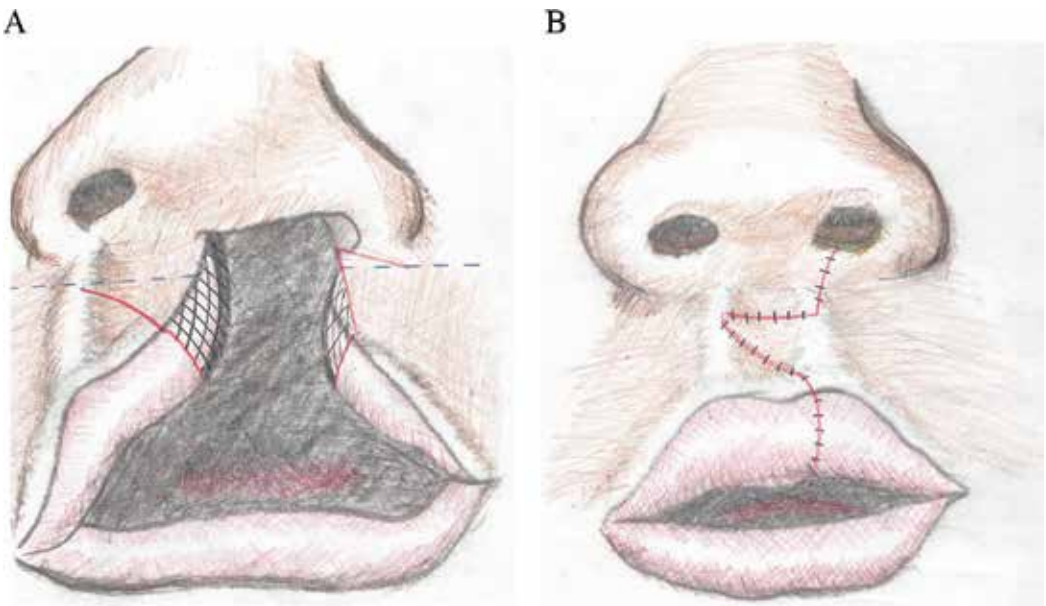

Figure 10. (A) Schematic representation of the incisions for a Pool repair. The blue dotted line represents a horizontal approximately 3 mm below the alar bases for planning the Z-plasty. (B) Schematic representation of the closure of a Pool repair.

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technique allowed a better contour of the lip, especially the curve of the columellar-labial juncture, which may be distorted by the transverse scar in higher rotation advancement techniques. The incisions also allow a "cut as you go" adjustment to the alar base for symmetry.

6.4. Lower lip flaps

6.4.1. Tennison-Randall repair

In 1952, Charles Tennison proposed a repair based on the Z-plasty principle to gain vertical lip length [29]. His technique, in particular, has proven to be advantageous in wide complete clefts. Peter Randall devised a mathematical system for designing the lip operation [30].

The base of the isosceles triangle of the lateral element is determined by the difference in lengths between the noncleft cupid's peak to the alar base and to the base of the columella. The isosceles triangle side length should equal the length of the 90° back cut of the medial element, as shown in **Figure 11A** and **B**.

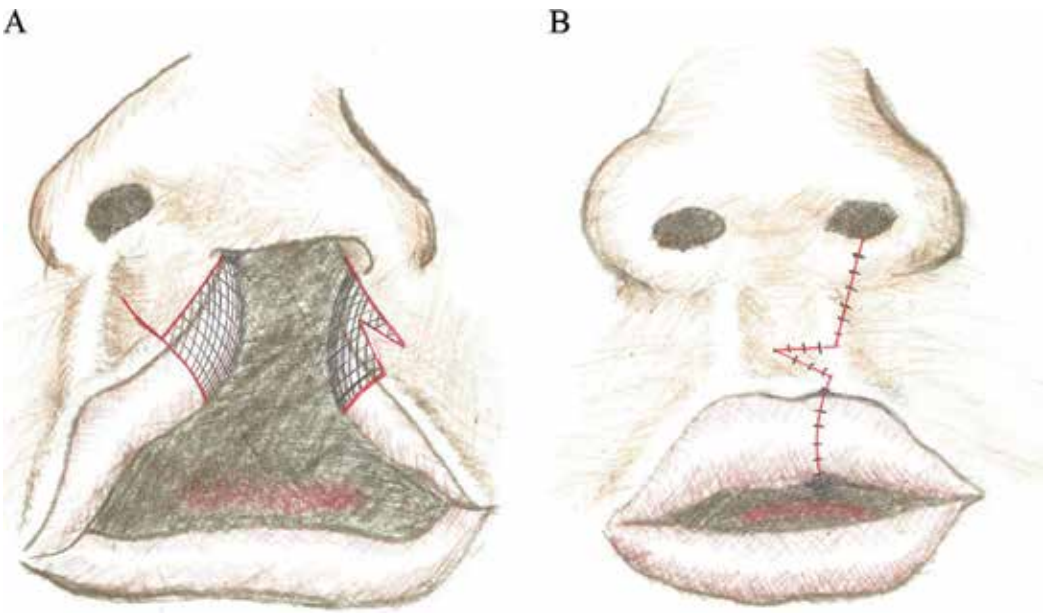

Figure 11. (A) Schematic representation of the incisions for a Tennison-Randall repair. (B) Schematic representation of the closure of a Tennison-Randall repair.

6.4.2. Fisher "anatomic subunit" repair

Fisher designed a repair utilizing the Rose-Thompson principle with close attention to the borders of aesthetic subunits of the lip, as well as a small lower lip triangular interpolation flap [31]. Many have found that this technique yields esthetic scars and achieves a natural contour of the upper lip (**Figure 12**).

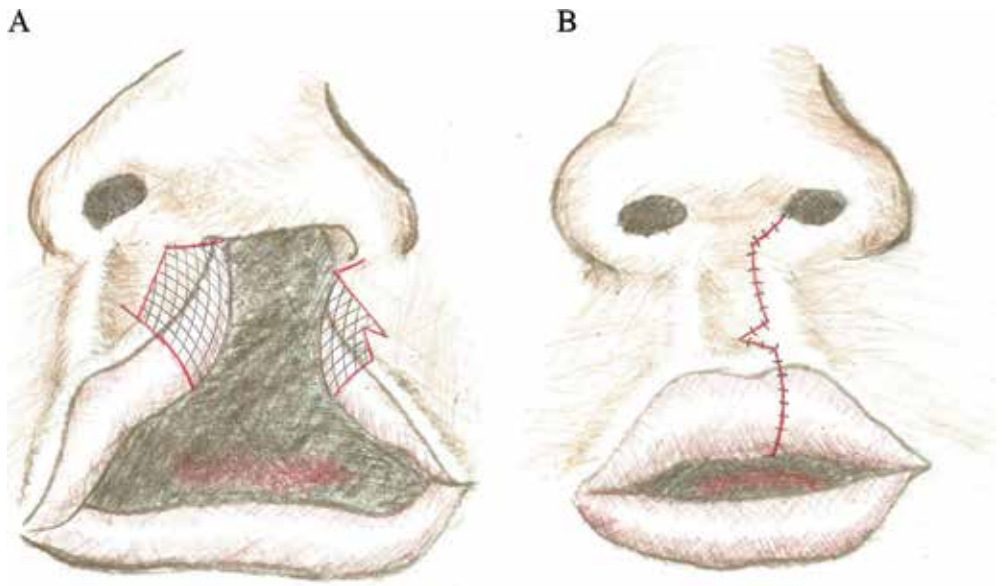

Figure 12. (A) Schematic representation of the incisions for a Fisher repair. (B) Schematic representation of the closure of a Fisher repair.

6.5. Vermilion flaps

6.5.1. Noordhoff technique

The Noordhoff technique utilizes a lateral lip triangular flap to reconstruct the dry vermilion [32]. A triangular flap is made on the lateral side of the cleft, where the vermilion height is the greatest, just before the red line converges to meet the white roll at the cleft edge (Noordhoff's point). The vermilion tissue medial to this triangular marking is used to augment the deficient vermilion underneath the cupid's bow. A straight cut is made on the medial side of the cleft to fit the inset of the lateral triangular flap (**Figure 13**).

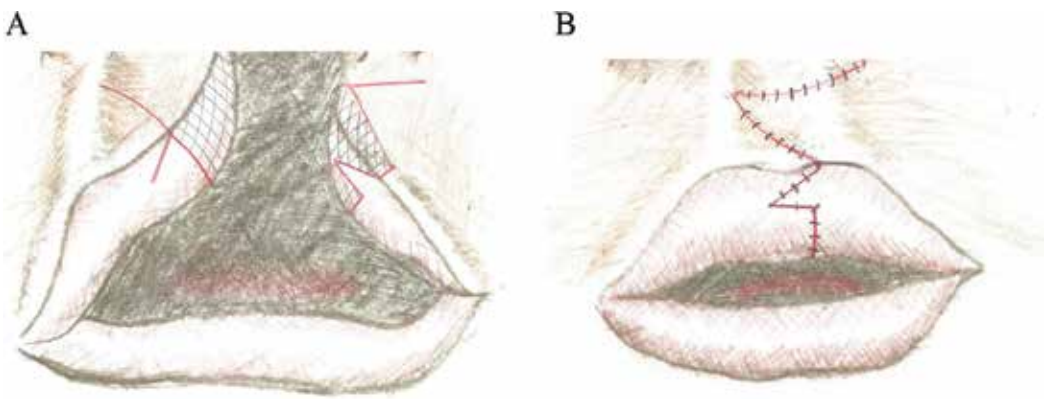

Figure 13. (A) Schematic representation of the incisions for a Noordhoff flap. (B) Schematic representation of the closure of a Noordhoff flap.

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6.5.2. Powar technique

The Powar Technique for unilateral cleft lip repair is a modification of the Noordhoff's lateral vermilion flap. The Powar technique not only maintains the parallel relationship of the muco-vermillion "red line" with the white roll but also more accurately matches the vermilion on the noncleft side [33]. In Power's modification, the vermilion deficiency is measured on the medial cleft segment and a custom matching triangular flap is created above the muco-vermilion junction on the lateral slide (**Figure 14**). This avoids the mucosal bulge that often is the result of the Noordhoff triangular flap inset.

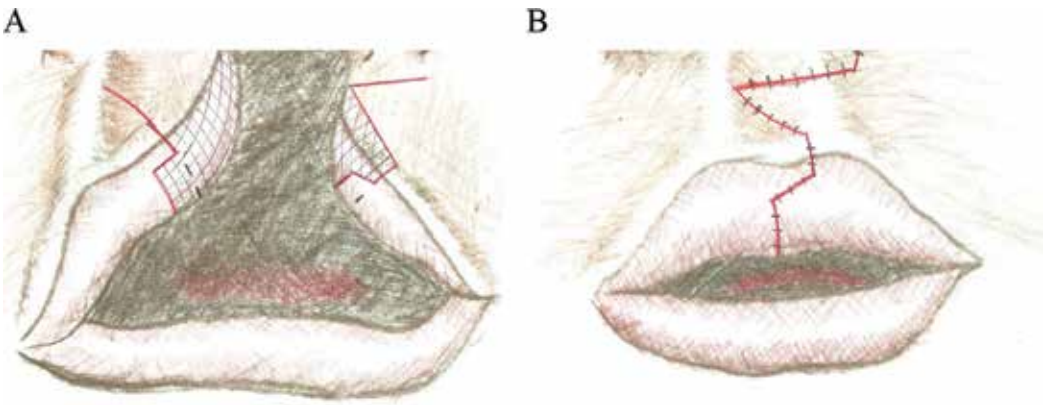

Figure 14. (A) Schematic representation of the incisions for a Powar flap. (B) Schematic representation of the closure of a Powar flap.

6.6. Adjuntive flaps

Creation of the cupid's bow is a critical aesthetic concern in cleft lip surgery and has two major elements: continuity of the white roll and sufficient caudal rotation. It is tempting for the surgeon, when faced with a wide cleft, to preserve as much tissue width as possible. However, preserving lip tissue with attenuated or absent white roll yields unsatisfactory outcomes. The vast majority of patients who present for a revision of cleft lip scar benefit from excision of scar to an accurately determined Noordhoff's point and meticulous suture approximation of the white roll.

A cleft lip repair may be unacceptable if the cupid's bow is not horizontal due to insufficient caudal rotation of the lip. A great advantage in the Pool technique is that it easily provides sufficient caudal rotation. In the case of insufficient rotation, enlarging the Z-plasty flaps, a flap "back cut," or a second Z-plasty may bring cupid's bow horizontal. A second smaller Z-plasty just above the white roll is a very useful tool: the tightness caused by the Z-plasty enhances the prominence of the white roll, and small flaps also break up a long linear scar (**Figure 15**). The Tennison and Fisher techniques employ this principle as part of their initial design.

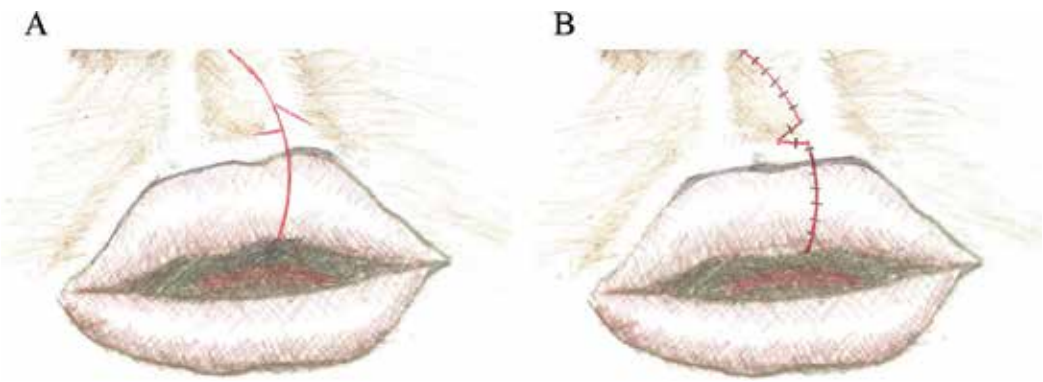

Figure 15. (A) Schematic representation of closure of a cleft repair with the cupid's bow under-rotated. The incisions for a second, smaller Z-plasty above the white roll are planned. (B) Schematic representation of the closure of Z-plasty.

6.7. Hard palate repair at the time of lip repair

Sommerlad advocates the Oslo Protocol for closure of the hard palate: a single-layer mucoperichondral flap of the vomarine septum simultaneous with primary cleft lip repair [34]. While the lip is incised and retracted, tissue exposure is optimal to the anterior palate. This technique seems not to have unfavorable outcome on maxillofacial growth [35].

6.8. Primary nasal repair

Early nasal reconstruction is important for the patient's self-esteem from a young age, and eliminates the need for correction of worsening nasal deformities as one matures and grows. The reparative success of cleft nasal deformity is dependent on dissection that frees the alar cartilage and its translocation into normal position.

6.8.1. McComb's technique

McComb's technique lifts the alar cartilage with its vestibular lining to shorten the cleft-side nose [36]. Dissection in a subcutaneous plane is performed from the upper buccal sulcus and also through the columella to release the medial and lateral crura. The dissection then is extended from the nostril rim to the tip, dorsum, and nasion. The alar lift is achieved with either one or two mattress sutures through the nasal lining at the intercrural angle, raising the cleft side lower lateral alar cartilages to a symmetrical position.

6.8.2. Anderl's technique

The Anderl technique utilizes the incisions made for cleft lip repair and wide undermining of the nasal skin. The Anderl technique has extensive mobilization by undermining of the nasal dorsum, supraperiosteal dissection on the surface of maxilla from the vestibule to the infraorbital rim and from the piriform aperture to the maxillary tuberosity [37]. This maneuver allows for greater medial excursion of the lateral element during repair of the lip and nose. The cartilaginous septum is also released from its base attachment to the hard palate, straightened and sutured to the anterior nasal spine.

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6.8.3. Salyer's technique

Salyer also uses extensive subcutaneous freeing of all elements and floating them above an abnormal skeletal base. He uses two intranasal-transdermal sutures to create the genu of the ala [38]. In the completion of the lip and nasal repair, additional sutures may be used to contour the alar base.

7. Outcomes assessments repair

"It is very difficult to understand the effectiveness of our actions without measurements."

—Steve Killelea

Most outcome studies for unilateral cleft lip-nose repair are single-surgeon experiences with their preferred techniques [39]. Outcomes are measured with postoperative photographs that assess various anatomic landmarks and features. Other studies compare results as surgeon's technique change over time [40, 41].

AmeriCleft, a large, multicenter study in the U.S., validated the use of the Asher-McDade rating scale, to audit four different institutions each with their own protocols [42]. The Asher-McDade system stratifies cleft patients on a seven-point scale in each of the following nasolabial characteristics [43]:

a. Nasal form
b. Symmetry of the nose
c. Shape of the vermillion
d. Nasal profile including upper lip

The EuroCleft, a large multicenter European study, found that physical metrics correlated poorly with satisfaction [44]. Furthermore, there are few studies that examine the functionality and quality of life of cleft patients postoperatively [45]. Future metric systems should be comprehensive, incorporating all patient-related outcomes in a cleft population.

8. Author's experience

"It is life's tragedy that we get old too soon and wise too late"

—Benjamin Franklin

The senior author (DL) was trained in plastic surgery residency, as many were, to repair unilateral cleft lips with the Millard rotation-advancement technique. Later, while on surgical missions to developing world countries, I had the opportunity and honor to work with Dr. Robert Pool, and learn his midlip Z-plasty technique of lip repair. Moreover, I also observed his meticulous surgical technique and attention to detail that brought the children on whom he operated such excellent results. When I began practice with the Vermont State Cleft/Craniofacial Center, I used the Pool technique.

Still later in my practice, I was quite intrigued by the extended Mohler technique advocated by Dr. Court Cutting. While in New York City attending Dr. Barry Grayson's excellent workshop on nasoalveolar molding, Dr. Cutting graciously invited me to observe him operating on an

infant with unilateral cleft lip. I observe his similar scrupulous attention to detail and excellent technique. I then began using this technique for a period of time. For reasons discussed below, I have returned to a midlip Z-plasty technique for surgical reconstruction of children with unilateral cleft lip.

In my experience, the upper lip techniques of lip reconstruction have the disadvantage of a transverse scar across the columellar-labial junction. The columellar-labial junction naturally has a gentle curved shape, but a transverse scar across this curve will frequently result in a tight, noncurved junction.

