DENTAL ARCH RELATIONSHIP IN BANGLADESHI CHILDREN WITH NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE (UCLP)

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DENTAL ARCH RELATIONSHIP IN BANGLADESHI CHILDREN WITH NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE (UCLP)

By

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Alhamdulillah, praise is only to Allah for his endless mercy and blessings that we can still breathe the fresh air and survive in this world for gratis. Allah says in Holy Quran: “Your Lord is best aware of you. If He will, He will have mercy on you, or if He will, He will punish you” (Holy Quran 17:54).

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LIST OF ABBREVIATIONS

BCLP	Bilateral cleft lip and palate
CLP	Cleft lip and palate
CS	Cleft side
CPI	Cleft palate isolated
CL	Cleft lip
DAR	Dental arch relationship
EI	EUROCRAN index
GY	GOSLON Yardstick
mHB	modified Huddart Bodenham
MAC	Maxillary arch constriction
NCS	Non cleft side
OFC	Orofacial clefts
PM	Palatal morphology
UCL	Unilateral cleft palate
UCLA	Unilateral cleft lip and alveolus
UCLP	Unilateral cleft lip and palate
V-Y palatoplasty	Veau-Wardill-Kilner Palatoplasty

PERTALIAN ARKUS PERGIGIAN DALAM KANAK-KANAK BANGLADESH DENGAN REKAHAN BIBIR SATU BAHAGIAN DAN LELANGIT NON SINDROMIK

ABSTRAK

Rekahan bibir dan lelangit adalah salah satu kecacatan lahir yang kerap berlaku. Banyak faktor yang bertanggungjawab ke atas pertalian arkus pergigian yang tidak digemari dalam rekahan bibir dan lelangit. Pertumbuhan muka yang terhenti, yang menjadi penyebab maloklusi kelas III, merupakan cabaran primer yang dihadapi oleh pesakit rekahan bibir dan lelangit. Faktor kongenital (jenis UCLP, bahagian UCLP, riwayat keluarga tentang rekahan, riwayat keluarga tentang kelas III) dan faktor rawatan postnatal (cheiloplasty, palatoplasty) boleh mempengaruhi hasil rawatan dalam kanak-kanak rekahan bibir dan lelangit satu bahagian, menyebabkan banyak protokol dan teknik pembedahan berbeza yang dipraktikkan di dunia. Tujuan kajian retrospektif ini ialah untuk menilai DAR kanak-kanak Bangladesh yang mengalami rekahan bibir dan lelangit non sindromik, dan untuk meneroka pelbagai faktor kongenital dan rawatan posnatal yang bertanggung jawab ke atas DAR yang tidak digemari. 84 model gigi di ambil sebelum rawatan ortodontik dan graf tulang alveolar. Purata umur ialah 7.69, 2.46 (purata, sisihan piawai). Semua subjek melalui pembedahan primer (cheiloplasty dan palatoplasty) di hospital yang sama. DAR dinilai secara buta tali oleh lima penilai menggunakan GOSLON Yardstick (GY) dan index EUROCRAN (EI) dan oleh dua penilai menggunakan sistem skor modified Huddart Bodenham (mHB). Tambahan pula semua subjek dibahagikan kepada dua kumpulan, digemari dan tidak digemari. Kumpulan dibahagikan sedemikian rupa kerana pesakit kumpulan digemari tidak memerlukan rawatan lanjutan selepas palatoplasty atau cheiloplasty atau mereka boleh dirawat dengan rawatan ortodontik konvensional, manakala pesakit daripada kumpulan tidak digemari mungkin menerima pembedahan pembetulan. Statistik kappa digunakan untuk

menilai persetujuan intra- dan inter pemeriksa, chi-square digunakan untuk menilai perkaitan dan analisis regresi logistik digunakan untuk meneroka faktor bertanggung jawab yang memberi kesan DAR. Sejumlah 37 subjek (44% daripada jumalah subjek) dikategorikan ke dalam kumpulan tidak digemari (kategori penilaian 4 and 5) menggunakan GY. Purata skor GOSLON adalah 3.238. Persetujuan intra- dan inter-penilai adalah baik. Menggunakan analisis regresi kasar dan kebelakang langkah demi langkah, pertalian signifikan didapati antara riwayat keluarga maloklusi rangka kelas III (p=0.015 dan p=0.014 masing-masing) dan DAR yang digemari. CLP lengkap (p=0.054) dan UCLP sebelah kiri (p= 0.053) juga berkait dengan DAR tidak digemari mengguna analisis regresi kasar dan kebelakang lanhkah demi langkah masing-masing tetapi perkaitan tidak signifikan. Sejumlah 47 subjek (56% daripada subjek) dikategorikan kepada kumpulan tidak digemari (kategori penilaian 3 dan 4) menggunakan EI. Purata skor EUROCRAN adalah 2.44 dan 1.93 untuk DAR dan morfologi lelangit (PM) masing-masing. Persetujuan intra- dan inter-pemeriksa adalah sederhana kepada amat baik. Menggunakan analisis regresi kebelakang langkah demi langkah, perkaitan signifikan didapati antra teknik Millard termodifikasi (p=0.047, p=0.034 masing-masing) cheiloplasty dan DAR tidak digemari. Morfologi lelangit menunjukkan perkaitan signifikan dengan jenis rekahan, jenis cheiloplasty dan jenis palatoplasty. Sejumlah 39 subjek (46% daripada subjek) dikategorikan kepada kumpulan tidak digemari (kategori penilaian lemah dan amat lemah) menggunakan sistem skor mHB. Sejumlah skor mHB ialah -8.26. Persetujuan intra- dan inter-pemeriksa adalah amat baik. Menggunakan analisis regresi kasar dan langkah demi langkah, perkaitan signifikan didapati antara riwayat kelas III positif (p= 0.025, p=0.030 masing-masing) dan DAR tidak digemari. Menggunakan ijan chi square, UCLP lengkap (p= 0.003) dan V-Y palatoplasty tolak belakang (p=0.005) terkait signifikan dengan DAR tidak digemari. Kajian variate berbilang mencadangkan DAR kanak-kanak Bangladesh UCLP non sindromik terkait signifikan dengan beberapa faktor congenital dan rawatan posnatal dengan menggunakan beberapa indeks berbeza.

