A PILOT STUDY OF RISK FACTORS IN CLEFT LIP/PALATE PATIENTS IN KELANTAN

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BAHAGIAN PENYELIDIKAN & PEMBANGUNAN

CANSELORI

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Laporan Akhir Projek Penyelidikan Jangka Pendek

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3) **Tajuk Projek:** A PILOT STUDY OF RISK FACTORS IN CLEFT LIP/PALATE PATIENTS IN KELANTAN

4) (a) **Penemuan Projek/Abstrak**

(Perlu disediakan makluman di antara 100 - 200 perkataan di dalam Bahasa Malaysia dan Bahasa Inggeris Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).

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(ABSTRACT)

Introduction: The risks of non-syndromic cleft lip with or without cleft palate and isolated cleft palate (CLP) are influenced by variations at several loci of the gene and these loci interact with environmental factors to determine disease risk. **Objective:** The aim of the study is to establish the relationship between environmental risk factors and incidence of cleft lip and palate. This finding will provide a base for further research activities in finding specific genetic factors that are sensitive to the risk factors. **Methodology:** This is a case controlled study of non-syndromic CLP patients attending combined clinic in Kota Bharu and patients attending outpatient clinic in HUSM. Information was obtained by interviewing parents using questionnaires. The information in the questionnaire includes paternal & maternal smoking habit, amount of tobacco used and general aspects like age, gender, position in the family, type and location of cleft. Other details include genetic consideration like consanguinity of parents and trends of occurrence in family members. Some environmental factors such as area of residence, birth dates, maternal problems, use of complementary medicine and diseases during pregnancy are explored. Details of socio-economic status are also obtained. 201 CLP patients and 212 controls were interviewed. The age of the control group was restricted to age of cleft patients. Univariate and multiple logistic regression analysis were used to analyze the data. **Results:** More than 90% of the subjects are Malays from lower socio-economic status. It was found that demographically there are variations to risks of non-syndromic CLP. People from Tanah Merah and Tumpat have 8.74-fold increased risk compared to people from Kota Bharu. There is an association between passive smokers and CLP (OR) = 2.45 (95% CI: 1.52, 3.94). Maternal and paternal history of cleft, occupation of father and position of child in the family increases the risk of CLP (p=0.009). **Conclusion** The study suggested that there are some geographical variations in the risk of CLP. Maternal exposure to cigarette smoke (passive smokers) showed increased risk of CLP. The seventh child and above have increased risk of CLP. This study was supported by the USM Short Term Grant: 304/PPSG/6131163

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(b) **Senaraikan Kata Kunci yang digunakan di dalam abstrak:**

Bahasa Malaysia	**Bahasa Inggeris**
.....	RISK FACTORS NON-SYNDROMIC
.....	CLEFT LIP/PALATE SOCIO-ECONOMIC
.....	STATUS GEOGRAPHICAL VARIATION
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5) Output Dan Faedah Projek

(a) Penerbitan *(termasuk laporan/kertas seminar)*
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbit/dibentangkan).

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DIBENTANGKAN DALAM BENTUK 'ORAL PRESENTATION' DI 'INTERNATIONAL ASSOCIATION FOR DENTAL RESEARCH CONFERENCE'

TARIKH : 21 FEBRUARI 2004

TEMPAT : UNIVERSITI MALAYA, KUALA LUMPUR

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(b) Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftaran Paten.
(Jika ada dan jika perlu, sila gunakan kertas berasingan)

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(c) Latihan Gunatenaga Manusia

i) Pelajar Siswazah DR. AYU ABDULLAH .....

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ii) Pelajar Prasiswazah: .....

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iii) Lain-Lain : .....

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6. **Peralatan Yang Telah Dibeli:**

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UNTUK KEGUNAAN JAWATANKUASA PENYELIDIKAN UNIVERSITI

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Final report satisfactory.
Forwards to me for publication
after adjustment for journal
format.