Linear scars the entire height of the lip often results in scar hypertrophy (**Figure 16**). The linear Cutting/Mohler surgical linear scar line mimics a natural philtral ridge, however may result in a hypertrophic scar of the vertical limb.

Figure 16. A child 5 months after cleft lip repair by the Cutting "Extended Mohler" technique and Powar vermillion flap. This is the child from **Figure 1B** and **Figure 4**. Note the somewhat hypertrophied straight-line vertical limb of the scar.

Continuity of orbicularis oris is the critical functional concern of cleft lip surgery. Midlip surgical techniques have a great advantage in that the incisions are made over the abnormal muscle bundles, and flap transposition redirects those muscle bundles with less extensive dissection (**Figure 17**).

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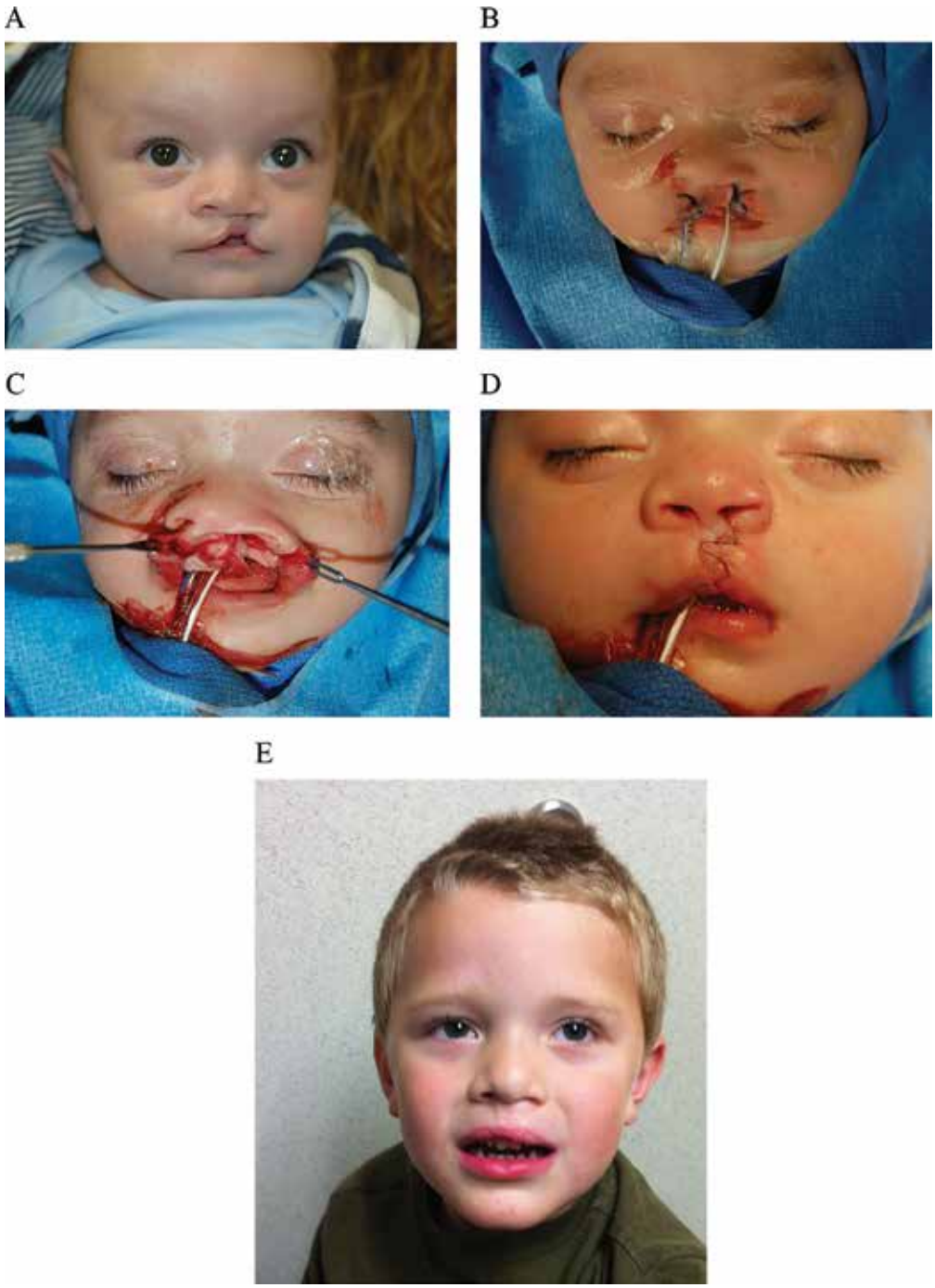

Figure 17. (A) An infant with a complete unilateral cleft lip. (B) The infant in the operating room with markings for a Pool midlip Z-plasty and Noordhoff vermillion flap repair. (C) The infant in the operating room with dissection completed. Because the Z-plasty design and muscles are freed from their abnormal insertions without as much undermining of the skin. (D) The infant in the operating room with surgical repair completed. (E) This child at 3 years of age.

In my opinion, this technique yields very satisfactory results (**Figure 18**).

Figure 18. (A) An infant with a wide, yet incomplete unilateral cleft lip. Note the narrow Simonart's band. (B) The infant after a Pool midlip Z-plasty and Powar vermillion flap repair. (C) The same child at 5 years of age.

At Vermont State Cleft/Craniofacial Center, we perform formal NAM presurgical orthopedics only on children with bilateral clefts who have premaxillary protrusion (**Figure 5**). Unfortunately, we have found that the frequent visits and lack of insurance coverage for NAM result in a high burden of care for families in Vermont. Because of this, we have not adopted this modality for children with unilateral clefts. We have found presurgical taping (**Figure 4**) to be an efficacious yet inexpensive modality and it offers an opportunity for parents to play an active role in their child's care.

Thoughtful selection of a surgical method and careful attention to detail in the execution of surgical technique will yield the best results. We hope that this chapter will help surgeons in the care of children with cleft lip.

Author details

Mustafa Chopan, Lohrasb Sayadi and Donald R. Laub*

*Address all correspondence to: Donald.Laub@uvmhealth.org

University of Vermont College of Medicine, Burlington, Vermont, USA

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Chapter 6

Tympanostomy Tube Placement for Otitis Media with Effusion in Children with Cleft Lip and Palate

Chin-Lung Kuo and An-Suey Shiao

Additional information is available at the end of the chapter

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Abstract

The condition of cleft lip/palate (CLP) in children is psychologically stressful for family members and debilitating for the patients themselves. These children must undergo a series of major invasive surgeries following birth, including cleft lip repair surgery, cleft palate repair surgery, bone grafting surgery, and dental implant surgery. Unfortunately, the clinical significance of otitis media with effusion (OME), a complication associated with CLP, is often overlooked, and very few studies have explored this condition in depth. This chapter reviews pathogenesis, clinical manifestations, consequences, examination, and diagnosis related to OME in children with CLP. Controversies surrounding the treatment of OME in CLP children are also discussed. We also provide a flowchart for management guidance in OME in children with CLP.

Keywords: otitis media, middle ear effusion, cleft lip and palate, conductive hearing loss, grommet tube, children

1. Introduction

Cleft lip/palate (CLP) is a congenital orofacial anomaly that is debilitating for patients and psychologically stressful for family members. Children with CLP are forced to undergo a series of major invasive surgeries, including surgery for cleft lip repair, bone grafting, and dental implants [1].

Otitis media with effusion (OME), also called serous/secretory otitis media or glue ear, is a collection of nonpurulent fluid within the middle ear space. OME is a common condition among infants and children between the ages of 1 and 3 years [2]. Compared to healthy children, children with CLP are more susceptible to OME [3]. Despite the fact that the vast majority of patients (about 80%) do not have OME at birth [4], statistics show that OME occurs

at least once before the first birthday in as many as 90% of the infants born with CLP [2]. In addition, as many as 97% of the infants born with CLP suffer concurrent OME within the first two years of life [5].

The clinical significance of OME is often overlooked, and very few studies have explored this condition in depth, despite it being a complication commonly associated with CLP. This chapter reviews pathogenesis, clinical manifestations, consequences, examination, and diagnosis related to OME in children with CLP. Controversies surrounding the treatment of OME in CLP children are also discussed. We also provide a flowchart for management guidance in OME in children with CLP. It is our hope that the results of this study will provide clinicians and patients/parents with a valuable reference.

2. Pathogenesis

Numerous factors have been cited in the development of OME in children suffering from CLP, including (1) immature development of the Eustachian tube, (2) abnormalities in the muscle associated with the Eustachian tube, and (3) craniofacial bone abnormalities [3].

2.1. Immature development of the Eustachian tube

The Eustachian tube of children is not yet fully developed and therefore shorter than that of adults. It is positioned at a more horizontal angle, and the opening to the nasopharynx is narrower. When upper respiratory tract infection causes swelling and inflammation of the respiratory mucosa, the narrow opening of the Eustachian tube can easily be clogged, leading to negative pressure in the middle ear. In addition, the position and length of the Eustachian tube allow viruses and bacteria from the upper respiratory tract to easily pass into the middle ear cavity, which can cause middle ear infection with effusion. Even after infection has been controlled, it is difficult to discharge fluid from the middle ear through the Eustachian tube to the throat, because the Eustachian tube is shorter and more horizontal with a narrow opening. The remaining fluid can lead to OME [6–9].

2.2. Abnormalities of Eustachian tube-associated muscle

Anatomical or structural defects associated with cleft palate can affect velopharyngeal function. In children with CLP, the abnormal reflux of food and fluid from the mouth into the nasal cavity due to velopharyngeal insufficiency can result in inflammation and edema of the Eustachian orifices and hypertrophy of adenoid pads, leading to tubal obstruction and secondary OME [6]. In addition, abnormal development of the tensor veli palatini (TVP) muscle and levator veli palatini muscle in children with CLP can cause maladjustment in the regular opening of the Eustachian tube [10, 11]. When the atmospheric pressure of the environment changes (e.g., during descent in an airplane) or the gas in the middle ear is absorbed by mucosa, the Eustachian tube is unable to open and thereby relieve pressure in the middle ear. The resulting negative pressure can cause the eardrum to retract, leading to the collection of fluid in the middle ear, which can again lead to OME [6].

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2.3. Craniofacial bone abnormalities

Other abnormalities in the structure of the Eustachian tube in children with CLP have also been associated with the pathogenesis of OME. These abnormalities include increased nasopharyngeal space, alterations to the medial pterygoid plate and hamulus, a shorter tube, larger angle between the cartilage and TVP, higher cartilage cell density, a smaller ratio of lateral and medial lamina area in the cartilage, less curvature of the lumen, less elastin in the hinge portion of the cartilage, and a lower insertion ratio of TVP to the cartilage [12, 13]. Kemaloglu et al. evaluated clinical and cephalometric data of 37 Japanese children with unilateral complete CLP or isolated cleft palate and compared them to 40 non-cleft children. They found that differences in the mastoid-middle ear-Eustachian tube system are associated with a tendency toward OME in CLP children. This fact helps to elucidate the pathogenesis of OME in children with CLP [14].

3. Clinical manifestations

Aside from mild conductive hearing loss, OME does not cause any other symptoms of discomfort and is therefore easily overlooked. In infants, OME combined with hearing loss may continue for weeks or even months without being detected. A child with OME may also suffer poor sleep quality [15]. Parents of children with CLP should pay particular attention to how their children interact with others and how they react to sound. If any abnormality is observed, the child should undergo expert evaluation. More importantly, children should visit an otolaryngologist for a regular otologic examination to ascertain whether they are suffering from OME. Early diagnosis and treatment are invaluable in preventing or alleviating future hearing loss.

4. Consequences of OME in CLP

Children with CLP may suffer recurrent or continuous OME, causing atelectasis, ossicular fixation, and tympanosclerosis [2, 16, 17], which can result in conductive hearing loss of up to 30 decibels (dB). Researchers have previously shown that, regardless of whether they have undergone cleft palate repair surgery, as many as 90% of children with CLP suffer from OME or conductive hearing loss, while 50% suffer from recurrent otitis media [2, 5, 18–20]. In comparison, the prevalence of conductive hearing loss among children without CLP is 12.9%. Although the likelihood of developing OME is reduced after reaching adulthood, it is estimated that 50% of these children suffer from permanent conductive hearing loss [21, 22]. Additionally, 0.9–5.9% of patients with CLP develop primary acquired cholesteatoma, the probability of which is 100–200 times higher among those without CLP [23, 24].

In addition, sensorineural losses have been ascribed to pathologic changes in the inner ear resulting from inflammation in the middle ear and presumably mediated via the round or oval window [3]. Toxins produced by long-term inflammation can pass through the round window or the oval window into the inner ear, causing permanent sensorineural hearing loss [17, 25].

Many studies have indicated that although reconstructive surgery for CLP improves linguistic ability, language development depends on the extent to which hearing ability is maintained [23, 26]. If OME is not treated properly, long-term hearing loss can negatively influence the language development of children [27]. Hearing loss in children suffering from CLP can also affect their academic comprehension and learning performance [20, 27, 28]. Bess et al. indicated that even if children suffer hearing loss in only one ear, academic performance can still be seriously affected in up to 33% of patients and up to 40% of patients are unable to participate in regular activities or interactions due to hearing loss [29]. It has been found that children with cleft palate are prone to specific psychological problems [30, 31]. Children suffering from this condition may also display behavioral difficulties due to feelings of isolation [29].

5. Examination and diagnosis

Up to 90% of infants born with CLP suffer from OME before their first birthday [2]; therefore, it is recommended that otologic tests be conducted as soon as possible after birth to ascertain whether fluid has collected in the middle ear [21, 32]. The use of a pneumatic otoscope is the fastest and most direct method used for the inspection of the eardrum for color and contour and determining whether fluid has collected in the middle ear. It should be noted that the effectiveness of a pneumatic otoscope to test for OME depends on the experience and skill of the clinicians, the patient's full cooperation, and the anatomical structure of the ear canal [2].

Another method for inspecting the eardrum is videotelescopy. A telescope is placed against the eardrum through the external ear canal, and a charge-coupled device (CCD) camera captures images of the eardrum. The resulting magnified images can be presented on a monitor, thereby allowing clinicians to accurately diagnose middle ear effusion [33]. Guo and Shiao conducted a prospective study on the diagnostic efficacy of videotelescopy, pneumatic otoscopy, and tympanometry for the detection of pediatric OME. Their results demonstrate that the sensitivity, specificity, and accuracy of the videotelescopy were 97.8, 100, and 98.0%, respectively. These values significantly exceed the accuracy of conventional tests using pneumatic otoscope and tympanometry [33]. Videotelescopy provides clinicians with visual information with which to validate the accuracy of the pneumatic otoscopy.

Pneumatic otoscopy and even videotelescopy are difficult to administer on newborns and small infants with CLP. Thus, objective acoustic immittance testing plays an important role in the diagnosis of OME in CLP patients [34]. Tympanometry is the most commonly used acoustic immittance test to measure pressure changes in the middle ear and the compliance of the eardrum [27]. Chen et al. found that the specificity of tympanometry, when used to test for OME in infants with CLP, was relatively low (only 59.6%). When used to test infants within 9 months of age, specificity dropped to only 37.5% [28]. Furthermore, when infants are crying or unable to cooperate during testing, it can be difficult to maintain airtight conditions in the ear, thereby preventing successful completion of the examination.

Pure tone audiometry can also be used to facilitate the diagnosis of OME; the results may reveal conductive or mixed hearing loss. The cooperation of children is required for this

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procedure, which means that it may be unsuitable for children under 3 years of age [35]. For patients in this age group, spectral gradient acoustic reflectometry (SGAR) may be an effective alternative to pure tone audiometry in the diagnosis of OME. SGAR transmits ultrasound waves to the eardrum, whereupon a microcomputer is used to filter, record, and analyze the ultrasound waves reflected back. SGAR is an efficient diagnostic tool for the detection of OME, requiring less than one second to complete the procedure. Although the sensitivity and specificity are somewhat low, SGAR is a noninvasive test that is unaffected by crying, cerumen, client cooperation, or the quality of the air seal in the ear, thereby making it useful for testing difficult infants [28, 36–38].

6. Watchful waiting for OME

Alt first identified the relationship between CLP and hearing impairment in 1878, and OME has since been the subject of investigation [39]. The severe complications caused by OME in CLP children can have far-reaching consequences; therefore, determining the optimal treatment strategy is a topic worthy of in-depth exploration.

Many researchers have recommended watchful waiting as a treatment of choice for OME among children with CLP, particularly when parents prefer to avoid or postpone surgery. Muntz reported that more than 50% of CLP children who develop OME naturally recover from OME and have no need to undergo ventilation tube surgery after 3 years of age [40]. Flynn et al. studied the longitudinal prevalence of OME in CLP children between 7 and 16 years of age and found that middle ear problems gradually dissipate between 7 and 13 years of age [41]. Rynnel-Dagoo et al. found that 82% of the CLP children with or without OME had a normal hearing at 3–4 years of age, indicating recovery from OME [42]. Smith et al. found that the Eustachian tube function of most children with CLP significantly improved by 6–7.5 years of age [43].

A number of researchers have reported that OME and Eustachian tube function improve as the patient grows older [41, 43, 44], recommending watchful waiting for CLP children with OME for a period of 3–6 months from the diagnosis of effusion [41, 43–45]. During the observation period, patients can wear hearing aids to attain the same hearing performance of children with ventilation tubes [45]; however, it should be noted that children may find hearing aids inconvenient or may worry about the social stigma associated with wearing such aids [27, 46].

7. Ventilation tube insertion (VTI) for OME

Previous studies have shown that 90% or more of the children who undergo palatoplasty for CLP still suffer recurrent OME [20], which is a reflection of persistent poor Eustachian tube function after repair surgery [47]. Thus, many doctors prefer to perform the repair of cleft palate and ventilation tube surgery simultaneously when the child is 1 year old [2, 17, 48–50]. This combined surgical approach is done in the hope of overcoming the problem of middle ear effusion and improving the hearing ability of children, thereby enhancing their long-term linguistic development.

This chapter summarizes previous studies that addressed the effectiveness of VTI for OME in CLP children aged 18 years or less. Each of the studies we summarize below measured outcomes using a variety of methods. We attempted to normalize those measurements. As for hearing outcomes, the natural effect measure refers to the difference in hearing ability. For studies using outcome measures on different scales, we summarized the findings as the percentage of ears presenting hearing loss or improvement. For the frequency of grommet insertion, measurements were summarized as the percentages of ears that underwent one or more grommet insertions and the number of times that insertion was performed. For complications or sequelae, the main summary measure was the occurrence of complications. For middle ear status, the effect measures included the rates of OME recurrence and resolution and the percentage of ears presenting various types of tympanogram.