DENTAL ARCH RELATIONSHIP IN BANGLADESHI CHILDREN WITH NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE (UCLP)

ABSTRACT

Cleft lip and palate (CLP) is one of the most common birth defects. Multiple factors are believed to be responsible for an unfavorable dental arch relationship (DAR) in CLP. Facial growth (maxillary) retardation, which results in class III malocclusion, is the primary challenge that CLP patients face. Congenital factors (UCLP type, UCLP side, family history of cleft, family history of class III) and postnatal treatment factors (cheiloplasty, palatoplasty) may influence treatment outcomes in unilateral cleft lip and palate (UCLP) children, which has led to a great diversity in protocols and surgical techniques by various cleft groups worldwide. The aim of this retrospective study was to evaluate DAR of non syndromic Bangladeshi UCLP children and to explore the various congenital and postnatal treatment factors that are responsible for unfavorable DAR. Eighty four dental models were taken before orthodontic treatment and alveolar bone grafting. The mean age was 7.69± 2.46 (mean± SD). All the subjects had primary surgery (cheiloplasty and palatoplasty) at the same hospital. DAR was assessed blindly by five raters using GOSLON Yardstick (GY) and EUROCRAN index (EI) and by two raters using modified Huddart Bodenham (mHB) scoring system. Furthermore, all the subjects were divided into two groups; favorable and unfavorable groups. This grouping was carried out because patients in the favorable groups may not need further treatment after palatoplasty or cheiloplasty or they could be treated with conventional orthodontics, whereas patients in the unfavorable groups sometimes required surgical correction. Kappa statistics was used to evaluate the intra- and inter-examiner agreements, chi square was used to assess the associations and logistic regression analysis was used to explore the responsible factors that affect DAR. Total 37 subjects (44% of all subjects) were categorized into unfavourable group (category rating 4 and 5) using GY.

The mean GOSLON score was 3.238. Intra- and inter-examiner agreements were very good. Using crude and stepwise backward regression analysis, significant association was found between family history of skeletal class III malocclusion (p = 0.015 and p = 0.014 respectively) and unfavourable DAR. Complete UCLP (p = 0.054) and left sided UCLP (p = 0.053) also seemed to be correlated with unfavourable DAR using crude and stepwise backward regression analysis respectively but no significant associations was found. Total 47 subjects (56% of all subjects) were categorized into unfavourable group (category rating 3 and 4) using EI. The mean EUROCRAN scores were 2.44 and 1.93 for DAR and palatal morphology (PM) respectively. Intra- and inter-examiner agreement was good to very good. Using crude and stepwise backward regression analyses, significant associations were found between the modified Millard technique (p = 0.047, p = 0.034 respectively) of cheiloplasty and unfavorable DAR. Complete UCLP (p = 0.017) was also significantly correlated with unfavorable DAR. The PM showed a significant association with the type of cleft, type of cheiloplasty and type of palatoplasty. Total 39 subjects (46% of all subjects) were categorized into unfavourable group (category ratings poor and very poor) using mHB scoring system. The total mHB score was -8.26. Intra- and inter-agreement was very good. Using crude and stepwise backward regression analysis, significant association was found between positive history of class III (p = 0.025, p = 0.030 respectively) and unfavorable DAR. Using chi square test, complete UCLP (p = 0.003) and V-Y pushback palatoplasty (p = 0.005) were also significantly correlated with unfavorable DAR. This multivariate study suggested that DAR of non syndromic Bangladeshi UCLP children was significantly correlated with some of congenital and postnatal treatment factors by using different indices.