T/TANGAN PENGERUSI
J/K PENYELIDIKAN
PUSAT PENGAJIAN

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ABSTRACT

Introduction: About 2-3% of pregnancies result in neonates with serious genetic diseases or birth defects causing disabilities, mental retardation, and in some cases early death. Non-syndromic cleft lip and palate (CLP) is a common craniofacial anomaly affecting between 1in 700 and 1 in 1000 births in the UK and USA respectively. In Malaysia, studies of school children showed the incidence of 1 in every 941 subjects examined. The risks of non-syndromic cleft lip with or without cleft palate and isolated cleft palate (CLP) are influenced by variations at several loci of the gene and these loci interact with environmental factors to determine disease risk.

Objective: The aim of the study is to establish the relationship between risk factors and incidence of cleft lip and palate and further enhance research activities in finding specific genetic factors that are sensitive to the risk factors.

Methodology: This is a case controlled study of non-syndromic CLP patients attending combined clinic in Kota Bharu and patients attending outpatient clinic in HUSM. Information was obtained by interviewing parents using questionnaires. Patients attending CLP clinic were first interviewed. The age of the control group was restricted to age. Univariate and multiple logistic regression analysis were used to analyze the data.

Results: More than 90% of the subjects are Malays from lower socio-economic status. It was found that demographically there are variations to risks of non-syndromic CLP. People from Tanah Merah and Tumpat are 8.74-fold increase risk compared to people from Kota Bharu. There is association between passive smokers and CLP (OR) = 2.45 (95% CI: 1.52, 3.94). Maternal and paternal history of cleft, occupation of father and position of child in the family increases the risk of CLP (p=0.009).

Discussion: The study suggested that there are some geographical variations in the risk of CLP. Copper et al (2000) believed that the variation could indicate environmental factors such as seasonal availability of nutrients, infectious disease circle and vitamin deficiency during pregnancy. Exposure to cigarette smoke (passive smokers) is shown to increase the risk of CLP. This is consistent with the findings of Wyszynski et al (1997). The seventh child and above have increased risk of CLP. This could be due to increased maternal age as consistently found in other studies.

Conclusion: This analysis suggests a small but statistically significant association between maternal cigarette smoking during the first trimester of gestation and increased risk of having child with CLP.

1. INTRODUCTION

Approximately 2-3% of all pregnancies result in a neonate with a serious genetic disease or a birth defect that can cause disabilities, mental retardation, and in some cases early death[1]. The occurrence of cleft lip with or without cleft palate is the most common dentofacial anomaly in the newborn. In the United States[2], it was found that 1 out of 500 birth has the disorder while in Malaysia, studies done in school children in 1997[3] showed the incidence of 1 in every 941 subjects examined. Such handicapping anomalies of the lip, palate or both have devastating psychosocial impacts[4] on an individual's life. This is because general facial appearance represents the identity of the individual. It is how we see ourselves and how others see us. It contributes to one's self esteem and to a larger extent affects one's self-confidence.

The risks of nonsyndromic cleft lip with or without cleft palate and isolated cleft palate are influenced by variation at several loci of the gene and that these loci interact with environmental factors to determine disease risk [5]. Cleft lip and palate also affect feeding, hearing, speech and eventually one's quality of life[6]. The treatment and management of such anomalies definitely require the expertise of a well-coordinated multidisciplinary team that comprise of the pediatrician, pedodontist, geneticist, anesthesiologist, neurosurgeon, oral maxillofacial surgeon, plastic surgeon, otolaryngologist, orthodontist, prosthodontist, speech therapist, community dentist and community nurse. This multidisciplinary approach is more meaningful but obviously involves a substantial amount of monetary allocations.

Realizing the multifaceted aspects of this handicapping anomaly, a local study is deemed necessary to look into various contributing risk factors. It is hoped that such efforts can shed some light into necessary work in establishing the polymorphic genetic marker and preventative measures that can be taken to reduce the occurrence of such deformities.

2. OBJECTIVES

2.1 General Objective:

The study is to look into the possible risk factors and confounding risk factors such as the environment, familial and drug induced tendencies, socio economic status and sex ratio with cleft lip and palate. The data obtained will be a valuable source of information for further enhancement of research activities at the Center of Craniofacial Sciences particularly into the more advanced molecular profile and genetic studies.

2.2 Specific Objectives

The aims of the study are to:

1. establish the relationship between risk factors and incidence of cleft lip and palate.