7.1. Comparative effectiveness for hearing outcome

7.1.1. CLP children versus age-matched non-CLP children

Two studies compared CLP children with age-matched healthy children with regard to hearing outcomes after VTI for OME [51, 52]. One prospective study with an excellent study design reported similar hearing outcomes between children with and without palate conditions (CLP group 10.5 dB versus control group 10.9 dB, $p > 0.05$, follow-up 5–7 years) over the short term [51]. The other retrospective study of moderate study design reported a significantly higher percentage of ears with hearing loss (CLP group 24% versus control group 0%, follow-up 3–5 years) [52]. However, 64% of children in the CLP group underwent VTI, while only 6% in the non-CLP group underwent VTI ($p < 0.0005$).

7.1.2. Pre-VTI versus post-VTI hearing outcomes

Hearing outcomes were evaluated in several case-series studies [16, 23, 43, 53–57]. Over the long term, between 50 and 94% of CLP children recovered normal hearing after being administered VTI in conjunction with palatoplasty (follow-up 5.5–15.4 years) [16, 43, 54–57]. Furthermore, children requiring a higher number of VTIs were at increased significant risk for long-standing hearing loss [16, 23].

7.1.3. VTI versus non-VTI

Zheng et al. conducted a randomized controlled trial to determine the effectiveness of grommets on hearing recovery among CLP children with OME [58]. The authors reported hearing improvement in only 22 of 39 CLP children with VTI; however, no hearing results were obtained from those that did not undergo VTI. Furthermore, the authors reported hearing outcomes over the short term (6 months of observation); however, little emphasis was placed on the long-term outcomes, which makes it difficult to interpret their results.

Several prospective [51, 59, 60] and retrospective [20, 44, 46, 52, 61–68] cohort studies evaluated hearing outcomes. Among these cohort studies, several studies compared VTI with non-VTI (i.e., myringotomy alone, hearing aids, watchful waiting) [44, 60, 62, 64–68]. It has been reported that the improvements in hearing afforded by VTI over the short term (within 18 months after VTI)

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are more pronounced than those of myringotomy, watchful waiting, or HA [64–66]. Potsic et al. found that, compared with CLP children without VTI for OME, those with VTI had a lower percentage of ears presenting hearing loss over the short term (less than 5 years) [68]. As for long-term hearing outcomes, Hubbard et al. reported that early VTI (3 month of age) could have a greater effect on hearing than that achieved when adopting a conservative approach to treatment [60].

Despite the fact that most studies on hearing outcomes have advocated VTI for CLP children, a number of researchers have expressed reservations, based on conflicting results. Some cohort studies observed that CLP children that had undergone VTI for OME presented worse hearing outcomes over the short term (less than 5 years) [44] or a higher percentage of ears with hearing loss after surgery over the long term (9–21 years), compared to children that did not undergo the procedure [62, 67].

7.1.4. Summary of evidence on hearing outcome

More than half (50–94%) of CLP children recovered normal hearing 5–15 years after VTI [16, 43, 54–57]. Moreover, compared with conservative management, most studies have shown that VTI is beneficial to hearing recovery over the short as well as long term [60, 64–66, 68]. There remains a belief that early VTI at the time of palatoplasty is beneficial; however [69], there is little evidence indicating the optimal timing for grommet insertion.

7.2. Comparative effectiveness for speech and language outcomes

7.2.1. CLP children versus age- and sex-matched non-CLP control

One article compared CLP children with age- and sex-matched non-CLP controls with regard to post-VTI speech and language outcomes [69]. Normal or near-normal speech intelligibility ratings were similar in CLP (90%) and non-CLP children (96%).

7.2.2. VTI versus non-VTI

Several studies have assessed speech and language outcomes in CLP patients with OME, including prospective [60] and retrospective cohort studies [44, 69–72]. Five articles compared children that were or were not administered VTI for OME [44, 60, 70–72]. No differences in speech or language development were observed in short-term (0–5 years) [44, 72] or long-term (8–10 years) [70, 71] follow-ups. With one exception, all investigators used the same number of CLP children matched for cleft type, age, sex, socioeconomic status, and birth order. After a 9-year follow-up, consonant articulation was found to be better after early VTI ($p = 0.03$) [60]. However, the authors performed myringotomy on the control group (when deemed necessary), which prevented the clear elucidation of differences in functional outcome between children that did or did not undergo VTI for OME.

7.2.3. Summary of evidence on speech and language outcomes

No differences in speech or language development were observed between CLP children that underwent conservative observation and those that underwent aggressive VTI, over the short

term (0–5 years) [44, 72] or long term (8–10 years) [70, 71]. Further, assessments of speech by Merrick et al. revealed a similar percentage of children with normal or near-normal speech intelligibility ratings in the CLP and non-CLP groups [69]. These findings appear to indicate that speech and language skills do not depend on the VTI approach to OME treatment, but rather on the timing of palatoplasty.

7.3. Complications of VTI for OME

7.3.1. CLP children versus age-matched healthy children

Two studies compared age-matched healthy control children with regard to VTI complications [51, 52]. One study showed that the prognosis of children with CLP that undergo early VTI is comparable to that of children without CLP [51]; however, the other study reported contradictory results with higher rates of complications among CLP children [52].

7.3.2. VTI versus non-VTI

Several retrospective cohort studies compared children with and without VTI (i.e., hearing aids or watchful waiting) with regard to post-VTI complications [44, 46, 61, 62, 66, 67, 72]. Those studies reported higher complication rates among children with VTI than among those without, over the short term (<5 years of follow-up) [44, 46, 61, 66, 72] as well as long term (9–21 years of observation) [62, 67]. All results were statistically significant; however, differences were not calculated in two of the studies [62, 72].

Among the various types of complications, tympanosclerosis and otorrhea generally present transient but common sequelae following VTI [73, 74], with other studies reported permanent perforations and cholesteatoma [73, 75, 76]. As for the occlusion of grommets, infection, and the presence of granulation tissue, the evidence was too limited and blurred to determine the direction of effects between VTI and adverse events in CLP children with OME.

7.3.3. Tympanosclerosis

Tympanosclerosis has little influence on hearing [16, 72, 77]; however, this is the most common VTI-related complication, the rates of which were in the range of 0–52% [4, 20, 44, 46, 52–54, 57, 58, 61, 65, 67, 72, 78]. Tympanosclerosis can, albeit rarely, cause conductive hearing loss if it extensively involves the ossicle chain [72].

7.3.4. Otorrhea

Otorrhea is a complication of the tympanostomy tubes in children who are otherwise healthy [79]. However, otorrhea has not been systematically studied in CLP children after VTI. Some studies have reported a low probability (4–11.5%) of post-VTI otorrhea in CLP children [44, 50, 66, 79], whereas others reported inconsistent results (55–68%) [31, 57, 78]. The evidence is inconclusive due to conflicting results among these studies. Otorrhea appeared to be more common in ears that underwent VTI than in those that did not [66]. However, the evidence is insufficient to reveal an association between the long-term use of grommets and otorrhea. Only one study on post-VTI otorrhea reported the management of otorrhea [72]. Freeland et al.

found that although 68% of infants developed otorrhea following the use of grommets over a mean duration of 3.9 months, the otorrhea usually responded promptly to antibiotic-corticosteroid drops or systemic antibiotic treatment in more resistant cases.

7.3.5. Eardrum perforation

In CPL children, eardrum perforation occurred in 0–19% of VT-treated ears in follow-ups of 1–15 years [4, 16, 20, 43, 44, 46, 50–54, 56–58, 60, 61, 66, 67, 70, 72, 78]. In a study by Shapiro, the rate of eardrum perforation was found to be as high as 50% after VTI [80]; however, the number of children with VTI (only six children) was too small to be of reference value (low-quality study design). In contrast, eardrum perforation was observed in only 0–7% of non-VT-treated ears (i.e., observation or hearing aids) during follow-ups of 1–4 years [61, 66, 72]. In non-CLP children with OME, only one study reported a 3% incidence of post-VTI eardrum perforation within a 5-year follow-up [51].

7.3.6. Cholesteatoma

Grommet insertion has been reported to be an iatrogenic cause of secondary acquired cholesteatoma [81–86]. The development of the disease is quite uncommon, with a reported rate of approximately 1% in non-CLP children with VTI [73, 87]. However, evidence has shown that the CLP children were at increased risk of developing cholesteatoma [66, 73], with a higher rate of 0–6.9% within 12 years after VTI [16, 23, 58, 62, 66, 67, 73, 80, 88].

It should be noted that Hornigold et al. reported an incidence of 29% for CLP children 21 years after VTI for OME [62], Similarly, Spilsbury et al. conducted a retrospective cohort study on the relationship between CLP and secondary cholesteatoma following VTI in children [73]. They examined the complete hospital in-patient history of a large unselected population (869 CLP children versus 56080 non-CLP children) over a 29-year period. The authors reported that children with CLP developed cholesteatoma 7.5 (95% confidence interval, 3.8–18.2) times faster after the first VTI, compared to children without CLP.

7.3.7. Summary of evidence on VTI complications

CLP children with VTI generally have a higher risk of complications than do those without, over the short-term (less than 5 years) [44, 46, 61, 66, 72] as well as long-term (9–21 years) follow-up [62, 67]. However, compared to non-CLP children with OME, there is insufficient evidence to draw any conclusions due to conflicting results among these studies on CLP and non-CLP children [51, 52].

7.4. Comparative effectiveness for middle ear status

Previous studies have compared the effect of VTI on middle ear by using outcome measurements including the rates of OME resolution, persistent OME, and OME recurrence. The rates of OME resolution were reported in three high-quality studies, including a randomized control trial, a prospective cohort study, and a retrospective cohort study [50, 51, 58]. The rates of OME resolution ranged from 48.7 to 86% within the first 6.5 years. These results were

supported by Goudy et al., who reported a median resolution time of conductive hearing loss of approximately 5 years [23]. Kuscu et al. observed that normal otoscopic examination findings were higher in CLP children without VTI than in those with VTI [89].

Persistent OME was observed in 29–52% of CLP children 4–7 years after VTI [20, 44, 68, 72]. Gordon et al. [67] found that only 5% of CLP children had persistent OME 9 years or more after palatoplasty with VTI, concluding that Eustachian tube function may be adequate by age of 9 years. These results are supported by Smith et al. [43], who found that Eustachian tube function eventually returned to normal in most CLP children and that the age of Eustachian tube normalization was approximately 8 years (1.5–17.3). As for OME recurrence, a number of studies have reported that 17–45% of CLP children had OME recurrence 3–6 years after VTI, at a mean age of approximately 7 years [20, 56, 57, 61].

7.4.1. CLP children versus non-CLP control

Four articles reported in post-VTI middle ear function in CLP and non-CLP children [51, 52, 59, 69], three of which included an age-matched non-CLP control group [51, 52, 69]. The results in studies by Ovesen and Blegvad-Andersen [52] and Broen et al. [59] were not considered for further interpretation because only 6 and 31% of the non-CLP children with OME underwent VTI, respectively. Merrick et al. reported comparable rates of persistent OME in children with and without cleft palate (24% versus 14%, $p = 0.31$) [69]. Valtonen et al. reported similar OME resolution rates in CLP and non-CLP children (64.1% versus 60.6%) [51]. In summary, the prognosis for middle ear recovery among CLP children with early VTI is comparable to that of children without CLP.

7.4.2. VTI versus non-VTI

Zheng et al. performed a randomized controlled trial comparing OME resolution rates between CLP children with and without VTI [58]. They reported a significantly higher OME resolution rate (48.7%) in children undergoing palatoplasty and VTI than in those undergoing palatoplasty alone (24.5%, $p < 0.01$). Children with VTI had a shorter observation period (6 months versus 20 months); however, the authors expected that the OME resolution rate would have been higher if the children had been followed up for the same period as those without VTI, such that the difference in resolution rate between the groups would become increasingly pronounced. In another study by Potsic et al., [68] the authors found that CLP children that did not undergo VTI had a significantly higher rate of persistent OME at the age of 5 years than did those with VTI. Freeland et al. [72] obtained the same result for CLP children at the age of 4 years. However, two other studies reported conflicting results, i.e., a higher rate of persistent OME in CLP children with VTI [44, 67].

7.4.3. Summary of evidence on middle ear status

Three high-quality studies reported that more than half (48.7–86%) of the CLP children that underwent VTI presented OME resolution within the first 6.5 years [50, 51, 58]. The median resolution time of conductive hearing loss was found to be approximately 5 years [23]. The high OME resolution rates were supported by four other studies, in which persistent OME

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was observed in less than half (29–52%) of the CLP children in the first 4–7 years after VTI [20, 44, 68, 72]. Eustachian tube function began to normalize by 7–9 years of age [20, 43, 44, 50, 51, 58, 67, 68, 72]. In addition, fewer than half of the CLP children (17–45%) presented OME recurrence within the first 3–6 years of follow-up [20, 56, 57, 61]. Importantly, the prognosis for CLP children that undergo early VTI was comparable to that of the children without CLP.

7.5. Frequency of grommet insertion

A significant proportion (53.2–98%) of CLP children with OME required VTI [4, 51, 54, 61, 78] with an average of between 0.55 and 2.2 VTIs per patient in the first 7 years of observation [20, 44, 59, 66]. Cleft defects play an important role in OME formation; therefore, it would be reasonable to assume a higher need for grommets in children with more overt palatal malformations. This assumption is supported by several studies [67, 71, 88], in which a relationship was established between the degree of clefting and the frequency of VTI, with severe or complete clefts more likely to involve grommet insertion. Children with cleft palate had a significantly higher frequency of VTIs than those without [51, 59]. However, this issue requires further investigation. Lithovius et al. reported that the severity of the cleft was not a significant factor related to the number of ventilation tubes required [90]. Surgical techniques used to repair the cleft palate are not significantly associated with the number of VTI required [90]; however, palatoplasty may indeed decrease the rate of ventilation tube reinsertion in children with cleft palate, as evidenced by a recent population-based study [91].

7.6. Summary of evidence pertaining to effectiveness of VTI for OME

Compared with a conservative approach, early VTI was shown to improve hearing, and this improvement was maintained in more than half of the CLP children 5–15 years after surgery. Nonetheless, VTI does not necessarily lead to improvements in speech or language development in CLP children, and the CLP children with VTI had a higher risk of complications than did those without. It appears that VTI is beneficial for the recovery from OME in CLP patients. There is insufficient evidence to suggest the optimal timing of VTI (e.g., at the time of repair of lip/palate); however, it may be convenient for surgeons to combine these procedures.

7.7. Limitations of previous studies

Despite considerable research into subgroups of CLP children with regard to the effectiveness of grommets for OME, heterogeneity in the design of studies has proven a formidable barrier to the synthesis of evidence [92, 93]. Most previous studies failed to clearly describe their criteria in the definition of OME. Previous studies included subjects of different ages with different types of cleft who had undergone different procedures and employed different criteria for VTI. Grommet insertion (unilateral or bilateral) was treated as a single procedure in some studies or as two procedures in other studies. The measures used in the studies were nonuniform; different time points were used for the determination of outcomes, and baseline measures were not always provided. Studies also varied in the length of observation periods.

Most studies in this review were retrospective studies. Only otologic findings during a particular month, or interpolation from examinations in adjoining months, were used in arriving at the monthly status of each ear. Thus, patient history was of limited value because it was difficult to determine when grommets had been extruded and if ear drainage was occurring. Due to mixed results, statistical differences could not be calculated for each complication, such that it is unclear whether the differences reached statistical significance. Finally, the issue of missing data was not taken into account.

8. Debate concerning selection of treatment strategy

A review of previous studies shows that there is currently no consensus as to the optimal method of treating OME, and many researchers are at odds regarding their views on the subject [46]. Most previous studies are based on retrospective analysis and vary widely in their design; therefore, it is difficult to make an informative comparison. Even in prospective studies on OME in CLP children [51, 58, 59], there remains a lack of high-quality, adequately powered randomized controlled trials. One reason may be that most parents require recommendations pertaining to treatment, rather than allowing their child to be randomly included in an experimental or control group, particularly children who have undergone or will undergo a series of major invasive surgeries. Thus, it is currently impossible to conduct a meta-analysis of previous research, which could be used to summarize treatment methods and/or provide guidance with regard to treatment choices [2, 45].

9. Clinical guidelines

9.1. NICE clinical guideline

The UK National Institute for Health and Clinical Excellence has published clinical guidelines for the surgical treatment of OME in children with or without CLP [45]. Those guidelines indicate that there is currently insufficient evidence to prove that simultaneous cleft palate repair surgery and ventilation tube surgery are effective approaches to the alleviation of OME. Thus, the simultaneous insertion of a ventilation tube during the surgical repair of a cleft palate is not recommended unless careful otological and audiological assessments have been performed. The guidelines recommend that treatment be based on the needs and desires of children and their parents and that ventilation tube surgery be viewed as an alternative to hearing aids in CLP children with persistent bilateral OME and hearing loss.

9.2. Clinical guidelines of AAO-HNSF, AAP, and AAFP

Updated clinical guidelines have recently been published for OME. These guidelines were codeveloped by the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) [94]. The guideline update group claims that it may

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be appropriate to offer tympanostomy tubes on an individualized basis for cleft palate infants with OME that persists after failing hearing tests. They claim that resolving the issue of middle ear effusion could facilitate the assessment of hearing status.

It is also recommended that clinicians evaluate children with cleft palate for OME and hearing loss at the time at which cleft palate is first diagnosed. Monitoring for OME and hearing loss should continue throughout childhood, including after palate repair. Specifically, the guideline update group recommends that middle ear status be assessed at 12–18 months of age, considering that this is a critical period in the development of language skills, speech, balance, and coordination. By 18 months of age, delays in language and speech development are easily identified.

In these guidelines, it is recommended that VTI be considered when type B tympanogram or OME persists for 3 months or longer. These recommendations are based on the assumption that the likelihood of spontaneous resolution is low. For children who do not receive tympanostomy tubes, the follow-up schedule to monitor OME and hearing loss until OME resolves should be more frequent than the 3- to 6-month intervals recommended for children without cleft palate.

9.3. PRISMA-compliant systematic review

Many clinical guidelines fail to provide clear recommendations with regard to treatment approaches, due to a lack of conclusive studies [27, 95]. Despite the fact that a number of reviews have been published on treatment choices for the management of OME in CLP children, a number of these are narrative reviews [3, 6, 96–98], whereas others are systematic reviews pertaining mainly to otherwise healthy children [27, 45, 77, 95, 99–105]. The lack of research on the CLP subgroup of children means that there is currently no evidence-based information for clinicians or parents with regard to the effectiveness of grommets for OME in CLP children.