CHAPTER 1

INTRODUCTION

1.1 Background of study

Any deformities (anatomical or chromosomal) that initiates during pregnancy and their effects have been detected after birth considered as congenital anomalies (Sekhon et al., 2011). Among them, Cleft lip and palate (CLP) is one of the most common congenital anomalies present at birth (Marazita et al., 2012). CLP can occur together or individually. Clinically, when CLP appears with other (usually two or more) malformations in recognizable pattern, it is classified as syndromic CLP. If it appears as an isolated defect or if syndromes cannot be identified, the term non-syndromic CLP is used (Kohli and Kohli, 2012). More than 400 syndromes have been already associated with CLP (Papadopulos et al., 2005). The etiology of CLP is still controversial. According to previous studies, it is to be thought that both genetic and environmental factors are responsible for CLP (Berkowitz, 2013; Haque et al., 2015)

CLP shows different prevalence in different civilization and races in addition to countries. World Health Organization (WHO) has recognized and included cleft deformities in their Global Burden of Disease initiative. It is estimated that the overall global prevalence of cleft deformities is one affected individual in every 600 new born babies. The management of a patient with cleft is complex and requires a large team of specialists working in tandem to bring out physical, psychological and social rehabilitation. In Asian population, CLP affects approximately 1.30 of every 1000 live births (Cooper et al., 2006). Moreover the prevalence rate of USA is 2.2 to 11.7 per 10,000 live births (Agbenorku et al., 2011).

Not only aesthetic problem, but also multifarious functional problems like feeding, speech, hearing, dental functioning and also psychological dilemma can happen to the patient. Likewise, maxillary arch constriction (maxillary growth retardation) is a common problem of CLP patients resulting concave facial profile, class III malocclusion, mid facial growth deficiency, congenitally missing and malformed teeth, orthodontic anomalies like crowding, rotation, malposition of teeth are frequently observed in CLP patient (Ranta, 1986; Haque and Alam, 2015). Maxillary growth retardation is often observed in patients with repaired unilateral cleft lip and palate (UCLP). Most often, the outcome of treatment for children with UCLP can be assessed by the dental arch relationship (DAR) (outcome of maxillary growth) after cheiloplasty and palatoplasty (Sandy et al., 2001 and Chiu & Liao, 2012).The timing and techniques of cheiloplasty and palatoplasty have been found to influence the outcome of the treatment of UCLP (Fudalej et al., 2011 and Liao et al., 2006). Moreover, type of UCLP, side of UCLP, family history of cleft and family history of class III malocclusion, and auxiliary intervention also influence the treatment outcome. The cause of adversely affect maxillary growth retardation is come into view either from iatrogenic/ postnatal treatment factor (cheiloplasty or palatoplasty) or intrinsic/ congenital factor (UCLP type, side, family history of cleft and family history of class III malocclusion). A lack of consideration of factors affecting the outcome of treatment in children with CLP has led to great diversity in protocols and surgical techniques by various cleft groups' worldwide (Alam et al., 2012). As a result, to ensure the success of the treatment, methods need to be based on sound evidence so that a surgeon can modify their timing or techniques if needed (Atack et al., 1997b).

Cleft deformities remain a significant and interesting challenge for the medical fraternity. An assessment of the DAR is considered being the most valuable benchmark of treatment outcome which can give obvious concept for facial growth as well as revealed an important indicator for worth of cleft treatment outcome.

Several indices such as the GOSLON (Great Ormond Street, London and Oslo) Yardstick (Mars et al., 1987), the 5-year-old index (Atack et al., 1997a), the GOAL (Goteborg (G), Sweden; Oslo (O), Norway; Aarhus (A), Denmark; and Linkoping (L), Sweden) index (Friede et al., 1991), EUROCRAN index (Fudalej et al., 2011), Huddart/Bodenham scoring system (Huddart and Bodenham, 1972), modified Huddart Bodenham scoring system (Mossey et al., 2003; Gray and Mossey, 2005) etc. are used to assess DAR in patients with CLP. Specific index has its individual uses and advantages.

In contemporary era, multitude of research on CLP has been done worldwide. In a typical developing country like Bangladesh, more than 5000 CLP patients are born every year in Bangladesh where the prevalence rate is 3.9 per 1000 live births (Ferdous et al., 2013). CLP patients in Bangladesh lead an extremely despondent life as they cannot provide financial supports so that sometimes they are unable to get essential surgical repairs or cleft associated treatment. Nowadays CLP patients in Bangladesh are treated by different organizations like NGO, private hospitals etc. But according to literature survey evaluation of treatment outcome or end results of these patients are still unknown. This is the shadow beneath the light. The present study evaluates for the first time the treatment outcome of Bangladeshi UCLP patients based on both congenital and postnatal treatment factors using GOSLON Yardstick (GY), EUROCRAN index (EI) and modified Huddart Bodenham (mHB) scoring system.

The treatment outcomes of a CLP patient depend on various factors. However, most of the researches all over the world evaluated treatment outcome based on individual factors (Sasaguri et al., 2014; Fudalej et al., 2012; Fudalej et al., 2011; Zaleckas et al., 2011; Apostol, 2008; Bongaarts et al., 2006) using different index. But, very few researches have been done considering various factors at a time to explore the responsible factor that affects DAR in UCLP children (Alam et al., 2008; Kajii et al., 2013) using GY.