2. enhance research activities in finding specific genetic factors that are sensitive to the risk factors.

3. METHODOLOGY

3.1 Research question :

What are the most probable local risk factors that contribute to cleft lip and palate ?

3.2 Study population:

Non-syndromic cleft lip with or without cleft palate patients attending Combine Clinic at Jalan Mahmood Dental Clinic, Kota Bharu will be defined as case. Cases confirmed by pedeatric genetist. Age restriction method was applied to control group without cleft attending Hospital Universiti Sains Malaysia (HUSM) outpatient clinic.

3.3 Sample size calculation:

The calculation was done using Power and sample size soft ware, based on different of two proportion.

Ratio of case to control is	: 1:1
Difference in proportion	: 10%
Level of significant (α)	: 0.05
Power of the study (1 - β)	: 80%
Required sample size for case	: 200
Required sample size for control	: 200

3.4 Sampling Method:

This is a case control study. Stratified random sampling of children attending combined clinic and random sampling of children attending outpatient clinic at HUSM. Consent from subjects will be obtained prior to the study.

3.5 Data collection

The required information in the questionnaire will be obtained through parental or other family members interview. Previous treatment records will also be reviewed. Patients attending cleft lip and palate clinic were first interviewed and the control group was restricted to the age.

The information in the questionnaire includes paternal smoking habit, maternal smoking habit, measurement of tobacco used and general aspects like age, gender, type of cleft and position of the defect. It will also include genetic consideration like consanguinity of parents and trends of occurrence in family members. Some environmental factors such as area of residence, birth date, maternal problems and diseases during pregnancy will also be enquired. Details of socio-economic status will also be explored.

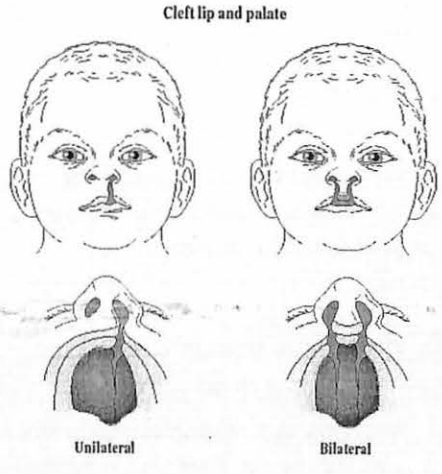
3.6 Method of statistical analysis:

Univariate analysis is used by using Student's t test for comparison of the means and chi square test for testing the significant association between categorical variables. Variables, which are found to be statistically significant in univariate analysis, will be included in Multivariate analysis. Multiple Logistic Regression is used to determine the associated factors to risk of developing cleft lip and palate. Results are presented in univariate analysis and adjusted odds ratio with 95% confidence interval and corresponding p value. Level of significant (α) are set at 0.05 with two-tailed fashion.

4. LITERATURE REVIEW

4.1 Epidemiology of cleft lip and palate

Cleft lip with or without cleft palate is one of the most common physical abnormalities present at birth. Cleft lip affects the upper lip and cleft palate the roof of the mouth. Cleft lip is also known as 'hare lip'. It occurs when the tissues that form the upper lip do not join in the middle. Instead, a gap occurs in the lip, usually below one or other nostril. This is called 'unilateral cleft lip'. Sometimes two gaps occur in the upper lip, each below a nostril, which is referred to as 'bilateral cleft lip'. Cleft palate occurs when the tissues that form the palate do not join in the middle of the roof of the mouth, which leaves a connection between the mouth and the nose.



Results of prevalence studies of cleft lip and palate have been not consistent. It varies between the ethnicity and geographic areas. It has been reported as 1.12 per 1000 live births in American white[7] and 0.54 per 1000 birth in nonwhite[8]. An epidemiological study of oral cleft in a large Latin American sample yielded a prevalence of 0.87 per 1000 live births for cleft lip with or without cleft palate[9]. In Malaysia, studies among school children in 1977 reported an incidence of 1 in every 941 subjects examined[3] while descriptive epidemiological study of nonsyndromic cleft lip with or without cleft palate in Shanghai, China from 1980 to 1989 revealed a prevalence of 1.2 per 1000 live births[10].