Ponduri et al. performed a systematic review on the routine early insertion of grommets for OME in CLP children [2]. The authors concluded that there is currently insufficient evidence on which to base recommendations pertaining to clinical practice in this area. However, they did not perform data synthesis with regard to patient-centered outcomes, nor did they provide a detailed, well-described protocol, such as The Cochrane [106] and PRISMA [107]. A systematic review based on predefined eligibility criteria conducted in accordance with a predefined methodological approach could facilitate the appraisal of review methods and reveal modifications to methods and selective reporting in completed reviews [108].

A recent systematic review by Kuo et al. published in *Pediatrics* addressed the effects of VTI in children with cleft palate and OME with regard to patient-centered outcomes [109]. The review followed the protocol outlined in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) to enable full and transparent assessment of the existing literature, in order to provide evidence-based information pertaining to the management of OME in children with cleft palate.

That review indicated that 38–53% of CLP children underwent VTI for OME and that more severe cases were more likely to undergo grommet insertion. Compared with a conservative approach, it appears that VTI may improve hearing outcomes in CLP children and that these improvements could remain for at least 1–9 years after surgery. In addition, children who have undergone VTI face a higher risk of complications than do those who have not received this form of treatment. The most common post-VTI complications include eardrum retraction and tympanosclerosis, with incidence rates of 11–37%. Of particular importance is the need to perform grommet insertion within a highly specified time frame. The authors concluded that existing evidence is insufficient to support any assertions with regard to the use of grommets, either therapeutically or prophylactically, at the time of palatoplasty or afterward.

9.4. Future research needs

In the future, there may be a need to develop rigorous methodologies for the examination of functional outcomes in CLP children after VTI. Further multi-institute prospective studies or well-designed randomized controlled trials are needed to develop a comprehensive base of evidence sufficient to clarify the effectiveness of VTI for OME in CLP children.

10. Recommendations for management

Strategies related to the treatment of OME in CLP children are still under debate, and there is insufficient evidence with which to establish absolute guidelines. We believe that the lack of consensus regarding the optimal treatment for OME in CLP children should prompt a relatively conservative approach. Patients and parents should also be given a range of treatment options based on their individual needs and desires.

Figure 1 presents a flowchart of recommended OME management in CLP children. From the time of birth, children with CLP should undergo continual and regular otologic examinations and audiological monitoring for the assessment of OME. Children with delayed speech and/or language development should be suspected of having OME, such that otolaryngology referral is indicated. Once OME is confirmed, the coexisting sensorineural component of hearing loss should be further investigated. It is recommended that children suffering from middle ear effusion without significant hearing loss (hearing threshold ≤30 dB) remain under observation [45]. Children with hearing loss exceeding 30 dB can be managed through active observation for 3 months or alternatively referred for surgery, in accordance with the child's developmental, social, and educational status. If a patient suffers OME in only one ear, the observation period may be extended to 6 months [49]. During the observation period, hearing aids could be considered [110]. Patients suffering from recurrent OME following surgery may undergo repeated ventilation tube surgery, and those in whom the disease persists after an observation period of 3–6 months may be referred for surgery.

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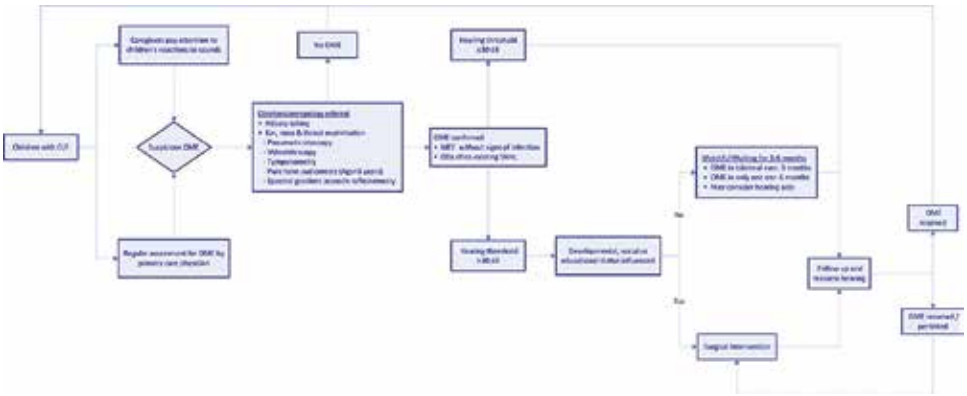

Figure 1. Flowchart of recommended management guidance for OME in CLP children. OME, otitis media with effusion; CLP, cleft lip/palate; MEE, middle ear effusion; DDX, differential diagnosis; dB, decibel; SNHL, sensorineural hearing loss.

11. Summary

Otitis media with effusion associated with Eustachian tube dysfunction can seriously affect hearing in children with CLP, which can lead to linguistic and speech disorders, and ultimately to the disruption of learning and development. Compared with watchful waiting or hearing aids, VTI has been shown to improve hearing in more than half of CLP children 5–15 years after surgery. VTI and the conservative approach do not appear to differ with regard to speech and language outcomes. CLP children that undergo VTI present a higher risk of complications than do children without VTI. It has been shown that VTI is beneficial in helping CLP patients to recover from OME. There is insufficient evidence with regard to the timing of VTI (e.g., prophylactic insertion during repair of lip or palate). This summary is based on underpowered studies, and the evidence for each outcome is inconclusive. The lack of concrete evidence regarding the optimal treatment for OME in CLP children should prompt a relatively conservative approach. Most importantly, the needs of children and their parents must be taken into consideration. Only a consensus between patients/parents and surgeons regarding the most suitable treatment strategy for OME can ensure the greatest benefits.

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Author details

Chin-Lung Kuo[1, 2, 3, 4]* and An-Suey Shiao[1, 2]*

*Address all correspondence to: asshiao@gmail.com; drkuochinlung@gmail.com

1 Department of Otolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

2 Department of Otolaryngology, National Yang-Ming University, School of Medicine, Taipei, Taiwan, ROC

3 Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan, ROC

4 Department of Otolaryngology, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan, ROC

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Section 3

Experiments and Genetics

Chapter 7

A Review of Orofacial Clefting and Current Genetic Mouse Models

Aram J. Keteyian and Yuji Mishina

Additional information is available at the end of the chapter

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Abstract

The prevalence of orofacial clefts (OFCs) is nearly 10.2 per 10,000 births in the United States and 9.9 per 10,000 births worldwide. OFCs occur as a result of a break (nonfusion) of orofacial structures during development. This can occur due to a variety of reasons;prenatal exposure to many drugs and environmental factors as well as genetic factors which are implicated in the development of OFCs. While approximately 15 types of clefts have been identified, there are at least four distinct classifications of OFCs. These include complete cleft palate with cleft lip; cleft of the anterior palate, which may/may not involve cleft lip; cleft of the posterior palate; and submucosal cleft. A number of candidate genes have been identified, including transforming growth factor beta (TGFβ) and homeobox genes (e.g., *MSX1*), among many others. What follows is a review of mouse models currently used in research and the classification of their overall contribution to known OFCs.

Keywords: orofacial, cleft lip, cleft palate, genomic, genetics, TGFβ, MSX1, knockout mice, craniofacial, molecular, palatogenesis

1. Introduction

The focus of this chapter is to review a comprehensive list of the genes with known involvement in generating cleft lip with (or without) cleft palate (CL/P) or cleft palate (CP) in mice. Additionally, the associated knockout (KO) and conditional knockout (cKO) models are discussed. Most of the research models currently in use focus on complete CP, and thus not as much is known of the other CP phenotypes. In particular, identifying specific risk genes for CL/P is made simpler when genomic sequencing is done, and clefting associated with syndromes (syndromic) has identified single genetic loci that are involved with abnormalities in palatogenesis. Current mouse models involve a somewhat surprisingly vast array of genes, however, including *Wnt*, *Msx1/2*, *Tbx*, *Pax9*, *Irf6*, *Tgfb*, and *Fgf*. Further elucidation and

categorization of these gene families and their associated defects—whether syndromic or non-syndromic—can aid us in further clarifying the molecular mechanisms underlying orofacial clefting and potentially lead us to targeted, more efficient treatments.

We currently utilize four distinct classifications for OFCs: complete cleft palate with cleft lip; cleft of the anterior palate, which may/may not involve cleft lip; cleft of the posterior palate; and submucosal cleft. Subdivided among these four classifications of OFCs are six categories of developmental defects that have been shown to result in cleft palate in KO or cKO mice. The numerous variants of CL/P can generally be found to fit within one of the following categories: [1]

1. Palatal shelf formation failure
2. Abnormal fusion of palatal shelves
3. Delayed/failed elevation of the palatal shelves
4. Failure of palatal shelf development post-elevation
5. Persistence of medial-edge epithelial cells
6. Secondary defect

Each of the known KO/cKO mice mentioned is bred such that the gene missing is one already known to play a role in the development of CL/P. Implicit within these categories are the KO genes known to lead to each particular type of defect, each of which will be outlined as we move through this chapter.

As we look into the future, OFCs need to be classified with more definitive nomenclature. Currently, we use arbitrary terms to define very broadly into which category these congenital malformations fall, i.e., syndromic versus non-syndromic. As studies are broadened to include a wider array of genetic variants and their regulatory regions, more risk genes for CL/P and CP will surely be identified. As a result, more specific phenotypic classifications will emerge as well. The etiology of OFCs is complex, and the presentation is wide ranging; it is important that we continue to use precise genetic mouse models in order to carefully define a given phenotype before reclassifying human cases. The models mentioned in this chapter and those developed in the future are critical to a more sophisticated understanding of OFC anomalies and etiologic variants. Their development and utilization will ideally lead to a greater breadth and depth of treatment intervention options for patients.

2. Current mouse models utilized for elucidation of molecular mechanisms involved in orofacial clefting

As alluded to previously, a great breadth of genes plays critical roles in palatogenesis. Upon further analysis, a subset of gene families and signaling pathways have emerged as containing the most significant molecules related to normal development of the palate. Of note are the following: transforming growth factor beta (TGFβ), hedgehog, Wnt, fibroblast growth factor (FGF), and the mitogen-activated protein kinase (MAPK) signaling pathway. Each signaling pathway has an expansive list of genes with known involvement in palatogenesis (**Table 1**).

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Gene	Syndromic/non-syndromic	Orofacial phenotype
Acvr1/Alk2	Submucosal cleft/fibrodysplasia ossificans progressiva	Und
Acvr2a	Und	Und
Akap8/Akap95	Und	Und
Alx1	Frontonasal dysplasia 3	CL/P
Alx3	Frontonasal dysplasia 1	CL/P
Alx4	Frontonasal dysplasia 2, parietal foramina 2, craniosynostosis 5	Cleft alae nasi
Anp32b	Und	Und
Apaf1	Und	Und
Arid5	Und	Und
Asxl1	Bohring-Opitz syndrome; myelodysplastic syndrome, somatic	CL/P
B9d1	Meckel syndrome 9	Und
Barx1	Und	Und
Bmp4	Microphthalmia, syndromic 6	CL/P
Bmp7	Und	Und
Bmpr1a/Alk3	Juvenile polyposis syndrome	CP
Cask	FG syndrome 4, mental retardation, and microcephaly with pontine and cerebellar hypoplasia	CL/P
Cdc42	Und	CL/P
Cdkn1c/p57kip2	Beckwith-Wiedemann syndrome, IMAGe syndrome	CL/P
Ceacam1	Und	Und
Chd7	CHARGE syndrome	CL/P
Chrd	Und	CL
Chuk/Ikk1/Tcf16	Cocoon syndrome	Und
Cited2	Atrial septal defect 8, ventricular septal defect 2	Und
Col2a1	Achondrogenesis, type II; Stickler syndrome, type I; Kniest dysplasia	CL/P
Crebbp/Cbp	Rubinstein-Taybi syndrome	Und
Crk	Und	Und
Ctgf	Und	Und
Ctnnb1	Mental retardation, autosomal dominant 19	Und
Cyp26B1	Craniosynostosis with radiohumeral fusions and other skeletal and craniofacial anomalies	Und
Cyp51	Und	Und
Dhcr7	Smith-Lemli-Opitz syndrome	CL/P

Gene	Syndromic/non-syndromic	Orofacial phenotype
Dhrs3	Und	Und
Dicer1	Rhabdomyosarcoma, embryonal, 2; goiter, multinodular 1; pleuropulmonary blastoma	Und
Dlg1/Dlgh/Sap97	Und	Und
Dlx1	Und	Und
Dlx2	Und	Und
Dlx5	Split-hand/foot malformation 1 with sensorineural hearing loss	CL/P
Dph1/Ovca1	Und	Und
Edn1	Auriculocondylar syndrome 3	CL/P
Efna5	Und	Und
Efnb1	Craniofrontonasal dysplasia	CL/P
Efnb2	Und	Und
Egfr	Und	Und
Eya1	Branchiootic syndrome 1; branchiootorenal syndrome 1, with or without cataracts; anterior segment anomalies with or without cataract	CL/P
Fgf10	Aplasia of lachrymal and salivary glands	Und
Fgf18	Und	Und
Fgf9	Und	Und
Fgfr1	Non-syndromic cleft lip/palate, Hartsfield syndrome, hypogonadotropic hypogonadism 2, Pfeiffer syndrome	CL/P
Fgfr2	Apert Syndrome	CL/P
Foxc2/Mfh1	Lymphedema-distichiasis syndrome	CL/P
Foxd3	Und	Und
Foxe1/Titf2/Fkhl15	Bamforth-Lazarus syndrome	CL/P
Foxf2	Und	Und
Fst	Und	Und
Fuz	Neural tube defects	Und
Fzd2	Und	Und
Gab1	Und	Und
Gabrb3	Epilepsy, childhood absence, susceptibility to, 5	CL/P
Gad/Gad67	Cerebral palsy, spastic quadriplegic, 1	CL/P
Gbr2	Und	Und
Gbx2	Und	Und
Gdf11/Bmp11	Und	Und

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Gene	Syndromic/non-syndromic	Orofacial phenotype
Glce	Und	Und
Glg1	Und	Und
Gli2	Culler-Jones syndrome, holoprosencephaly-9	CL/P
Gli3	Greig cephalopolysyndactyly	CL/P
Gpr124	Und	Und
Grb2	Und	Und
Gsc	Short stature, auditory canal atresia, mandibular hypoplasia, skeletal abnormalities	Und
Gsk3b	Und	Und
Hand2/dHand	Und	Und
Hic1	Und	Und
Hoxa2	Microtia with or without hearing impairment	Und
Hs2st1	Und	Und
Hspb11/Ift25	Und	Und
Hspg2	Dyssegmental dysplasia, Schwartz-Jampel syndrome, type 1	Und
Ilk	Und	Und
Impad1/Jaws	Chondrodysplasia with joint dislocations, GRAPP type	CL/P
Inhba	Und	Und
Inpp5e	Mental retardation, truncal obesity, retinal dystrophy, and micropenis	Und
Irf6	Van der Woude syndrome, orofacial cleft 6, popliteal pterygium syndrome 1	CL/P
Itgb1	Und	Und
Itgb8	Und	Und
Jag1	Alagille syndrome	Und
Jag2	Und	Und
Jmjd6/Ptdsr	Und	Und
Kat6a/Moz/Myst3	Und	Und
Kcnj2	Andersen syndrome, atrial fibrillation, familial, 9; short QT syndrome 3	CL/P
Kif3a	Und	Und
Lhx7	Und	Und
Lhx8	Und	Und
Lrp6	Und	Und

Gene	Syndromic/non-syndromic	Orofacial phenotype
Luzp1	Und	Und
Map3k7/Tak1	Und	Und
Mef2c	Chromosome 5q14.3 deletion syndrome, mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations	Und
Meox2	Und	Und
Mn1	Meningioma	Und
Mnt	Und	Und
Msx1	Ectodermal dysplasia 3, Witkop-type Orofacial cleft 5	CL/P
Msx2	Craniosynostosis, type 2; parietal foramina 1, parietal foramina with cleidocranial dysplasia	CL/P
Nabp2/Obfc2b/hSSB1	Und	Und
Nprl3	Und	Und
Ofd1	Joubert syndrome 10, oral-facial-digital syndrome I, Simpson-Golabi-Behmel syndrome, type 2	CL/P
Osr2	Und	CL/P
Pak1ip1	Und	Und
Pax9	Tooth agenesis, selective, 3	Und
Pbx1	Leukemia, acute pre-B-cell	Und
Pdgfc	Und	CL/P
Pdgfra	Gastrointestinal stromal tumor, somatic	CL/P
Pds5a	Und	Und
Pdss2	Coenzyme Q10 deficiency, primary, 3	Und
Phc1/Rae28	Und	Und
Piga	Multiple congenital anomalies-hypotonia-seizures syndrome 2; paroxysmal nocturnal hemoglobinuria, somatic	Und
Pitx1	Clubfoot, congenital, with or without deficiency of long bones and/or mirror-image polydactyly, Liebenberg syndrome	CL/P
Pitx2	Axenfeld-Rieger syndrome, type 1; iridogoniodysgenesis, type 2; Peters anomaly	Und
Pkdcc/Vlk	Und	Und
Pnn	Und	Und
Prdm16	Cardiomyopathy, dilated, 1LL; left ventricular noncompaction 8	
Prickle1	Epilepsy, progressive myoclonic	Und
Prrx1/Prx1/Mhox	Agnathia-otocephaly complex	CL/P
Ptch1/Ptc1	Basal cell nevus syndrome (Gorlin syndrome)	CL/P

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Gene	Syndromic/non-syndromic	Orofacial phenotype
Pygo2	Und	Und
Rad23b	Und	Und
Rax	Microphthalmia, isolated 3	Und
Recql4	Baller-Gerold syndrome, RAPADILINO syndrome, Rothmund-Thomson syndrome	CL/P
Ror2	Robinow syndrome, autosomal recessive	CL/P
Rspo2	Und	Und
Runx2	Cleidocranial dysplasia	CL/P
Ryk	Und	Und
Ryr1	Central core disease, King-Denborough syndrome, minicore myopathy with external ophthalmoplegia	Und
Sall3	Und	Und
Satb2	Glass syndrome	CL/P
Sc5d/Sc5dl	Und	Und
Schip1	Und	Und
Sdccag8	Bardet-Biedl syndrome 16, Senior-Loken syndrome 7	Und
Serpinh/Hsp47	Osteogenesis imperfecta, type X	Und
Shh	Holoprosencephaly-3	CL/P
Shox2	Und	Und
Sim2	Und	Und
Slc32a1/Viaat	Und	Und
Smad4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	Und
Smad7	Und	Und
Smo/Smoh	Basal cell carcinoma, somatic	Und
Smoc	Microphthalmia with limb abnormalities	CL/P
Snai2	Piebaldism	Und
Sox11	Mental retardation, autosomal dominant, 27	Und
Sox5	Und	Und
Sox9	Acampomelic campomelic dysplasia	CL/P
Sp8	Und	Und
Spry1	Und	Und
Spry2	Und	Und
Sumo1	Orofacial cleft 10	CL/P
Tbx1	DiGeorge syndrome	CL/P

Gene	Syndromic/non-syndromic	Orofacial phenotype
Tbx2	Und	Und
Tbx22	Cleft palate with ankyloglossia	CL/P
Tcof1	Treacher-Collins syndrome	CL/P
Tctn2	Meckel syndrome 8	CL/P
Tgfb2	Loeys-Dietz syndrome, type 4	CL/P
Tgfb3	Arrhythmogenic right ventricular dysplasia 1	CL/P
Tgfbr1/Alk5	Loeys-Dietz syndrome, type 1	CL/P
Tgfbr2	Loeys-Dietz syndrome, type 2	CL/P
Trp63/Tp63	Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3; orofacial cleft 8, Hay-Wells syndrome, limb-mammary syndrome	CL/P
Tshz1	Aural atresia, congenital	Und
Ugdh	Und	Und
Vax1	Microphthalmia, syndromic 11	CL/P
Vegfa	Und	Und
Wdpcp	Und	Und
Whsc1	Und	Und
Wls/Gpr177	Und	Und
Wnt5a	Robinow syndrome, autosomal dominant	CL/P
Wnt9b	Und	Und
Zeb1	Corneal dystrophy	Und
Zic3	Congenital heart defects, non-syndromic; heterotaxy, visceral, 1; VACTERL association	CL/P
Zpf640/Mzf6d	Und	Und

Genes highlighted here are specifically mentioned in the pathways discussed in this chapter and listed separately in **Tables 2–7**. Phenotypes included are derived from the Online Mendelian Inheritance in Man (OMIM).