We have, therefore, paid particular attention to evaluating the treatment outcomes of Bangladeshi UCLP patients based on both congenital (UCLP type, UCLP side, family history of CLP, family history of class III malocclusion) and postnatal treatment (cheiloplasty, palatoplasty) factors using the GY, EI and mHB.

The characteristics of each index are as follows:

GY:

- Can assess the DAR in patients with UCLP.
- Can be use in the late mixed and early permanent dentition.
- Valuable in predicting treatment need (orthodontic treatment, surgical treatment)

EI:

- Can assess the surgical outcomes in patients with UCLP.
- Can be applied to evaluate the degree of malocclusion in both antero-posterior and vertical dimensions, as well as the palatal form will be used to assess both DAR and palatal morphology (PM).

mHB scoring system:

- Measures maxillary arch constriction (MAC) based on DAR in patients born with UCLP.
- Applicable in any type of cleft.

Measures severity of the crossbite and each maxillary tooth can be score according to its relationship with the corresponding tooth in the mandible.

Hence, these indices provide room for further research to allow more understanding in its potential clinical application in local population.

1.2 Justification of study

Treatment outcome based on the DAR is necessary to help surgeons to justify modifications of their timing or techniques, and to provide better understanding on the variable response of growing tissues to surgical repair.

Many studies have proven that clefting has significant effects on DAR. Besides post-surgical results are not predictable because the response of growing tissues to surgical repair is often variable. Results vary from one centre to another and according to the surgical protocol used. We have applied the GY, EI and mHB scoring system on UCLP children in patients in Queens Hospital (pvt) LTD, Jessore, Bangladesh to determine the treatment outcome based on the DAR. The understanding of treatment outcome based on the DAR in non-syndromic UCLP children in Queens Hospital (pvt) LTD, Jessore, Bangladesh will:-

1. Facilitate decision making and treatment planning of CLP.
2. Determine to which extent the surgery that could bring those patients to the normal limits.
3. Publish a database for further future studies.

4. Reduce treatment cost.

1.3 Objectives

General Objectives:

To determine the treatment outcome based on the DAR by the GY, EI and mHB system of non-syndromic Bangladeshi UCLP children.

Specific objectives:

By GY:

1. Determine the intra- and inter-examiner reliability of GY scoring
2. Determine the DAR of Bangladeshi UCLP children using the GY
3. Determine favorable and unfavorable groups based on the DAR.
4. Evaluate the associations between congenital and postnatal treatment factors with favorable and unfavorable DAR.
5. Explore the associations between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis.
6. Explore the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis.
7. Present global and present study GY score.

By EI:

1) Determine the intra- and inter-examiner reliability of EI scoring.

2) Determine the DAR and PM of Bangladeshi UCLP children using the EI.

3) Determine favorable and unfavorable groups based on the DAR.

4) Evaluate the associations between congenital and postnatal treatment factors with favorable and unfavorable DAR and PM.

5) Explore the associations between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis.

6) Explore the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis.

7) Present the global and present study EI scores.

By mHB scoring system:

1. Determine intra- and inter-examiner reliability of mHB scoring.

2. Determine DAR of Bangladeshi UCLP children using mHB–

    - Incisor score

    - Buccal cleft side score

    - Buccal non cleft side score

    - Total mHB score

3. Determine favorable and unfavorable group based DAR.

4. Evaluate the associations between congenital and postnatal treatment factors with favorable and unfavorable DAR.

5. Explore the associations of individual factor with favorable and unfavorable DAR using crude logistic regression analysis.

6. Explore the responsible factor with favorable and unfavorable DAR using stepwise backward logistic regression analysis.

7. Present global and present study mHB score.

1.4 Research question

By GY:

1. Is there any association between congenital and postnatal treatment factors with favorable and unfavorable DAR?

2. Is there any association between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis?

3. Is there any association between the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis?

By EI:

1. Is there any association between congenital and postnatal treatment factors with favorable and unfavorable DAR and PM?

2. Is there any association between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis?

3. Is there any association between the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis?

By mHB scoring system:

1. Is there any association between congenital and postnatal treatment factors with favorable and unfavorable DAR?

2. Is there any association of individual factor with favorable and unfavorable DAR using crude logistic regression analysis?

3. Is there any association between the responsible factor with favorable and unfavorable DAR using stepwise backward logistic regression analysis?

1.5 Null Hypothesis

By GY:

1. There is no association between congenital and postnatal treatment factors with favorable and unfavorable DAR.

2. There is no association between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis.

3. There is no association between the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis.

By EI:

1. There is no association between congenital and postnatal treatment factors with favorable and unfavorable DAR and PM.

2. There is no association between individual factors in terms of favorable and unfavorable DAR using crude logistic regression analysis.

3. There is no association between the responsible factors for favorable and unfavorable DAR using stepwise backward logistic regression analysis.

By mHB scoring system:

1. There is no association between congenital and postnatal treatment factors with favorable and unfavorable DAR.

2. There is no association of individual factor with favorable and unfavorable DAR using crude logistic regression analysis.