However, a peer-reviewed literature[11] in 1998 agreed that while there are ethnic and geographic differences, the average birth prevalence of orofacial clefting in western population is often quoted as 1:1000 total births. It is also agreed that the Asian origin have a higher incidence than the Caucasian which in turn have a higher incidence than the African population.

Gender is involved in the distribution of clefting. WHO report on global strategies to reduce the health-care burden of the craniofacial anomalies suggested that cleft lip and palate are more predominance in male whereas the cleft palate alone are more frequent in female[11] this is similar to the finding of epidemiologic studies conducted in Shanghai, China[10], Philippines[12], Latin America[9], Iran[13] and Japan [14]. It is possible because females close their palate later in development[9]. It is also reported that female were more severely affected[10].

4.2 Etiology of cleft lip and palate

The lips and palate originate from three areas of the baby's developing face. These areas are also called prominences. They are the Central or "Frontal Nasal" prominence, the Left "Maxillary" prominence, and the Right "Maxillary" prominence. The Central prominence will grow and become the infant's forehead, nose, middle portion of the upper lip (called the philtrum or Cupid's bow) and the primary palate, which is the part of the upper jaw that holds the middle four teeth. The Left and Right "Maxillary" prominences will grow and become the lower face, the lower lip and jaw, all but the middle portion of the upper lip and jaw, and the "secondary" palate (this is the part of the palate from behind the middle four upper teeth to the back of the mouth.). Normally, the three prominences on the child's developing face will grow towards the center of the face and fuse together during the sixth to thirteenth weeks of pregnancy. When this happens correctly the lips, mouth, and palate of the child develop normally. However, sometimes this growth process is disturbed in some way, preventing the prominences from meeting. When growth is disturbed, the lips and mouth do not form properly, leaving a cleft in the lip.

The causes of cleft lip and palate remains uncertain. Both genetics and environmental factors are considered instrumental in causing clefts [5,10, 15, 16]. When the face and skull of a foetus form, the upper lip and palate develop from tissues that lie on either side of the tongue. In normal development, these tissues grow towards each other to meet in the middle and so form a complete palate and upper lip. In cleft lip, it seems that the tissues that form the upper lip grow normally but simply fail to join up in the middle of the face. In cleft palate it appears that some obstruction may prevent the tissues that form the palate from joining.

Some evidence indicates genetic factors may be involved. If a close relative has a very severe cleft lip and palate, there is a higher chance of a baby being born with these abnormalities[13, 14, 17]. In relation to genetic factors, consanguineous marriage had been explored and reported result have shown both significant [13, 17] and non-significant association [18, 19].

There are also conflicting evidence of maternal age and cleft lip and palate. Five studies have shown that cleft lip and palate are more common in the children of older couples [9,20, 21,22, 23, 24]. However, Czeizal A. et al. found not association [21]. There are evidence showing that lifestyle during pregnancy can cause a cleft lip or palate, but nevertheless it should be strict about known dangers such as drinking alcohol, cigarette smoking and folic acid deficiency[24,.25].

4.3 Classification and distribution of cleft lip and palate

In 1942, Fogh-Andersen has classified orofacial cleft as cleft lip with or without cleft palate and isolated cleft palate [26]. There are 4 categories for organizing cleft palate cases based on the variations of their supposed inheritance patterns. These categories are as follows :

a. Nonsyndromic cleft lip with or without cleft palate

b. Nonsyndromic cleft palate

c. Syndromic cleft lip with or without cleft palate

d. .Syndromic cleft palate

5. RESULTS

5.1 Profile of study group (Socio-demographic characteristic)

PROFILE	CASE	CONTROL	TOTAL
GENDER:			
Male	100	111	211
Female	101	101	202
TOTAL	201	212	413
ETHNICITY			
Malay	201	188	389
Chinese	-	15	15
Others	-	9	9
TOTAL	201	212	413
SOCIO-ECONOMIC			
Class I	8 (1.9 %)		
Class II	96 (23.3 %)		
Class III	22 (5.3 %)		
Class IV	287 (69.5 %)		
TOTAL	413		

Total number of subjects is 413 with 201 and 212 in case and control group respectively. The numbers of male and female is almost the same. 100% of case group are Malay ethnicity. Majority of subjects is from Registrar general Class IV socio-economic status.