Table 1. Summary of genes with known involvement in the etiology of orofacial abnormalities in mice.

Upon cross-referencing the KO mice available through the Jackson Laboratory (http://www.informatics.jax.org/diseasePortal) and performing a literature search on PubMed, Web of Science, and similar scholarly databases, we can provide an accurate account of all currently available mouse models with phenotypes concurrent with our understanding of CL/P. Furthermore, physicians and researchers alike are searching for a coalescence of treatment strategies, including gene therapy, to replace our current therapeutic approaches that consist mainly of a lifetime persistence of surgeries with less than consistent results due, in part, to non-standardization of procedures. What follows is an in-depth look, in order of current dominance in the landscape of research, at the mouse models currently being used to study the etiologic determinants of orofacial clefting.

2.1. TGF beta (TGFβ) signaling pathway

A number of genes from the TGF beta (TGFβ) signaling pathway that play a role in palatogenesis in mice are many (**Table 2**). Members of this "superfamily" play an important role in the development of Meckel's cartilage and the mandible— thus, alteration or inactivation of particular members can lead to cleft palate [2]. TGFβ receptors are dimeric and consist of two types—type I and type II—of receptors with serine/threonine kinase activation. Once activated, these receptors function in such a way that SMAD transcription factors are phosphorylated, and through a cascade, eventually these SMADs make it into the nucleus where they function to modulate the transcription of particular subsets of genes [3]. The SMADs can either activate or repress the gene to which they bind. As such, a combination of dimeric receptors and ligands can result in any number of outcomes for a cell. In particular, TGFβ is

Gene	Syndromic/non-syndromic	Orofacial phenotype
Acvr1/Alk2	Submucosal cleft/fibrodysplasia ossificans progressiva	Und
Acvr2a	Und	Und
Bmp4	Microphthalmia, syndromic 6	CL/P
Bmpr1a/Alk3	Juvenile polyposis syndrome,	CP
Chrd	Und	CL
Cited2	Atrial septal defect 8, ventricular septal defect 2	Und
Foxc2/Mfh1	Lymphedema-distichiasis syndrome	CL/P
Foxd3	Und	Und
Foxe1/Titf2/Fkhl15	Bamforth-Lazarus syndrome	CL/P
Foxf2	Und	Und
Fst	Und	Und
Gdf11/Bmp11	Und	Und
Inhba	Und	Und
Map3k7/ Tak1	Und	Und
Smad4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	Und
Smad7	Und	Und
Tgfb2	Loeys-Dietz syndrome, type 4	CL/P
Tgfb3	Arrhythmogenic right ventricular dysplasia 1	CL/P
Tgfbr1/Alk5	Loeys-Dietz syndrome, type 1	CL/P
Tgfbr2	Loeys-Dietz syndrome, type 2	CL/P

Table 2. TGF beta/BMP signaling pathway.

involved in several critical functions that take place during embryogenesis, including proliferation, apoptosis, and cell differentiation.

Also, critical to normal development of the palate is the temporal and spatial distribution of the members of the TGFβ signaling pathway. The importance of this timing aspect may be that these structures, similar to morphogens, inducing specific tissue formation at identifiable time points in development [4]. This information can be used in the development of novel treatment strategies in humans with known gene mutations or deficiencies.

Typically, TGFβ receptor activation recruits and phosphorylates SMAD2 and SMAD3 at the carboxyl terminus via TGFβ receptor I. This method of signaling is generally what is meant by the term SMAD-dependent TGFβ signaling. However, TGFβ signaling can occur in lieu of SMAD activation via phosphorylation—pathways known to be activated in this manner include MAPK pathways (i.e., ERK, NJK, and p38) [5]. Inherently, this creates a purported "balance" between the levels of SMAD-dependent and SMAD-independent TGFβ signaling that exists through the development of normal palatogenesis. When we discuss the SMAD-independent pathways, it has been proposed that these are the result of posttranslational modifications which occur to either of the two types of TGFβ receptors. These mechanisms and their subsequent cascades are under current investigation and not yet entirely known [5].

Distinct members of the TGFβ superfamily, utilizing a separate series of SMAD proteins (SMAD1/5/9), are the bone morphogenetic proteins (BMPs). There are a number of BMP ligands known and two distinct receptor types—type I and type II. As mentioned, there appears to be a temporal and spatial distribution of this family, which is critical for the function of BMPs, which are very well researched with regard to palatogenesis. In particular, *Bmp4* cKO mice show clefting of the lip, both uni- and bilaterally [6]. Understandably, BMP receptors play a role in orofacial clefting as well; in addition, there is a distinct involvement in tooth morphogenesis for BMP receptors, notably *Bmpr1a* [7]. This molecule and its related receptors have an essentially unparalleled significance in the etiologic pathogenesis of CL/P. *Bmpr1a* cKO embryos, while also showing tooth morphology defects, die from orofacial clefting [6, 7].

2.2. Hedgehog signaling pathway

When one first thinks of SHH, it is likely that we recall the molecule's importance in left-right patterning of the embryo, dorsal-ventral establishment of the neural tube, and brain development, among other functions. Intrinsic properties of these morphogenic functions include signaling for cell proliferation and survival. The alteration of these properties can lead SHH receptors and/or ligands to function abnormally, thus, in some cases, altering the patterning of cranial neural crest cells during embryonic development. Modulation of the molecules involved in hedgehog signaling has been shown to present with CL/P phenotype in mice.

The full breadth of hedgehog signaling molecules with known involvement in orofacial clefting in mice spans several other pathways (**Table 3**). A notable characteristic of the mechanism of action for *Shh* can be observed in nasal epithelium of mice where *Shh* is reported absent. These mice develop cleft palate, while mice with overexpressed *Shh* are shown to express failure of growth of the maxillary processes and thus no fusion; this leads to cleft palate and several missing bones within the nasal process [8].

Gene	Syndromic/non-syndromic	Phenotypes
Gli2	Culler-Jones syndrome, holoprosencephaly-9	CL/P
Gli3	Greig cephalopolysyndactyly	CL/P
Ptch1/*Ptc1*	Basal cell nevus syndrome (Gorlin syndrome)	CL/P
Shh	Holoprosencephaly-3	CL/P
Smo/*Smoh*	Basal cell carcinoma, somatic	Und

Table 3. Hedgehog signaling pathway.

Another notable molecule involved in the hedgehog signaling pathway is *Ptch1*, a transcriptional target of *Shh* as well, which displays a gradient mimicking that of *Shh* in the palatal shelves during early palatogenesis, at E13.5 [8]. Similarly, the palatal mesenchyme adjacent to the medial-edge epithelium (MEE) present in the nasal epithelium expressed *Smo* in significant amounts [9]. In each case with the hedgehog signaling molecules, there is expression in the palatal mesenchyme, with the highest level of expression for most molecules adjacent to the palatal oral epithelium [9]. The awareness of this spatial and temporal expression provides a niche for the insertion or potential innervation of gene products given therapeutically. The effects of an abnormal amount of SHH signaling are palpable. Restoration of the proper balance of SHH signaling throughout development may play a role in treatment options in the near future, and delivery methods are currently underway to target particular areas of known involvement in CL/P.

2.3. Wnt signaling pathway

The Wnt signaling pathway plays another exceptional role in craniofacial morphogenesis in mice (**Table 4**). There are 19 known Wnt proteins found in humans, with combinations of differing ligands and receptors allowing for a mixture of modulatory effects from similar molecules. Between the receptors available, there exist three distinct pathways: the β-catenin-dependent (canonical), β-catenin-independent planar cell polarity (PCP), and β-catenin-independent Ca^{2+} pathways. β-Catenin is a transcription factor that, when Wnt ligands are present, will persist and

Gene	Syndromic/non-syndromic	Phenotypes
Ctnnb1	Mental retardation, autosomal dominant 19	Und
Edn1	Auriculocondylar syndrome 3	CL/P
Fzd2	Und	Und
Gsk3b	Und	Und
Lrp6	Und	Und
Prickle1	Epilepsy, progressive myoclonic	Und
Wnt5a	Robinow syndrome, autosomal dominant	CL/P
Wnt9b	Und	Und

Table 4. Wnt signaling pathway.

translocate into the nucleus; the factor is otherwise degraded [7]. The Wnt pathway is involved in a variety of embryogenic and developmental events, similar to the SHH pathway. In terms of craniofacial development, we see a critical role for the Wnt signaling pathway when we observe the generation, migration, proliferation, and survival of cranial neural crest cells [10].

A notable Wnt ligand involved in canonical signaling is *Wnt9b*. Expressed between the facial processes, alterations in signaling of this molecule have shown to express clefting in mice. Additionally, *Wnt9b* null mice have a distinctly shorter nasal process and shortened maxillary processes, a direct link to bilateral CLP [11]. This expression is apparent with FGF molecules, one of the many molecules involved with and expressively determined by Wnt signaling. A deletion of either the epithelium in which *Wnt9b* is found or a KO of the ligand (gene product) itself results in a similar cleft lip phenotype [11].

While the plethora of numerous other Wnt signaling targets and mediators exist, a receptor of particular interest and importance currently is *Lrp6*. This receptor functions in the canonical Wnt pathway as well and contains members of the Frizzled family as well as a co-receptor, which can be low-density lipoprotein receptor-related protein 6 (LRP6). Research has shown that *Lrp6* null mice demonstrate bilateral clefting of the lip as well and cleft palate and midline clefting of the mandible [12]. These mice also express defects in the neural tube, eye, and brain among others. The orofacial clefting defects were observed at E13.5 in these *Lrp6* null mice, with full penetrance of CLP and mandibular defects [12]. Again, we see a pattern that current research has established wherein a spatial and temporal time table has been created. This knowledge, as it continues to expand with further genomic testing and mouse model availability, should prove highly useful in the development of novel therapies.

2.4. FGF signaling pathway

While it has already been briefly discussed, one can see that the FGF signaling pathway also expands across several currently known molecular cascades. In humans and in mice, mutations resulting in dysfunction of the FGF signaling pathway are known to result in a variety of craniofacial abnormalities and syndromes—one proponent of which is orofacial clefting. An important role of FGF signaling is seen in the induction of the neural crest while being widely expressed in epithelial-mesenchymal interactions elsewhere. Particularly in the facial primordia, FGF signaling is absolutely critical in the proper development and formation of the palate as it is present in both endochondral (i.e., Meckel's cartilage) and intramembranous bones [13]. When we consider palatogenesis, FGF molecules have been shown to be involved in multiple stages—from palatal shelf elevation to fusion of MEE. KO mice have played a key role in our understanding of the function of various FGFs and their relation to orofacial clefting.

There are 23 distinct FGF ligands known and four receptors to which they bind. Alternative splicing generates several receptor variants which allows for multiple binding combinations and, thus, different functionalities temporally during embryogenesis. Various receptors are located in the epithelium and mesenchyme throughout the embryo, and research has elucidated many roles that these molecules play; for our interest, much emphasis has been placed on suture fusion (craniosynostosis) and palatogenesis.

Mutations in FGF receptors have been shown to present with a variety of midfacial syndromes in mice as well (**Table 5**). For example, in humans, gain-of-function mutations in *FGFR2* and *FGFR3* have been consistently observed in individuals with Crouzon syndrome—a genetic disorder that includes craniosynostosis in its list of defects associated with the syndrome. More relevant here, however, is that a KO mouse model in which the *Fgfr1* receptors are missing in the cranial neural crest (CNC) cells directly results in CLP due to failures in the proliferation and migration of said cells [14]. Likewise, research has shown that ectopic activation of *Fgf8* results in increased proliferation and a failure of the palatal shelves to elevate properly [15]. This is exceptionally interesting in that it is a rare case in which an increase in cell proliferative activity has resulted in CP; in many cases, CP is the result of an obvious decrease in the amount of cell proliferation. In the case of *Fgf8* activation, the palatal shelves were still unable to elevate in a normal manner, and thus the palatal morphology was altered, and a CP phenotype was observed.

Gene	Syndromic/non-syndromic	Phenotypes
Fgf10	Aplasia of lachrymal and salivary glands	Und
Fgf18	Und	Und
Fgf9	Und	Und
Fgfr1	Non-syndromic cleft lip/palate, Hartsfield syndrome, hypogonadotropic hypogonadism 2, Pfeiffer syndrome	CL/P
Fgfr2	Apert syndrome	CL/P
Gbr2	Und	Und
Spry1	Und	Und
Spry2	Und	Und

Table 5. FGF signaling pathway.

The FGF signaling pathway has been, and is currently being, extensively studied. Spatial expression of the molecules involved in the pathway has been seen widely throughout the developing mouse embryo, while the temporal expression continues to be expounded upon. Investigations are ongoing to further our knowledge of why characteristically opposing molecular processes (i.e., reduction versus activation of cellular proliferation) may result in the same phenotype. In all, what remains important is that future treatment options are expanding all the time. The more we learn about all the plethora of molecular signals that interact during embryogenesis—which is similar enough between mouse and human—the more physicians and surgeons are able to generate new and better therapies.

2.5. MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) signaling pathway—also known as the ERK pathway—plays a role in craniofacial development of mice as early as E10.5 [16]. MAPK is a protein kinase that functions in conjunction with two others, MAPKKK (e.g., RAF) and MAPKK (e.g., MEK1/2). Upon activation, these effector molecules can act in either the cytosol or the nucleus. Growth factors, including TGFβ, BMPs, and fibroblast growth factor (FGF),

can modulate this same protein kinase cascade, and each of the molecules listed is also known to be involved with development of the palate [17]. Additionally, analysis of the potential spatial representation of active (phosphorylated) ERK1/ERK2 in the palate has resulted in the discovery this pathway persists in both the epithelium and the mesenchyme associated with the developing palatal shelves [17].

Immunohistochemistry using an antibody against an activated form of ERK has shown ERK signaling in the frontonasal process, brachial arches, and extraembryonic ectoderm, among other craniofacial-associated regions [16]. Research has also shown associations between MAPK signaling and growth factor pathway genes that include *Fgf9/10/18*, *Alk5*, and *Itgb1* among others and vary craniofacial clefting and defects in mice, including mandibular osteogenic and tongue abnormalities [17]. The inclusion of the mandible and tongue is important in that it adds to the overall complexity of the defect, thus making treatment options that much more of a priority. Current investigations are ongoing to pinpoint time points and the distribution of MAPK signaling and its numerous molecular effectors during embryogenesis in mice (**Table 6**).

Gene	Syndromic/non-syndromic	Phenotypes
Chuk/Ikk1/Tcf16	Cocoon syndrome	Und
Egfr	Und	Und
Grb2	Und	Und
Pdgfra	Gastrointestinal stromal tumor, somatic	CL/P
Crk	Und	Und
Itgb1	Und	Und

Table 6. MAPK signaling pathway.

2.6. Homeobox proteins

Homeobox proteins and their respective KO/mutant mouse models are used to represent easily observable phenotypes. Some of the most well-studied homeobox genes in mice include *Msx1/2*, *Pax9*, and *Alx1* [1]. The reason for their grouping and relatively well-known actions has to do with the fact that transcription factors encoded by homeobox genes act in a site-specific manner [18]. These gene products exist, segmentally, throughout the body and are palpable during nearly all stages of development. As such, we know that there are Hox homeogenes which control bone patterning in the limb buds; similarly, there are separate homeogenes that are associated with craniofacial development in mice (**Table 7**).

Specifically, research has shown that a human *MSX1* missense mutation can lead to orofacial clefting as well as selective tooth agenesis [19]. Mutations in this gene, as seen in other homeogenes, can lead to dysfunctional protein products that act via transcriptional repression. In the case of *Msx1*, the homeodomain interacts directly with the TATA-binding protein (TBP) and acts directly at the start of transcription by repressing the gene completely to which it translocates. In some scenarios, heterodimers will form between homeodomain proteins, and a balance must persist in which they are co-regulatory.