3. There is no association between the responsible factor with favorable and unfavorable DAR using stepwise backward logistic regression analysis.

CHAPTER 2

LITERATURE REVIEW

2.1 Definition of CLP

Cleft lip with or without cleft palate is a congenital malformation characterized by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard or soft palate. This definition exclude midline cleft of upper or lower lip and oblique facial fissure going towards the eye (www.icbd.org).

2.2 Prevalence of CLP

Orofacial clefts (OFC) are known to be the most common craniofacial defects and one of the most common structural birth defects with published birth prevalence ranging from 1.0/1000 to 2.69/1000 throughout the world. (Christensen et al. 2004) These clefts involve the lip and/or palate or isolated clefts of the palate (Mossey and Castilla 2001). Many epidemiologic studies have been carried out on incidence and prevalence of cleft lip, cleft palate and CLP worldwide. The reported outcome varies between racial groups, type of cleft and sex.

On a worldwide level, OFC affect approximately 1 in every 600 newborn babies (Mossey and Little 2002). However, American Indians or Asians descent have the highest incidence and prevalence of CLP; 1 in 500 live births or higher whereas African populations are the lowest at 1 in 2500 live births (Gorlin et al., 2001; Murray, 2002; Cooper et al., 2006; Dixon et al., 2011).

Five studies have been performed in the United States and reported that the incidence of cleft lip, cleft palate and CLP for American Indians ranged from 0.79 to 3.62 per 1000 live births (Tretsven, 1963; Gilmore and Hofman, 1966; Niswander and Adams, 1967; Emanuel et al., 1973; Niswander et al., 1975). The highest prevalence of orofacial cleft was reported among

the Bari Indians of Western Venezuela. It is about 10 in 1000 live births, which is ten times higher the rate reported for United States populations (Vanderas, 1987).

According to the twenty eight studies that have been performed in several centers and found the incidence rate of CLP ranged from 0.91 to 2.69 per 1000 live births in Caucasian populations. Nine of those studies were performed in Europe and found the incidence ranged between 1.30 and 1.94 per 1000 (MacMahon and Mckeown, 1952; Fogh Andersen, 1961; Knox and Braithwaite, 1962; Moller, 1965; Leck, 1969; Czeizel and Tusnadi, 1971; Saxen and Lahti, 1974; Saxen 1975; Owen et al., 1985). Two studies were performed in Canada and found incidence rate between 1.06 and 1.97 per 1000 live births (Hixon, 1951; Lowry and Trimble, 1977). Four studies conducted in Australia reported incidence ranged from 1.21 to 1.73 (Rank and Thomson, 1960; Chi and Godfrey, 1970; Brogan and Woodings, 1974; Spry and Nugent, 1975). Only one study was performed in Israel (Tal et al., 1974) and the rest thirteen studies were conducted in United States in different places, and found incidence ranged from 0.95 to 2.69 per 1000 live births (Davis, 1924; Grace, 1943; Lutz and Moor, 1955; Loretz et al., 1961; Ivy, 1962; Woolf et al., 1963; Conway and Wagner, 1966; Gilmore and Hofman, 1966; Chung and Myrianthopoulos, 1967; Hay, 1971; Emanuel et al., 1973; Myrianthopoulos and Chung, 1974; Ching and Chung, 1974).

In Asia, Cooper et al performed a study on Asian oral facial cleft birth prevalence and found CLP affects about 1.30 in every 1000 live births among the Asian populations (Cooper et al., 2006). This study also has revealed that the Japanese are the most affected followed by the other Asian population namely Malaysians, Singaporeans, Filipinos, Koreans, Vietnamese and Laotians with the Chinese population the least affected. It affects the Japanese approximately 1.41/1000 live births, 1.25/1000 live births in the other Asian populations and 1.21/1000 live births among the Chinese (Cooper et al., 2006).

According to literature survey, only one study has been conducted in Bangladesh and found more than 5000 CLP patients are born every year in Bangladesh where the prevalence rate is 3.9 per 1000 live births (Ferdous et al., 2013).

2.3 Embryology of UCLP

Embryologically, CLP is due to failure off using of maxillary and nasal processes. In the development of normal embryo, the first arch grows down from the neural crest.

During the itinerary of growth of the maxillary processes, it fuses with the lateral nasal processes and the medial nasal processes, before meeting with its fellow of opposite side to form primary palate, from which develops the upper lip and palate anterior to the incisive foramen. These processes are essentially the mesodermal tissues covered by ectoderm. During the fusion, the covering epithelium of these processes at the site of union disintegrates and mesodermal tissues and mesodermal tissues come in contact with each other and unite. Failure of this union due to any other cause will produce total cleft of primary palate, while partial fusion will produce sub-total cleft (Langman and Sadler, 2004).

The secondary palate develops from a pair of palatal shelves arising from the inner and side of maxillary process, which unite with the nasal septum from before backwards any arrest of union thus result in a defect that varies from a bifid uvula to a complete cleft of a secondary palate.