5.2 Types of cleft

Type of Cleft	Frequency	Percent	Cumulative
Unilateral Cleft Lip	37	18.4 %	18.4 %
Cleft Palate	44	21.9 %	40.3 %
Cleft lip bilateral	4	2.0 %	42.3 %
Unilateral Cleft lip and palate	85	42.3 %	84.6 %
Complete bilateral cleft	31	15.4 %	100 %

From 201 cases selected it was found that majority suffered from unilateral cleft lip and palate (42.5%)

5.3 Demographic variation, Position in Family , Age and Risk of Oral Facial Cleft

Variable	Adjusted OR	95% CI	p Value
Place			
Kota Bharu, Bachok	1.0	-	-
Pasir Puteh, Others	2.50	(1.46, 4.28)	0.001
Pasir Mas	4.44	(1.56, 12.65)	0.005
Tumpat, Tanah Merah	8.74	(3.59, 21.31)	0.000
Position in Family			
Child number 1 to 6	1	-	-
Child number 7 to 14	2.51	(1.25, 5.02)	0.009
Age	1.08	(1.03, 1.13)	0.002

Results showed an association between geographical variation and increased risk of cleft lip and palate, whereby people from Tumpat and Tanah Merah are at 8.74 times (p=0.000) increase risk of oral facial cleft from those from Kota Bharu. While those from Pasir Mas are 4.44 times (p=0.005) and Pasir Puteh are 2.50 times (p=0.001) at risk of oral facial cleft. Interestingly it was also found that child born after the sixth sibling is at 2.51 times (p=0.009) increased risk of oral facial cleft. Older patients are of 1.08 times (p=0.002) increased risk of oral facial cleft.

5.4 Pasive smoker, Maternal & Paternal History of Cleft Socio-economic Status and Risk of Oral Facial Cleft

Variable	Adjusted OR	95% CI	p Value
Passive Smoker			
No	1.0	-	-
Yes	2.45	(1.52, 3.94)	0.000
Maternal History of Cleft			
No	1.0	-	-
Yes	10.15	(2.79, 36.92)	0.000
Paternal History of Cleft			
No	1	-	-
Yes	18.49	(2.34, 145.79)	0.006
Socio-economic satus			
Registrar General Class II	1	-	-
Registrar General Class IV	3.97	(1.83, 8.64)	0.001

Mothers who are exposed to cigarette smoke of their husband and family members are 2.45 times (p=0.000) increased risk of giving born to baby with oral facial cleft compared to those whose are not exposed to cigarette smoke of their family members. Maternal history of cleft and paternal history of cleft showed 10.15 time (p=0.000) and 18.49 times (p=0.009) times increased risk of oral facial cleft respectively. Child born to family of low socio-economic status (Registrar General Classification, Class IV) is 3.97 times increased risk of born with oral facial cleft compared to the child born from other socio-economic status.

5.5 Variables that are not significant

OTHER VARIABLES
• History & frequency of miscarriage
•Taking medication during pregnancy
•Taking traditional medicine (jamu)
•Mother suffering from any illness
•History of trauma during pregnancy
• Consanguineous marriage
•Mother age at birth
•Father age at birth
•Birth weight
•Mother occupation
•Mother smoking habit
•Type of cleft

6. DISCUSSION

Demographically there is a variation in risk of developing CLP. From the study it was found that those born in Tumpat and Tanah Merah are 8.74 more at risk than those from Kota Bharu and Bachok. Copper et al (2000) believed the variation could indicate environmental factors such as seasonal availability of nutrients, infectious disease circle and vitamin deficiency during pregnancy.

Exposure to cigarette smoke (passive smokers) is shown to increase the risk of CLP. This is consistent with the findings of Wyszynski et al (1997).

lThe seventh child and above have increased risk of CLP. This could be due to increased maternal age as consistently found in other studies.

7. CONCLUSION

lThis analysis suggests a small but statistically significant association between exposure to cigarette smoke during pregnancy, geographical variation, position of child in the family, paternal and maternal history of CLP and increased risk of having child with CLP.

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