Gene	Syndromic/non-syndromic	Phenotypes
Alx1	Frontonasal dysplasia 3	CL/P
Alx3	Frontonasal dysplasia 1	CL/P
Alx4	Frontonasal dysplasia 2, parietal foramina 2, craniosynostosis 5	Cleft alae nasi
Barx1	Und	Und
Dlx1	Und	Und
Dlx2	Und	Und
Dlx5	Split-hand/foot malformation 1 with sensorineural hearing loss	CL/P
Gbx2	Und	Und
Gsc	Short stature, auditory canal atresia, mandibular hypoplasia, skeletal abnormalities	Und
Hoxa2	Microtia with or without hearing impairment	Und
Msx1	Ectodermal dysplasia 3, Witkop-type orofacial cleft 5	CL/P
Msx2	Craniosynostosis, type 2; parietal foramina 1, parietal foramina with cleidocranial dysplasia	CL/P
Pax9	Tooth agenesis, selective, 3	Und
Pitx1	Clubfoot, congenital, with or without deficiency of long bones and/or mirror-image polydactyly, Liebenberg syndrome	CL/P
Pitx2	Axenfeld-Rieger syndrome, type 1; iridogoniodysgenesis, type 2; Peters anomaly	Und
Prrx1/Prx1/Mhox	Agnathia-otocephaly complex	CL/P
Rax	Microphthalmia, isolated 3	Und
Shox2	Und	Und
Vax1	Microphthalmia, syndromic 11	CL/P

Table 7. Homeobox protein signaling pathway.

As a result of these proteins acting within their respective zones (or "sites"), one can assume that there is an overlap with the adjacent homeodomain. Such overlap is observed between *Msx1* and *Msx2* throughout the craniofacial structures during development—including the skull, suture mesenchyme, and teeth [20]. Inherent in their molecular categorization is the idea that we know where, and upon which tissues, these proteins interact. There are a number of homeogenes involved in craniofacial development that modulate palatogenesis and patterning, among a variety of other roles. Due to their known functions during embryogenesis, further research is ongoing regarding the effect of varying homeogene mutations on cell proliferation, survival, and adhesion. The culmination of knowledge that lies within these determinants of normal development will indubitably result in opportunities for the future application of therapeutic modalities.

2.7. Remaining mouse strains exhibiting CL/P phenotype

Here, we have put into one table a list of the genes with a known association, whether syndromic or non-syndromic, to the development of the palate in mouse (**Table 1**). It should be noted that not all genes in this table have shown their identical, cross species phenotype in humans.

2.8. The future of CL/P therapy

A bonafide surgical protocol remains to be standardized for the repair of CL/P. Fortunately, ongoing research concerning therapeutic interventions for this relatively common birth defect has recently begun to delve into new and improved options for repair with, hopefully, more consistent and stable results for patients. The current "golden standard" treatment option for pediatric oral surgeons involves bone grafting, or alveoloplasty, usually from autogenous sites—but this has many complications associated with both the grafting procedure and the agreed-upon effectiveness in reconstructing the palate over time [21]. Postoperative follow-up has shown success rates ranging from 41 to 73%, which is far from standardized, while there also exists the possibility (in 11–23% of patients) of oronasal fistulas, which come with their own brand new set of complications for the patient [22]. In short, the most effective interventions in use today are far from ideal for the patent and result in long-term risk of complications from grafting procedures, disturbance of adjacent craniofacial development, and, over time, a significant financial encumbrance on the patient. Techniques including gene delivery, in vitro engineered tissue transplantation, and regenerative medicine are being probed for efficacy, and some are showing promising results thus far.

An exceptionally exciting modality is the use of stem cells. One method of delivering these cells is via a biocompatible scaffold upon which cells that have been previously harvested were cultured and attached. Materials including collagen, hyaluronic acid, and hydroxyapatite have been utilized in attempts to develop such scaffolds [23–25]. These scaffolds have been engineered as injectable gels, mesh networks, and foams. Ideally, this aids in the procedure being as minimally invasive as possible while also providing maximum benefit and adequate delivery to the area of interest. This therapy can be modified to include signaling molecules and other types of differentiated cells—which preferably have a known clinical outcome and avoid the possibility of rejection and/or disunity with the surrounding host cells—and injected in a similar fashion or applied to previously engineered palates. Currently, autogenous mesenchymal stem cells (MSCs) are regarded as the optimum choice for in vivo osteogenic reconstructions; these can come from umbilical cord blood, Wharton's jelly, and even the patient's own bone marrow [26]. Tissue regenerative-specific repair of CL/P has been demonstrated with some success, and some are now advocating for in depth considering of its potential to replace traditional autogenous grafting procedures [27].

Regarding clinical studies in progress, one group has shown that in vitro differentiated MSCs derived from bone marrow were delivered with platelet-derived growth factor and significant improvement was observed 3 months post-op [28]. Similarly, recombination therapies are being used to induce osteoblastic differentiation with BMPs formed from stem cells, and resulting immunohistological analysis of the bone that formed has shown normal, vital

structure [29]. Finally, platelet-rich plasma (PRP) is being studied with regard to its potential for tissue repair in vivo. A wide variety of growth factors are present in a platelet-rich solution and have been shown to promote angiogenesis and extracellular matrix formation [30]. This intervention has some positive results—it has been shown that PRP can enhance bone regeneration and thus may be a useful alternative to traditional procedures for CL/P patients [31].

A number of prospective therapeutic interventions are currently being investigated, many with exciting outcomes thus far. CL/P etiology is not yet completely understood and is extremely complex. In order to properly apply this research to the human subjects, we must further our research to bridge the gap between an understanding of the signaling pathways, the rescue of the animal phenotype, and the translation of this knowledge into human treatment. As research continues on the pathways mentioned in this chapter, further clinical trials should become available, and treatment outcomes for patients can rapidly and significantly improve. Moving forward, more work is needed to establish a new standard of care and a protocol for various differing types of orofacial clefts, but progress has proceeded rapidly in recent years, and the outlook is bright for the future of care for CL/P patients.

In summary, it remains within animal research where the next steps in the elucidation of potential treatments for CL/P must be made. Understanding the biological, molecular signaling pathways and identifying a broad cause for the clefting phenotype are only the first steps in understanding how to treat it. Now, we need to look toward a greater understanding of the critical downstream events that occur as a result of the KO or cKO models being used; what types of tissue-tissue interactions are changing? What is the scope of the molecular activity being altered as a result of changing the capabilities of one gene? Once more of these questions are answered in animal models, the translation of lab research to the rescue of human phenotypes will become more clear. Until then, it is crucial to continue to identify all that we can in order to bridge the gap between KO/cKO mice, the expansive etiology surrounding their conditions, and the rescue of their control phenotypes.

Author details

Aram J. Keteyian* and Yuji Mishina

*Address all correspondence to: aketeyia@umich.edu

Department of Biologic and Materials Science, School of Dentistry, University of Michigan, Ann Arbor, MI, USA

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Chapter 8

Cleft Lip and Palate in the Dog: Medical and Genetic Aspects

Enio Moura and Cláudia Turra Pimpão

Additional information is available at the end of the chapter

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Abstract

The same types of cleft lip and/or cleft palate (CL/P) that affects humans also naturally affect dogs. Therefore, the dog has become an important spontaneous animal model for the study of human oral clefts. In order to provide an overview of CL/P in dogs to people with an interest in this area, we present in this chapter the main medical aspects, ranging from the etiology to the prevention, and also the main genetic aspects, including inheritance mechanisms and highlighting the homology between the two species, and the most recent molecular findings.

Keywords: dog, cleft lip, cleft palate, cleft lip and palate, oral clefts, genetics

1. Introduction

In the last 20 years, the domestic dog has become one of the main animal models for the study of genetic disorders and congenital defects due to advances in genetics and genomics. The frequent occurrence of birth defects in dogs, with the cleft lip and palate being among the most common, is a byproduct of breeding practices. Since the mechanisms responsible for the morphogenesis of mammals are highly conserved and the genomic similarity between dogs and humans is high, in addition to sharing the same environment, spontaneous cases of cleft lip and palate in dogs are exceptionally useful for studies on the pathogenesis and genetics of oral clefts and the morphogenesis of the face [1–3].

In this chapter, we present an overview of the medical and genetic aspects of cleft lip and palate in dogs, in the hope that it will be useful to veterinary clinicians, researchers, and other professionals interested in genetics and developmental biology.

2. General considerations

2.1. Considerations on homology

It is easy even for a layperson to see that human anatomy and physiology have their equivalence throughout the zoological scale of vertebrates, especially when it comes to tetrapods. It is also not difficult to deduce that the mechanisms of development are similar or even identical, especially when we compare eutherian mammals. However, when we think of genes, genotypes, and their mechanisms of action, there is a tendency to conclude that everything is quite different. Nevertheless, in reality, "our genome" is not as exclusively ours as we generally imagine. Dogs and mice share over 90% of our genes [4], enabling us to suppose that genetic programs that control embryonic development are similar in the three species. Genes with a common evolutionary origin, maintaining the same function in different species, are known as orthologs (**Figure 1**). They are clear evidence that the homology of structures among species also have a molecular base. For instance, the *ADAMTS20* gene is one of the necessary genes for the normal palatogenesis of mice, to the extent that homozygous individuals for a mutation with loss of function have a palatal cleft [5]. Recently, a recessive mutation in the canine ortholog was identified in dogs with a cleft palate [6].

Knowledge of the developmental biology and genetics of one species helps us to understand those of another. Much has been learned regarding craniofacial morphogenesis by studying chickens and mice [7–9]. The dog, which has contributed so much to the development of

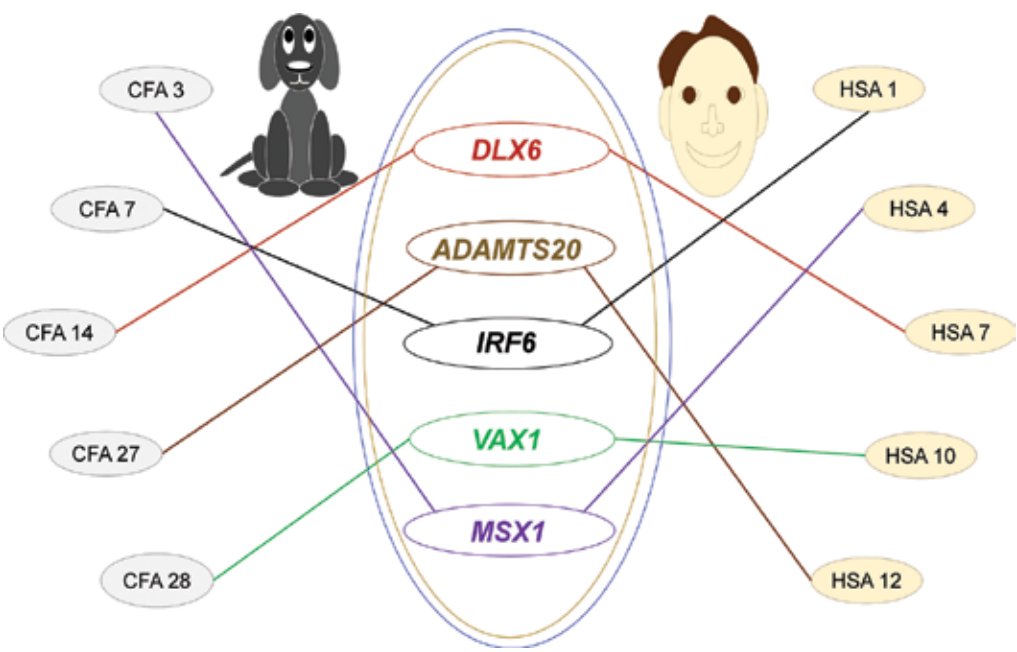

Figure 1. Shared genome. Examples of orthologs with the respective chromosomal assignment in the dog (CFA) and man (HSA). In two of them (*ADAMTS20* and *DLX6*), mutations are known that cause cleft lip and palate in a breed of dogs, while in the other three, mutations are known that have been associated with cleft lip and palate in humans.

surgical techniques used today to correct oral defects, can also help to expand our knowledge of the pathogenesis and genetics of orofacial defects.

2.2. Considerations on the morphogenesis of the lip and palate

Orofacial development is a sequence of events in space and time that involve cellular multiplication, migration and differentiation, tissue fusion, and apoptosis and are dependent on the action of various signaling molecules and transcription factors [10].

The primitive mouth is called the stomodeum. It emerges as a slight depression on the ectodermal surface, delimited by mesenchymal structures where cells from the neural crest proliferate. Although these cells are ectodermal in origin, they settle and integrate with the mesenchyme of the head of the embryo. They are fundamental to the development of the craniofacial structures. Five structures surround the stomodeum: frontonasal prominence, from which the primary palate will originate; right and left maxillary prominences, from which the secondary palate will originate; and right and left mandibular prominences, from which the mandible will originate (**Figure 2**). The maxillary and mandibular prominences are derived from the first branchial arch [10, 11].

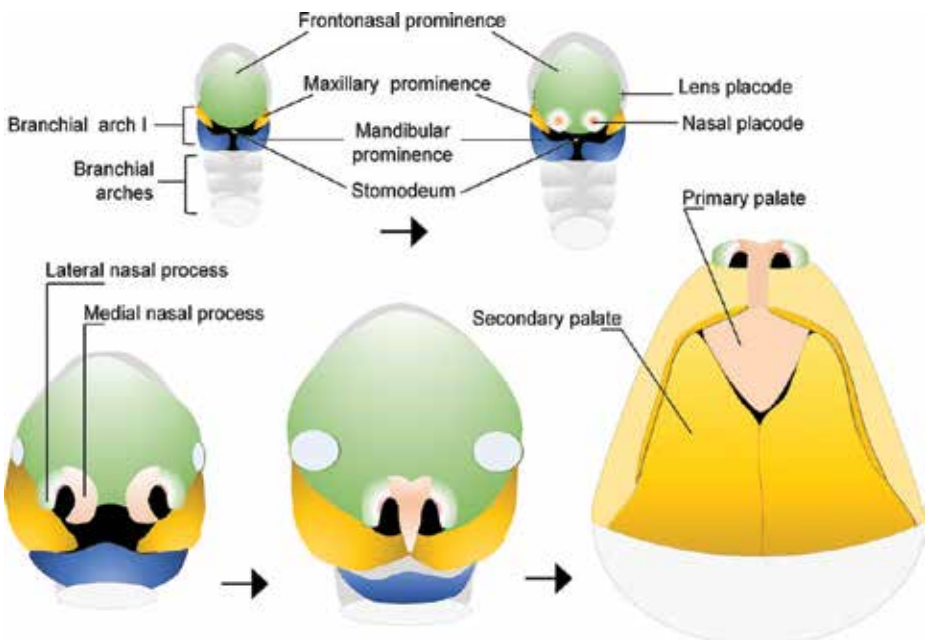

Figure 2. Palatogenesis. Semischematic drawing representing the formation of the primary and secondary palate in dogs.

2.2.1. Formation of the primary palate

The primary palate is the primordium of the hard palate (incisive bone) rostrally located at the incisive fissures (incisive foramen in humans). During development, the frontonasal prominence forms a pair of lateral and medial nasal processes. The fusion of the lateral and medial parts of each process delimits the nasal cavities that are forming. The medial processes

are then lengthened and projected between the maxillary prominences, are fused with them, and transformed into the primary palate and medial part of the upper lip [11].

2.2.2. Formation of the secondary palate

The secondary palate is the primordium of the palate caudally located at the incisive fissures (hard palate and soft palate, so-called because its formation is completed after the formation of the primary palate). Initially, the maxillary prominences are projected vertically by the sides of the tongue, and are then raised and projected horizontally on the tongue until they meet. A fusion then occurs between the two in the medial line forming a continuous epithelial seam, which will subsequently disappear. Rostrally, the secondary palate is also fused with the primary palate and, dorsally, with the projection (nasal septum) formed by the united medial nasal processes. The maxillary prominences also form the lateral parts of the upper lip [11].

At approximately 23 days of gestation, in the canine embryo it is possible to see the frontonasal, maxillary, and mandibular prominences. At approximately 28 days, the first ossification of the maxilla and mandible occurs [12].

3. Medical aspects

3.1. Frequency

A cleft lip and/or palate can affect purebred dogs or mongrels. Any canine breed can be affected, especially if we consider cleft lip and palate caused by environmental teratogens. However, the relatively frequent occurrence in some breeds indicates a strong contribution of genetic factors [13].

Indeed, certain breeds of dog are more likely to have cleft lip and palate, especially brachycephalic dogs [14]. At least, this is the clear impression of numerous veterinary practitioners who work with small animals worldwide. Unfortunately, no statistics are yet available that enable definitive statement regarding frequency in different breeds, nor in canine species as a whole.

In boxers, a frequency of 0.6% has been recorded, while in beagles has been 0.11%, and in Pyrenees shepherd dogs, 2.2%. In Portuguese water dogs, cleft palate has been reported in 2.3% of litters [15–18].

In some cases, the high frequency observed at veterinary clinics in certain breeds may be due to the popularity of those breeds at a given time. It is also possible that the frequency is high in certain lines due to constant inbreeding, but not high in the breed as a whole. In a lineage of old Spanish pointer dogs a frequency of 15–20% was found [19].

Table 1 shows the breeds that are considered as having a predisposition to oral clefts or for which cases have been registered.

Affenpinscher	Chihuahua	Nova Scotia duck-tolling retriever
Akita inu	Collie	Old Spanish pointer dog
American cocker spaniel	Dachshund	Papillon
American pit bull terrier	English bulldog	Pekingese
American Staffordshire terrier	English pointer	Poodle
American water spaniel	English toy spaniel	Portuguese water dog
Australian shepherd	Finnish spitz	Puli
Australian terrier	Fox terrier	Pug
Basset hound	French bulldog	Pyrenees shepherd dog
Beagle	German shepherd dog	Rottweiler
Bearded collie	Giant schnauzer	Samoyed
Bernese mountain dog	Golden retriever	Schipperke
Bichon frise	Great Pyrenees	Scottish terrier
Boston Terrier	Irish setter	Shetland Sheepdog
Bouvier des flandres	Italian greyhound	Shih Tzu
Boxer	Labrador retriever	Silky terrier
Brittany spaniel	Maltese	Staffordshire bull terrier
Brussels griffon	Manchester terrier	Swiss sheep dog
Bull terrier	Mastiff	Welsh corgi, cardigan
Bullmastiff	Miniature pinscher	West Highland white terrier
Cairn terrier	Miniature schnauzer	Yorkshire terrier
Cavalier King Charles spaniel	Norwegian elkhound	

Refs. [13, 14, 17–23].

Table 1. Breeds with records of CL/P.

3.2. Classification

Successful communication between professionals (veterinary practitioners, geneticists, surgeons, dentists, etc.) who treat patients with CL/P depends on an appropriate and correct registration of these abnormalities adhering to common criteria by everyone involved. Thus, the adoption of a classification is highly important. Furthermore, a consistent register based on a classification helps to establish the cause, planned treatment, prognosis, and studies of comparative anatomy [24].