Cleft involving the lip and palate are the most commonly seen congenital deformities that occur at the time of birth.

2.4 Classification CLP

Pathologist A. Forster from Wurzburg, Germany was the first who classify malformations of the face in the year 1861(Forster, 1861). With improved consideration of the embryology of the malformation, other classifications have been established over time (Koch et al., 1995), some examples in harmony to timeline are: Veau, 1931, Kernahan and Stark, 1958 and Kriens, 1989.

The choice of classification in this study is based on Kernahan and stark 1958.This classification is well established and develops the understanding of embryology origin where

the incisive foramen marks as a boundary, dividing clefts of the primary palate from those of the secondary palate. The primary palate refers to the lip, alveolus and the palate anterior to the incisive foramen. The secondary palate refers to the soft and hard palate, up to the incisive foramen. A complete CLP simply mean the involvement of the full thickness of the structures of lip, alveolus or palate. (**Figure 2.1**)

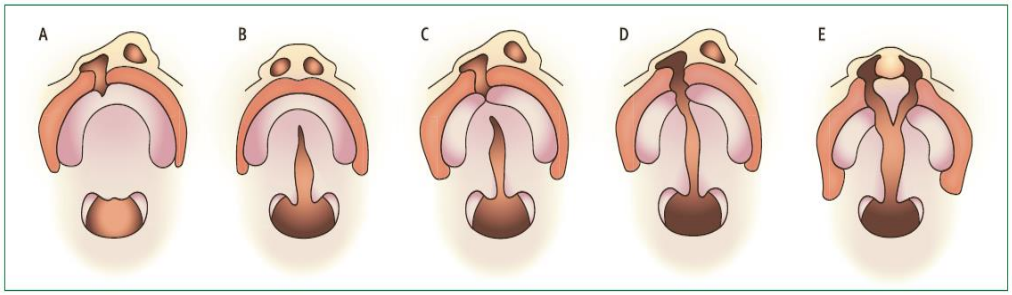

Figure 2.1: Non-syndromic orofacial clefts: (A) Cleft lip and alveolus. (B) Cleft palate. (C) Incomplete unilateral cleft lip and palate. (D) Complete unilateral cleft lip and palate. (E) Complete bilateral cleft lip and palate. (Copied from Mossey et al., 2009, p1774)

2.5 Etiology of CLP

The etiologies of CLP are multifaceted and occupy genetic influences with unpredictable associations from environmental factors. Many studies have been done regarding the etiology of CLP to recognize or to predict the causes of affecting the CLP but there is still no precise answer. The combination of genetics and environmental factors contribute to cleft formation in human (Murray, 2002).

2.5.1 Genetic involvement of CLP

It is indispensable to highlight the gene involvement in CLP patients according to literature survey.

Carinci et al. reviewed the genes and available loci in the literature whose participation in the beginning of non syndromic OFC have more sound scientific proof. It is established from several genetic studies on human populations have that CLP and cleft palate isolated (CPI) have different genetic backgrounds and, therefore, environmental factors probably disclose only these malformations. OFC from 1 to 10 have been accredited in CLP several loci. The first locus, OFC1, has been charted to chromosome 6p24. Other CLP loci have been charted to 2p13 (OFC2), 19q13.2 (OFC3) and 4q (OFC4). OFC5—8 are acknowledged by mutations in the MSX1, IRF6, PVRL1, and TP73L gene. OFC9 maps to 13q33.1-q34, whereas OFC10 is related with the SUMO1 gene. In cleft inception, MTHFR, TGFB3, and RARA play a role in additionally. At present TBX22 is also identified in CPI (Carinci et al, 2007).

On chromosome 6, inside the region 6p24.3, studied using YACs proved the existence of a major dominant gene referred to as OFC1, placed closely to HGP22 and AP2 genes involved in the morphogenesis of human face. In some populations the association of CLP with mutations of the TGFA gene located on chromosome 2p13 (locus OFC2) was strongly proved (Tudose & Bara, 2008) A similar study about gene involvement in CLP revealed that the risk factor of CLP were associated with TGFA, TGFB2, TGFB3, MSX1, MTHFR, BCL3 & RARA (Rajion & Alwi, 2007). Kohli and Kohli, discussed the etiology of CLP from recent data and conducted a search of the MEDLINE database (Entrez Pub Med) from 1986 to 2010. They established that several genes responsible for syndromic CLP. Three of them are TBX22, PVRL1, and IRF6 were responsible for causing cleft palate X-linked (CPX), CLP ectodermal dysplasia syndrome, Van der Woude and popliteal pterygium syndromes, correspondingly they were also implicated in non syndromic CLP (Kohli and Kohli, 2012).