The different classifications used in human medicine can be adapted for use with dogs, as has been done by some researchers based on the first classifications of human oral clefts [24, 25]. Many of the classifications of human clefts are modifications of the classification of Kernahan and Stark [26], which will be adopted here for the purposes of this chapter. It is based on the

morphology and pattern of embryonic development of mammals. The clefts are clustered into three groups, each with three subgroups, with all of them considering the degree of impairment of the structures as total or partial (**Figures 3** and **4**):

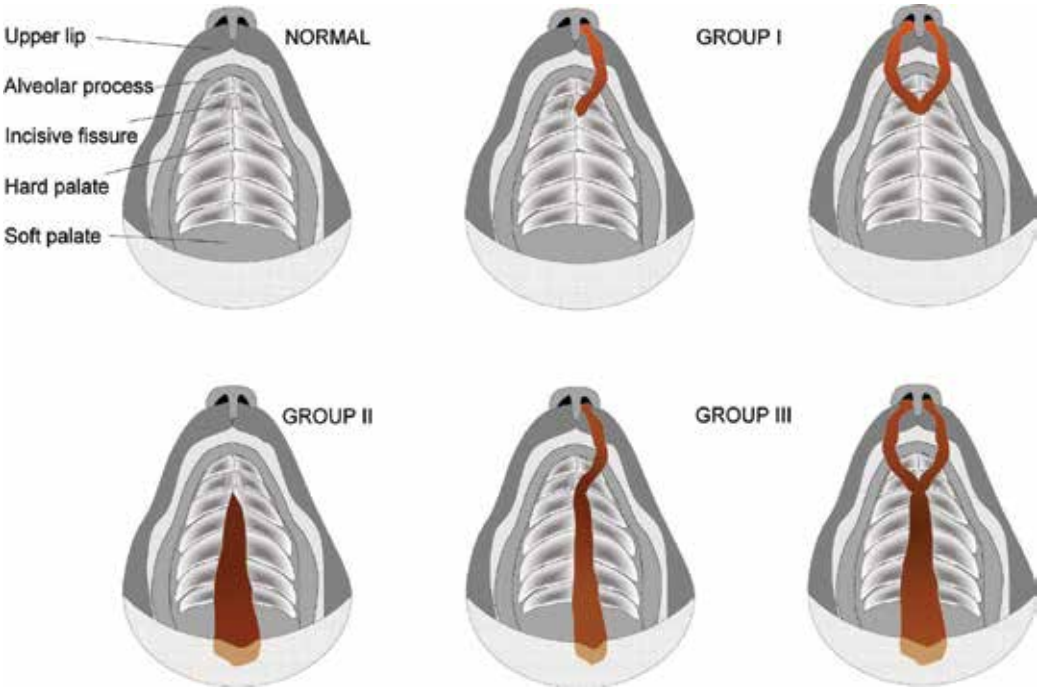

Figure 3. Types of cleft. In each group, complete unilateral or bilateral clefts are shown. However, a cleft from Group I can be left- or right-sided and affect only the lip, the lip and the alveolar process, or include the entire extension of the primary palate, as shown in the illustration. Likewise, a cleft from Group II may affect only the soft palate or the soft palate and the hard palate.

Figure 4. Dogs with nonsyndromic (A–C) and syndromic (D) clefts. (A) Left-sided unilateral cleft, affecting the upper lip, alveolar process, and incisive bone (primary palate); (B) cleft palate only; (C) bilateral cleft (upper lip, hard palate, and soft palate); (D) anophthtalmia and CLP. Photographs (A–C) reprinted from Moura and Pimpão [35].

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Group I. Primary cleft palate (total or partial impairment)

1 – unilateral left or right; 2 – medial; 3 – bilateral

Group II. Secondary cleft palate only

1 – total; 2 – partial; 3 – submucous

Group III. Primary and secondary palate (total or partial impairment)

1 – unilateral left or right; 2 – medial; 3 – bilateral

The criteria for defining a cleft as partial (incomplete) or total (complete) is subjective. Thus, with broader objectives, especially for epidemiological studies and minute comparison with human clefts, we suggest using the numerical system adapted by Schwartz et al. [27] from the striped Y of Kernahan [28], known as the RPL system, or one of the others that are available.

3.3. Etiology

Cleft lip and/or palate (CL/P) in dogs, as in humans, are etiologically heterogeneous, and can be caused by genetic factors, environmental factors, or a combination of these two groups of factors [29, 30].

Mutations in different genes, both in murine models and human beings, have been associated with CL/P [29]. As these genes have the respective homologs that are also present in the canine genome, the same situation is expected to occur in dogs (see Section 4).

The environment of an embryo is represented by the amniotic sac, uterus, maternal body, and the place where the mother lives. Thus, the potentially negative influences of this environment include amniotic abnormalities, uterine abnormalities, maternal metabolic disease, viruses, chemical substances swallowed by or administered to the mother, and maternal exposure to chemical or physical environmental pollutants [31]. Few studies of dogs associate a given environmental factor to oral clefts. Furthermore, these studies focus on substances administered to the mother of the affected dogs during gestation, such as 6-diazo-5-oxo-L-norleucine, aspirin, and vitamin A [32–34]. However, it should be remembered that in the case of aspirin and vitamin A, excessive doses were used, much higher than therapeutic doses. Based on the data obtained in other species (mice, rats, cats, goats, etc.), or personal impressions, it has been suggested that maternal exposure to various substances such as hydroxyurea, griseofulvin, anabasine, metronidazole, primidone, sulphonamides, and corticosteroids can cause oral clefts in dogs [30]. Indeed, as the morphogenic processes are highly conserved [35], the same causes of oral dysmorphogenesis known in man can also be found in other species of mammals, including dogs, and vice versa (**Table 2**).

The interaction between genetic and environmental factors is a known underlying phenomenon of the development of certain phenotypes [38]. Evidence has already been found in humans, linking certain genetic markers to CL/P. For example, maternal smoking in combination with the variants of the *GSTT1* and *IRF6* genes increases the risk of clefts [29]. It should be remembered once again that dogs and humans have high genomic homology and share the same environment [1]. Therefore, similar or even identical interactions may occur.

Amoxicillin	Maternal hyperthermia
Anticonvulsants (diazepam, phenytoin, phenobarbital, topiramate)	Maternal obesity
Cholesterol deficiency	Retinoic acid
Corticosteroids	Smoking
Folate deficiency	Stress
Fluconazole	Viral infections
High parental age	Vitamin B complex deficiency
Hyperglycemia	Zinc deficiency
Ionizing radiation	
Maternal alcohol consumption	Others (occupational exposures, environmental pollutants)

Obs.: Not all the risk factors presented in this table are definitely associated with CL/P, and further studies are required. Several factors (amoxicillin, corticosteroids, maternal obesity, stress, etc.) have not shown a consistent association and there are discrepancies between the studies.
Refs. [29, 36, 37].

Table 2. Presumed or confirmed risk factors that have been associated with CL/P in humans.

3.4. Pathogenesis

Due to its etiology, a cleft lip or palate may be the result of an originally abnormal development process or negative interference in a normal development process, corresponding to the concepts of malformation and disruption, respectively, used in dysmorphology [35].

The heterogeneous etiology, in cases of malformation and disruption, assumes varied mechanisms in the development of CL/P. While some mechanisms impair the morphogenesis of various structures in addition to the palate, resulting in syndromic clefts, others act only in the palatogenesis, resulting in nonsyndromic clefts [29, 35].

Developmental field (or morphogenic field) theory aids understanding because different factors can cause the same type of defect. In the early stages, the whole embryo represents a developmental field (primary field). Later, a developmental field is a region or part of the body of the embryo which responds as a coordinated unit to embryonic induction and gives rise to multiple or complex anatomic structures [39, 40]. The induction depends on influences, both physical and chemical, that one developing tissue has on another (or others) in embryogenesis [39]. Developmental fields are systems that control the progressive differentiation of the structure and size, in addition to the temporal and spatial distribution of complex organ components [40]. During blastogenesis, the interactions of the primary field (embryo) generate the progenitor fields (primordia of the final structures) that, in turn, create the secondary fields that produce the final structures during organogenesis [41].

Defects in a structure or in part of the body result from disturbances in one or more secondary fields and are known as monotopic field defects, such as nonsyndromic oral clefts. Multiple defects are the result of disturbances in the primary field or progenitor fields, as occurs in

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individuals with various defects, including CL/P (syndromic clefts). Correlated defects that emerge early during blastogenesis and affecting structures in different parts of the body are polytopic field defects [41].

At any time during embryogenesis, disturbances in the developmental fields can reflect negatively on fusion mechanisms between the lateral and medial nasal processes, and the medial nasal processes with the maxillary processes (Group I clefts); and/or the mechanisms of development, elevation, and fusion of the palatal shelves and the disappearance of the midline epithelial seam (clefts in Groups II and III).

3.5. Patient evaluation

The diagnosis is conducted by visual inspection of the entire extension of the oral cavity, from the premaxilla (incisive bone) to the soft palate. Without this precaution, smaller clefts may go undetected, especially those that affect the soft palate only.

Cleft lip is evident, however, it indicates the need for a thorough and detailed examination of the oral cavity of the patient and the entire organism in search of other congenital abnormalities to determine whether the cleft is an isolated (nonsyndromic) defect or part of a larger (syndromic) condition.

In newborns, difficulty in nursing, nasal reflux of milk, and fault in development are frequent clinical signs. In older patients, in addition to delayed development, choking, coughing, and sneezing during feeding are common. Nasal discharge is also frequent, but the existence of one or more clinical signs and their intensity depends on the location and gravity of the cleft. It is important to be attentive to clinical manifestation resulting from complications, especially signs of pneumonia, a condition that requires immediate treatment.

Detailed record of the oral cleft is essential for adequate planning of treatment, evaluation of postsurgery progress, and studies with different purposes.

Evaluation of the general condition of the patient may include routine laboratory tests and X-rays. Computerized tomography may be useful for planning surgical treatment [3]. The simultaneous existence of oral cleft and other congenital defects justifies a karyotype test.

Irrespective of the existence of obvious abnormalities or clinical signs, inspection of the oral cavity should be part of the physical examination of all newborns.

3.6. Complications

Cleft lip in general means no complications or complications limited to suction problems. However, clefts that affect the incisive bone and, above all, those that affect the secondary palate cause problems of feeding, breathing, and malocclusion. They cause rhinitis, rhinosinusitis, and occasionally otitis media [42, 43]. They can also cause aspiration pneumonia with risk of death. Malnutrition, dehydration, and accumulation of food in the cleft are commonplace.

Unlike in humans and for obvious reasons, difficulty in emitting sounds is not important in dogs and speech defects do not exist.

3.7. Treatment

Cleft lip and palate require corrective surgery to enable adequate function and for esthetic reasons. However, the decision to undergo surgery falls to the owner of the dog. Although many opt for euthanasia, every day, people seek veterinary clinics to inquire about treatment for a dog born with a CL/P.

If the owner opts for treatment, it is necessary for him to be fully aware of the intensive work involved before the patient is old enough for surgery. It is also important to give the owner careful guidelines regarding feeding and cleaning procedures for his dog. He should also be warned of the need to be constantly on the lookout for possible complications. Clefts that affect only the lip or the lip and the alveolar process require little of the owner, but the more extensive clefts may require a lot of dedication.

An efficient and minimally invasive technique for feeding dogs with a cleft palate was described by Martínez-Sanz et al. [19] using baby bottle nipples and customized palatal prostheses made of dental thermoplastic plates. During the breastfeeding period, dogs were fed with a commercial maternal milk substitute using a baby bottle with a customized nipple. After weaning, which occurred during the fifth week of life, palatal prostheses were made every week in keeping with the development of the dogs. The palatal prosthesis was kept in the mouth during the day and removed at night. The technique did not impede oral development and the materials used are easily obtained from dental suppliers. The cost is relatively low and accessible to most veterinary clinics [19].

In cases of severe clefts, it is necessary for the newborn to be fed through a stomach tube to ensure its height and weight development and good nourishment. It may even be necessary to create an esophageal or gastric stoma for feeding and hospitalize the patient [30]. These procedures can be found in several textbooks of veterinary hospital techniques.

In any situation, the owner must be duly trained to deal with the patient's condition and clean the oral cavity adequately after feeding. Alternatively, the owner should take the dog to a veterinary clinic every day for adequate care. A collaborative, patient, and well-informed owner is essential for dogs with cleft lip and palate to develop and be ready for a surgical procedure.

The age that most surgeons consider appropriate for the first corrective procedure is between 4 and 6 months, i.e., it is advisable to await permanent dentition eruption. Before this time, dental development may be harmed. It is also important to consider that oral clefts tend to diminish with growth and become stable at around 6 months [30, 44, 45].

The surgery should be carefully planned and all preoperative care should be taken, including stabilization of the nutritional status and the solution of any complications that may arise. Rhinitis or rhinosinusitis should be treated with antibiotics and secretolytic agents. The same medication is used to treat aspiration pneumonia together with oxygen, bronchodilators, and, in some cases, corticosteroids [30].

Several techniques are available to correct cleft lip and cleft palate, ranging from those that use a mucosal flap or mucoperiosteal flap to autologous bone grafts and prostheses in the case of larger clefts. There are also promising procedures that use mesenchymal stem cells of the

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iliac bone with hydroxyapatite particles [44, 46–49]. When the correction is done in stages, the functional rehabilitation and esthetic results are better [50]. Although the main purpose is the rehabilitation of the patient, veterinary procedures in plastic surgery and dentistry are now available and would provide a really good esthetic effect in a final step.

Like all surgery, postoperative care is essential for success. Thus, supportive measures and the administration of antibiotics, analgesics, and antiinflammatory medicine should be followed strictly. Care should also be taken regarding the patient's feeding and hygiene.

3.8. Prevention

The prevention of oral clefts in dogs follows the same principles as prevention in humans. In other words, educating people regarding the risk factors and genetic counseling, with appropriate adaptations.

Pregnant dogs should be given a balanced diet and their health should be monitored. They should also be protected from viral agents. The environment where they live should be free of chemical products. Breeders and owners should be warned of the risk to the embryo/fetus from the administration of certain medicines. Before prescribing medicine, veterinary practitioners should check the teratogenic potential of the drug.

In humans, advanced parental age is linked to an increased probability of oral clefts in offspring [51]. However, in dogs, there are not studies on this aspect. Assuming that this is the case with dogs, a preventive measure is to use good sense and avoid crossing very young animals or much older ones.

As in human medicine, in veterinary medicine, mineral and vitamin supplements have been recommended, especially folic acid and vitamins B6 and B12 [52, 53]. However, the results are not definitive and there have been discrepancies between studies [29, 54].

A daily supplement of 5 mg of folic acid in pregnant French bulldogs, beginning on the 15th day and ending on the last day of pregnancy, reduced the frequency of cleft palate by 48.54% in a research period of 18 months [53]. In Boston terriers, a reduction of 76% was observed [52]. In pugs and Chihuahuas, there were reductions of 60 and 66.67%, respectively. A supplement of 5 mg/day was given to pugs and 2.5 mg/day to Chihuahuas from the beginning of estrus to the 40th day of gestation [55].

Considerations on genetic counseling will be given later in Section 4.3.

4. Genetic aspects

The genetic basis of cleft lip and palate is extremely complex due to the potential number of genes involved, their behavior (mode of inheritance, gene interaction, penetrance, expressivity, etc.), number of alleles in each gene, independent segregation (two or more genes), epistasis, and gene linkage, in addition to environmental factors that might cause phenocopies. This complexity, added to the difficulties of maintaining and handling the affected animals,

has severely limited clinical and genetic studies of orofacial clefts in dogs. Consequently, few are available and these will be summarized as follows.

4.1. Syndromic and nonsyndromic clefts

Canine oral clefts may be isolated abnormalities, affecting the lip, lip and palate, or only the palate. They may also coexist with abnormalities in other areas of the body. The former are nonsyndromic clefts and the latter are syndromic clefts. The term "syndromic," as used here, is well established and corresponds to a syndrome in a general sense, i.e., a set of abnormalities that occur jointly, but does not necessarily correspond to the concept used in clinical genetics, in which a set of abnormalities can indeed be a syndrome, but also an association or sequence [39].

In dogs, there are no conclusive data on the frequency of each of these two groups. However, the clear perception of veterinary practitioners is that the nonsyndromic forms are far more common than the syndromic. In humans, approximately 70% of cleft lip and palate are isolated abnormalities, while 30% are part of multiple abnormalities due to chromosome aberrations, monogenic inheritance, teratogens, or unknown causes [56].

In veterinary clinics, the common procedure for dogs with multiple abnormalities is immediate euthanasia. This is often performed by the owners or breeders, with no records or study. Consequently, little is known about the syndromic forms of cleft lip and palate.

4.1.1. Syndromic clefts

We have seen bilateral anophthalmia and cleft lip and palate in mongrels, omphalocele, and cleft palate in Siberian huskies, and anencephaly and cleft palate in Yorkshire terriers, to name three examples. Most of the few reports available have to do with cases in which it was not possible to identify a cause. However, in four cases, a hereditary pattern was established or presumed and, in two cases, the mutation that was responsible was identified [6, 57–59].

In 2015, Wolf et al. [6] studied 13 cases of CL/P with a phenotypic spectrum ranging from bilateral cleft in the nasal wings to complete CLP in Nova Scotia duck tolling retrievers. Furthermore, 10 of the affected animals had syndactyly in the third and fourth toes, varying from incomplete in only one paw to complete in all four paws. As for the other three dogs, whether they had syndactyly was not known. These abnormalities were the result of autosomal recessive inheritance and were a syndromic form of CL/P with variable expressivity. A mutation in the *ADAMTS20* gene was associated with this phenotype. In 2014, Wolf et al. [57] had already identified another mutation in the same breed: an insertion of a LINE-1 in the *DLX6* gene, causing CP and brachygnathia with a pattern of autosomal recessive inheritance. More details on these mutations are given in the section on molecular aspects.

In 1998, Villagómez and Alonso [58] described four individuals from a litter of six Saint Bernard dogs, the offspring of normal parents. They had a cleft palate, bilateral anotia, supernumerary vertebrae and ribs, bifid tongue, and bilateral pedal preaxial polydactyly. In two of these dogs, there was also a cleft lip and one did not have polydactyly. The parents, in four previous gestations, had 28 offspring, 22 of which were normal and 6 had the same clinical phenotype as the

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four affected individuals. As the parents were normal and had affected male and female offspring, the authors of this report concluded that the abnormalities could be a recessive mutation of an autosomal gene, although the action of teratogens could not be discarded.

In 1985, Sponenberg and Bowling [59] studied a family of Australian shepherds in which there was a syndrome lethal only to the males. The affected animals had a cleft palate and multiple skeletal defects (scoliosis, brachygnathia, short tibia and fibula, polydactyly, syndactyly). In the females, the defects were less severe and there was no cleft palate. The authors of this report raised the hypothesis of X-linked inheritance.

There are also brief reports of omphalocele and bilateral cleft of primary palate in Yorkshire terriers [23], cleft lip and unilateral left-sided anophthalmia in a French bulldog [60], and bilateral cleft of the primary palate, anencephaly, and macroglossia in a dog of unspecified breed [61].

4.1.2. Nonsyndromic clefts

Most genetic nonsyndromic clefts occur in families in accordance with the multifactorial inheritance model. However, there are cases in which a Mendelian pattern of inheritance has been documented.

Monogenic inheritance. Monogenic inheritance is one that depends on a single gene and the type that has so far been confirmed in dogs is autosomal recessive. In other words, the phenotype only manifests if the individual has two copies of the mutant allele. Like all monogenic inheritance, it has a characteristic pattern as follows and is shown in **Figure 5** [62]:

- The phenotype occurs approximately with the same frequency in males and females;
- The parents of an affected individual are generally heterozygotes ($Aa \times Aa$) and thus phenotypically normal; although there is the possibility of an affected individual having one or both parents affected, such situations are improbable;
- The phenotype tends to skip generations;
- The risk of recurrence in descendants of the parents of an affected individual is 25%;
- There is a 50% chance of the parents of an affected having heterozygous descendants like them;
- Normal siblings of an affected individual have a chance of approximately 67% of being heterozygotes; and
- Consanguineous unions increase the chance of the phenotype occurring.

This pattern of inheritance was registered in cases of nonsyndromic CL/P in dogs of the Brittany spaniel, Pyrenees shepherd, and boxer breeds.

In Brittany spaniels, Richtsmeier et al. [63] studied dogs belonging to an intensely inbred colony. In 12 litters, 52 individuals were born, 14 of which had a cleft palate (CP). One of them also had a cleft lip (CL). In 10 of these 12 litters, the number of males and females was

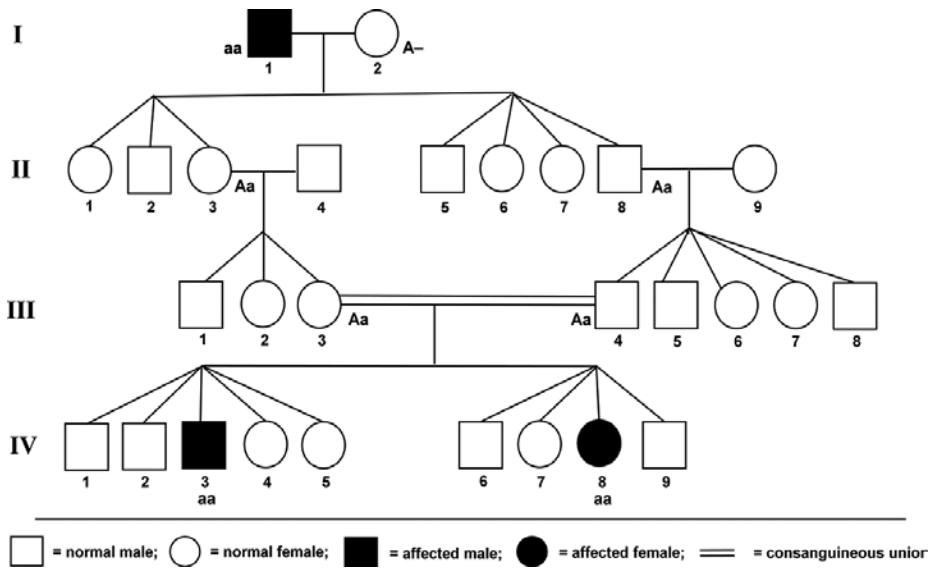

Figure 5. Autosomal recessive inheritance. Consanguineous unions increase the probability that both individuals are heterozygotes, such as couple III-3 X III-4. The risk of recurrence in the offspring of this couple is 25%. The likelihood of having more heterozygous descendants is 2/4 (50%). However, for any one of the normal descendants (male or female) that have already been born, the likelihood is 2/3 (67%).

registered (15 males and 29 females). Of those affected (11), there were more females than males (9 females and 2 males). In all crossings, the parents were normal.

In Pyrenees shepherd dogs, Kemp et al. [17] analyzed the records of a club for this breed over a 20-year period (1984–2004), corresponding to a population of 2104 dogs. They found 47 cases (24 males and 23 females) born in 37 litters with a total of 163 pups and normal parents. Some were only affected by a CP, while others had a cleft lip with or without a cleft palate (CL ± P).

In boxers, Moura et al. [64] found four affected dogs (two males and two females) in two litters with 11 pups born of a consanguineous union (uncle and niece) between normal individuals. All the dogs had essentially the same phenotype (bilateral CLP). Previously, Turba and Willer [15] had raised the hypothesis that in this breed, CLP had a monogenic autosomal recessive pattern of inheritance.

Bleicher et al. [65] reported a case of cleft palate in a beagle together with its pedigree, which is suggestive of autosomal recessive inheritance. There were five affected individuals of both sexes and, in all crossings, the parents were normal.

An older report on cleft palate is suggestive of autosomal recessive inheritance in bulldogs. It presents 33 pups (24 normal and nine affected) born in six litters of a supposedly heterozygous couple [66].

Regarding autosomal dominant inheritance, two reports have described possible cases in which there was nasal cleft, cleft lip, and cleft palate, occurring separately or in association in Bernese mountain dogs (Bernese sennenhund). An affected male that crossed with a normal

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female and then with a female German shepherd fathered 26 pups, 11 of which were affected [67, 68]. An abnormality with some similarity was also observed in a Portuguese pointer [69]. However, no further data were published to confirm the mode of inheritance in these dogs.

It should be remembered that, in principle, clefts with different patterns of inheritance could be present in the same lineage, which would hinder the interpretation of the gene segregation mechanism.

Multifactorial inheritance. Nonsyndromic clefts are normally distributed in families without following any monogenic pattern of inheritance, but recurrence in generations is undeniable evidence of a genetic basis. The theoretical model that explains this inheritance assumes the contribution of several genes (polygenic inheritance) with an additive effect. The presence of a determined number of liability alleles would create a critical threshold and different degrees of expression of the phenotype, which can also depend on the influence of environmental factors. For instance, if we represent four genes, segregating independently and with the liability alleles identified by the number 2, and that from five number 2 alleles the critical threshold emerges, then several genotypes would be possible ($A_1A_2\ B_1B_2\ C_1C_2\ D_2D_2$; $A_2A_2\ B_1B_2\ C_2C_2\ D_1D_2$; $A_1A_2\ B_2B_2\ C_2C_2\ D_2D_2$; $A_1A_1\ B_2B_2\ C_2C_2\ D_1D_2$; etc.). Thus, with any combination of five number 2 alleles, the cleft would occur, and the higher the quantity of these alleles, the more serious it would be, with environmental factors also contributing to this. **Figure 6** illustrates this example. There may also be a principal gene that would have a greater effect than the others. In real situations, the number involved is probably much higher than four genes.

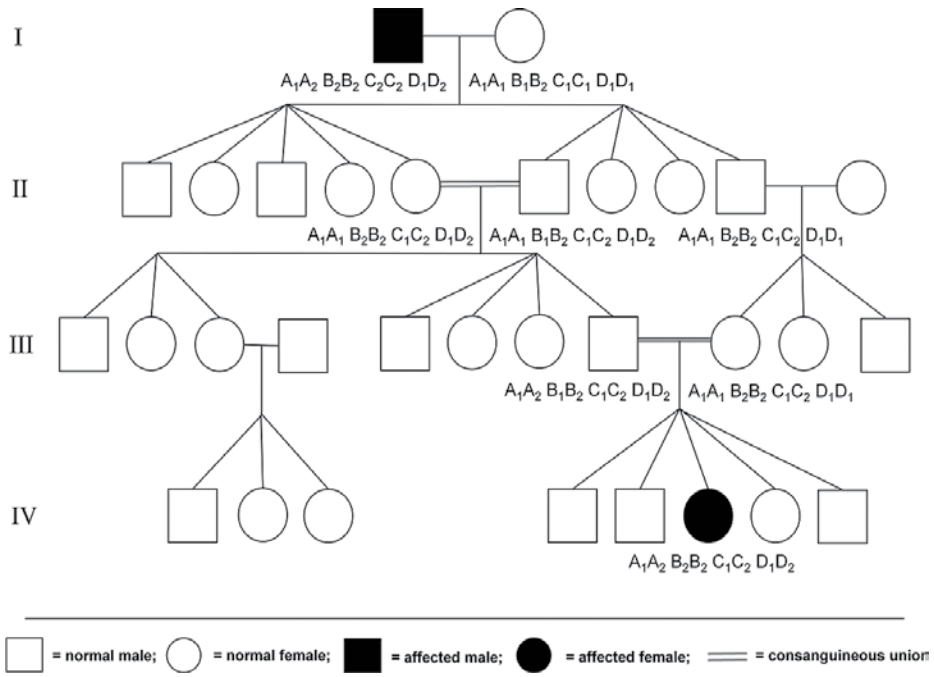

Figure 6. Polygenic inheritance. In this hypothetical pedigree, the individual who inherited at least five number 2 alleles shows the clinical phenotype.

When canine families with high degrees of consanguinity are considered, the critical threshold is more frequent than in families with less or no inbreeding (**Figure 7**). Likewise, the artificial selection process that formed certain breeds led to an increased frequency of liability alleles, making the critical threshold closer than in other breeds and, consequently, leading to a higher frequency of CL/P. As stated previously, there may be a principal gene that increases the risk, as occurs in brachycephalic breeds [70].

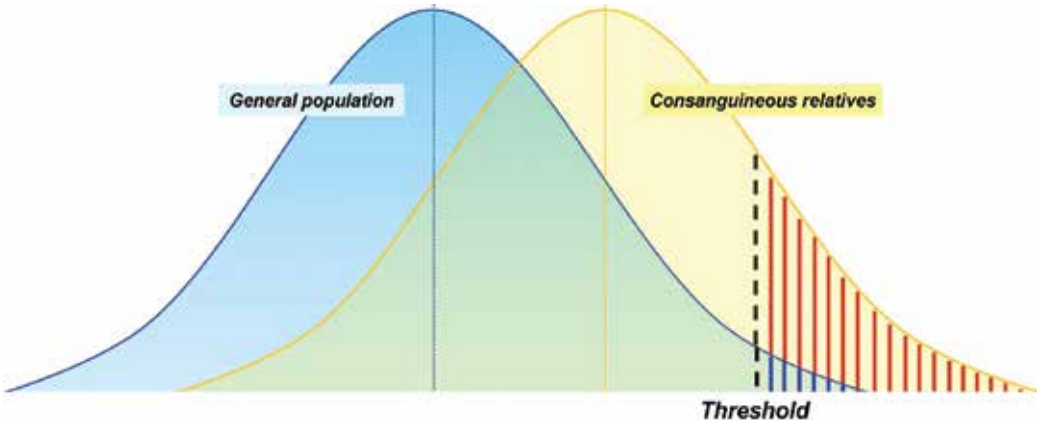

Figure 7. Distribution of genotypes in polygenic inheritance. Comparison of the threshold between the general population and consanguineous relatives or inbred lines.

4.2. Molecular aspects

Modern molecular biology techniques and the use of murine models have enabled the identification of many genes that may be associated with CL/P, and, with each new study, the number of candidate genes grows. The evidence suggests that mutations in these genes, in addition to environmental factors, can act alone or interact with several signaling pathways, negatively interfering in the development of the lip and palate [10]. These genes, and the complex signaling pathways with which they interact, are generally highly conserved in vertebrates and therefore a high degree of homology between man and dog is expected. The identification of mutations in canine genes opens up possibilities for identifying human genes and vice versa, as has happened with the discovery of mutations in mice genes [71]. **Table 3** shows several examples of candidate genes related to CL/P in humans and, potentially, in dogs.

Recently, in Nova Scotia duck tolling retrievers (NSDTR) with a cleft palate and other abnormalities, mutations have been identified in two genes: *DLX6*, located in chromosome 14 of the dog (CFA 14), and *ADAMTS20*, located in chromosome 27 (CFA 27).

In the *DLX6* gene, a LINE-1 insertion was found in the intron 2 jointly segregating with the phenotype (CP and brachygnathia) and obeying an autosomal recessive pattern of inheritance. The presence of the LINE-1 insertion disrupts the transcription of the *DLX6* gene in such a way that only 25% of the normal levels of expression occur, which is not sufficient to prevent CP and mandibular abnormalities. It is located in a noncoding region that is highly conserved,

Gene (abbrev.)	Gene name	Chromosomal assignment (human)	Chromosomal assignment (dog)
IRF6	Interferon regulatory factor 6	1	7
VAX1	Ventral anterior homeobox 1	10	28
BMP4	Bone morphogenetic protein 4	14	8
FGFR2	Fibroblast growth factor receptor 2	10	28
FOXE1	Forkhead box E1	9	11
MAFB	MAF bZIP transcription factor B	20	24
MSX1	msh homeobox 1	4	3
CRISPLD2	Cysteine rich secretory protein LCCL domain containing 2	16	5
FGF8	Fibroblast growth factor 8	10	28
GSTT1	Glutathione S-transferase theta-1-like	22	26
MTHFR	Methylenetetrahydrofolate reductase (NAD(P)H)	1	2
PDGFC	Platelet derived growth factor C	4	15
PVRL1	Poliovirus receptor-related 1 (herpesvirus entry mediator C)	11	5
SUMO1	Small ubiquitin-like modifier 1	2	37
TGFA	Transforming growth factor alpha	2	10
TGFB3	Transforming growth factor beta 3	14	8

Refs. [29, 38, 75].

Table 3. Examples of genes (human and dog orthologs) that have been associated with CL/P in humans.

disturbing a binding domain for SUZ12, a molecule that plays a significant regulatory role in the development of the embryo [57]. Dlx genes form an important family for the development of the first branchial arch, regulating genetic programs that direct the formation of the pattern of the maxilla and mandible [72]. The inactivation of *Dlx5* and *Dlx6* in mice causes serious defects in the craniofacial, axial, and appendicular skeleton, leading to perinatal death [73].

In the *ADAMTS20* gene, a deletion of two nucleotides (AA) was found, segregating together with the phenotype (CL/P and syndactyly) and adhering to an autosomal recessive pattern of inheritance. This deletion represents a frameshift mutation in the metalloprotease domain and should cause the truncation of 1461 amino acids of a protein of 1916 amino acids [6]. The *ADAMTS20* gene is a member of a gene family that encode zinc-dependent proteases. In mouse embryos, its expression is detected in the first branchial arch and between the medial nasal processes [74]. In the palatal mesenchyme, it directs the formation and extension of the palatal shelves [5].

In parallel with the study on NSDTR dogs, Wolf et al. [6] conducted a family-based genome-wide association analysis in a population of native Guatemalans. They identified a significant

association between cases of CL/P and the *ADAMTS20* gene, lengthening the list of candidate genes for the etiology of oral clefts in humans.

4.3. Genetic counseling

Like any genetic abnormality, the main recommendation in cases of CLP in dogs is that affected individuals should not be crossed, nor should normal couples with affected descendants ever be crossed again. As the majority of oral clefts in dogs appear to be multifactorial or recessive, it should be noted that owners of normal dogs who have had affected offspring are not always willing to follow this recommendation, especially when the dogs have characteristics of their breed that are highly valued. Therefore, if the owners/breeders decide to cross them again, and are sure that the cleft lip or palate is genetic in nature, the risk of recurrence should be seriously taken into consideration [35].

To avoid autosomal recessive clefts, an important strategy is never to cross individuals that are known to be heterozygotes one with another, such as those that have already had affected offspring. When there is a family history of recessive cleft and the zygosity of an individual is not known, consanguineous unions should be avoided. For X-linked recessive phenotypes, normal female offspring of affected father are all carriers, i.e., heterozygotes, and should not be crossed even when the males are normal. For multifactorial clefts, the main strategy is to avoid crossing dogs that have any relationship. This will reduce the probability of reaching the critical threshold [35].

5. Final considerations

Always bearing in mind that greater knowledge results in a correct diagnosis, suitable management of each case, and definition of criteria that give consistency to guidelines for prevention of CLP, the first step to expand knowledge is appropriate details when publishing new canine cases, using one of the classifications established in human medicine. This will facilitate international communication between professionals from the different fields in question.

Breeds, lineages, or families of dogs in which CLP occurs more frequently are a valuable source of information on the molecular biology and genetics of oral clefts. Genome-wide association studies (GWAS) with genotyping using arrays based on single nucleotide polymorphisms (SNP) are powerful means for mapping of regions of interest. The current technologies of next-generation sequencing (NGS), with increasingly robust platforms and increasingly expanded panels, facilitate the identification of candidate genes, allowing studies that confirm the role of these genes in the etiology of oral clefts.

It should also be remembered that a chromosomal analysis in syndromic cases should be routine. Analyses with fluorescence *in situ* hybridization (FISH) and comparative genomic hybridization (GCH) may identify chromosomal aberrations and describe new syndromes, as well as establishing a correlation with human syndromes.

An interface of knowledge on human and canine species opens up new paths in both veterinary and human medicine. This promotes quality and more humane and competent clinical practice. It is also clearly reflected in the fields of genetics, developmental biology, and evolutionary biology.

Author details

Enio Moura[1]* and Cláudia Turra Pimpão[2]

*Address all correspondence to: enio.moura@pucpr.br

1 Service of Medical Genetics, Faculty of Veterinary Medicine, School of Life Sciences, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil

2 Department of Animal Science, School of Life Sciences, Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil

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In Designing Strategies for Cleft Lip and Palate Care it was aimed to link the epidemiology from different areas in the world with the interspecialty surgical care and the future genetic research projects. The objective is to concisely discuss the methodology of interspecialty care and stimulate future ideas for prophylactically managing or preventing such deformities. I am confident that one day the surgical interventions that bombard the patients from the day of newborn delivery and throughout the years of youth should be significantly decreased based on the genetic prophylactic intervention, probably.

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