An investigation of the role of maternal folate intake was done by Chevrier et al. Their assessment was about diet or vitamin supplementation and found CLP and CPI was on risk because of MTHFR polymorphism and their interaction (Chevrier et al., 2006). 262 case-parent triads from a population-based study of OFC in Norway were selected and analyzed TGFA, TGFB3, and MSX1 which were responsible for OFC or not. 174 triads of CLP cases and 88 triads of CPI cases were taken for examination. A little participation was observed of

any of these genes with CLP and the robust association was a 1.7-fold risk with two copies of the TGFB3-CA variant. Among CPI cases, there was a 3-fold risk with two copies of the TGFA TaqI A2 allele, and no increase with one copy. Among children homozygous for the MSX1-CA A4 allele, TGFA genotype was even stronger raising the possibility of interface between these two genes (Jugessur et al., 2003).

TBX22 was scrutinized with a large number of CLP patients with no pre-selection for legacy or ankyloglossia which was a familiar feature of CPX. Mutations in CPX families and united phenotype/genotype analysis of the familial cases have been observed by Marcano et al. Cleft palate and ankyloglossia together were commonly shown by males but CPO and/ or ankyloglossia were shown by families which indicating that defects are distinct parts of the phenotypic spectrum. It can be apprised that for cleft palate, a significant risk factor is TBX22 (Marcano et al., 2004).

Distinctive mutation is occurred in CPX by TBX22. According to their explanation, in early human development, TBX22 is noticed in the palatal shelves and is highest prior to elevation to a horizontal position above the tongue. In case of CPX patients mRNA was also identified in the frenulum area of the base of the tongue which is communicated with ankyglossia. However, they completed their study with the CPX phenotype, TBX22 is completely reliable gene factor (Braybrook et al., 2002).

In a study also executed DNA marker linkage of a large British Columbia (B.C.) Native family with CPX found DXYS12 and DXS17 was responsible gene for CPX which were located to theXq21.3-q22 region (Gorski et al., 1992). TGFB3 rs2300607 (IVSI+ 5321) gene is associated with non syndromic CLP and may be a good screening marker for non syndromic CLP (Singh et al., 2011).

In a study assessing various factors affecting degree of malocclusion as favorable and unfavorable dental arch relationship of Japanese unilateral CLP patients revealed, clefts patients tend to develop unfavorable dental arch relationship not only as an effect of primary surgery but also due to a genetic influence of family history of class III (Alam et al., 2008)

The results of literature survey of involvement of gene involvement in CLP patients are shown in **Table 2.1**

Table 2.1: Gene involvement in CLP patient (literature survey)

Author & year	Type of cleft	Susceptible loci/locus	Chromosomic location	Mutation identified	Association
Carinci et al. (2007)	NS CL+-P	OFC1	6p24-p23	Occur	
		OFC2	2p13		Found
		OFC3	19q13.2		Found
		OFC4	4q21-q31		Found
		OFC5/MSX1	4q16	Occur	
		OFC6/IRF6	1q32.3-q41	Occur	
		OFC7/PVRL1	11q23.3	Occur	
		OFC8/TP73L	3q28	Occur	
		OFC9	13q33.1-q34		
		OFC10/SUMOL	2q33		
		MTHFR	1q36	Occur	
		TGFB3	14q24		Found
		RARA	17q21.1		Found
	CPI		2q32	Occur	
	CPX	TBX22	X 49.0	Occur	
Tudose&Bara(2008)	CL+-P	OFC1	6p24.3		
		OFC2-TGFA	2p13	Occur	Found
Rajion&Alwi(2007)	CL+-P	TGFA	2p13	Occur	Found
		TGFB2	1q41		Not found
		TGFB3	14q24	Occur	Found
		MSX1	4q25	Occur	Found

		MTHFR	1q36	Occur	Found
		BCL3	19q13.2		
		RARA	17q21-q24		Found
Kohli & Kohli (2012)	S CLP	TBX22	Xq21	Occur	
		PVRL1	11q23	Occur	Found
		IRF6	1q32	Occur	
	NS CLP	TGFA	2p13		Found
		MSX1	4p26	Occur	Found
		MTHFR	1p36		Found
		TGFB3	14q24		Found
		SATB2	2q32	Occur	
		ACOD4	4q21	Occur	
		CLPTM1	19q13	Occur	
			6p23	Occur	
Chevrier et al.(2006) [6]	NS CLP	MTHFR			
Jugessur et al. (2003)	CP	TGFB3	14q24		Not found
		MSX1	4p16		Found
		TGFA	2p13		Found
	CL+-P	TGFB3	14q24		Little association found
		MSX1	4p13		Little association found
		TGFA	2p13		Little association

					found
Marcano et al (2004)	CPX	TBX22		Occur	
Braybrook et al. (2002)	CPX	TBX22	Xq21	Occur	
Gorski et al. (1992)	CPX	DXYS1	Xq21.3	Not occur	
		PGK1	Xq13	Occur	
Singh et al. (2011)	NS CLP	TGFB3 rs2300607	14q24	occur	

In all-purpose, the genetic cause of CLP is still controversial because of genetic intricacy of clefting. Consequences from earlier studies support the presence of heterogeneity among populations and the presence of multiple genes concerned in the etiology of CLP. Furthermore, current scientific advances in gene manipulation promises a motivating time ahead for CLP research

2.5.2 Environmental Factors

The association of environmental factor in clefting was forecasted when Warkany and colleagues found that there was a significant association between cleft palate and nutritional deficiency (Warkany et al., 1943). The other predictable factors that cause clefts comprise maternal alcohol and cigarette use (Wyszynski and Beaty, 1996).

Smoking

Association between maternal smoking and CLP thought to be significant and it can increase risk for CLP (Little et al., 2004; Shi et al., 2009). Smoking may raise the possibility of genes in certain metabolic pathways which may have a role in the development of CLP, namely fetal glutathione s-transferase theta 1 (GSTT1) (van Rooij et al., 2001; Shi et al., 2007). Furthermore, van Rooij and co-workers found that the combination with smoking and GSTT1 could increase the risk of CLP (van Rooij et al., 2001). Beaty et al reported the risk of CLP increased by 7.16 times in maternal smoking and infant with MSX1 genotype (Beaty et al., 2002).

Alcohol use

Heavy maternal drinking will cause fetal alcohol syndrome. Apart from that, it also will increase the risk of CLP for the baby. Maternal drinking will increase risk of CLP from 1.5 to 4.7 times in a dose dependent manner (Munger et al., 1996). Similar results have been reported by Shaw and Lammer and found that mothers who consumed more than five drinks per occasion had a 3.4 times the risk of CLP developing in their offspring (Shaw and Lammer, 1999). However, low level of alcohol consumption did not seem to increase the risk of OFC (Natsume et al., 2000).

Multivitamins use

The risk of CLP could be tripled if the vitamin supplements were not taken during early pregnancy (Shaw et al., 2002). In a meta-analysis, multivitamins use was associated with a 25% reduction in birth prevalence of OFC (Johnson and Little, 2008). Data suggest that a possible interaction between maternal hyperthermia during pregnancy and the use of vitamin supplements will diminish the increased risk for OFC associated with hyperthermia (Botto et al., 2002).

Folic acid deficiency in animal experiments can cause clefts (Asling et al., 1960). It is also associated with increased risk of CLP in humans (Hernandez et al., 2000). The true mechanisms in human cleft disorders are uncertain however Bliek et al reported that folate deficiency disturbs normal cell development (Bliek et al., 2008). In addition, the risk of CLP increased in folic acid deficiency with the background of TGFA Taq1 C2 genotype in humans (Jugessur et al., 2003). The intake of folic acid can reduce the risk of OFC

(Badovinac et al., 2007; Wilcox et al., 2007). However, only high dose of supplementary intake of folic acid (10mg/d) could reduce about 65% the risk of CLP significantly (Tolarova and Harris, 1995).

Vitamin B6 deficiency, increased serum concentration of homocysteine in blood and zinc deficiency also associated with increased risk of orofacial clefts. Low level of vitamin B6 was found in Netherland populations (Wong et al., 1999) and in Philippines populations (Munger et al., 2004) and it was associated with OFCin that populations. Among Asian, vitamin B6 deficiency is common due to high intake of polished rice and they seem to have high rate of cleft lip, CLP and cleft palate alone (Munger et al., 2004).

Wong et al and van Rooij et al reported that high concentration of homocysteine found in mother's blood of infants with cleft lip, CLP or cleft palate alone (Wong et al., 1999; van Rooij et al., 2001). Besides that, zinc is also essential for fetal development. In animal experiments, zinc deficiency can cause isolated cleft palate and other malformations (Warkany and Petering, 1972). In Netherland population, researchers found low concentration of zinc in the mother's blood of children with cleft lip, CLP or cleft palate alone (Krapels et al., 2004) as well as the same result in the Philippines population (Tamura et al., 2005).

2.6 Problems associated with CLP

CLP affected patients suffer a multitude of problems, and alleviating the functional and aesthetic consequences of CLP is particularly challenging.

Patients with CLP may demonstrate various clinical problems including

1. Dental
2. Esthetic
3. Feeding
4. Speech

5. Hearing
6. Psychological (Cassolato et al., 2009)

Dental Problems

This part has been given in details on 2.7

Esthetic Problems:

1. The orofacial structure may be malformed and congenitally missing.

2. Deformities of the nose can also occur (Cunningham and Jerome, 1997).

Feeding problem

In CLP babies, feeding is very difficult due to communication between oral cavity and nasal cavity as the underdeveloped musculature is not properly oriented to produce the necessary negative pressure in their mouth, making sucking ineffective. This problem is managed through the use of specially designed nipples that are elongated and extend further into the baby's mouth. Positioning of the baby that is slightly more upright also ensures minimal nasal regurgitation.

Speech Problem

Speech defects in CLP patients are mainly due to velopharyngeal insufficiency, where the soft palate is not able to make an adequate contact with the back of the pharynx to close off the nasal airway. It can also be secondary to poor hearing. It is generally accepted that early closure of palate leads to improved speech results; however, late repair leads to improved maxillofacial growth, hence giving rise to the controversy in timing of palatoplasty. Currently, the recommendations are to close the palate by approximately 12 months of age (Senders and Sykes 1993). If the child is healthy and can tolerate surgery sooner, satisfactory