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A case-control study of environmental exposures for nonsyndromic cleft of the lip and/or palate in eastern Guangdong, China

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ABSTRACT

Objective: To study the relationship between environmental factors and nonsyndromic cleft of the lip and/or palate (NSCLP) in eastern Guangdong for the prevention of NSCLP.
Methods: A 1:1 retrospective case-control study was carried out. Data from 479 children with NSCLP who accepted comprehensive care in our center were recruited as cases from April 2010 to April 2013. An equal number of controls were recruited from pediatrics during the same period. Then we conducted face-to-face interviews with both parents using a structural questionnaire to identify the relationship between NSCLP and environmental risk factors.
Results: Univariate Chi-square analysis identified 23 factors ($P < 0.05$) as being significantly related to NSCLP. Stepwise multiple logistic regression analyses demonstrated that there were 16 factors significantly associated with this disease. Being male (OR = 0.609), parental childbearing age of 25–29 years (OR_{father} = 0.633; OR_{mother} = 0.469), higher parental education level (high school or greater) and folic acid supplementation (OR = 0.360) were protective factors against NSCLP. However, positive family history of NSCLP (OR = 54.132), positive maternal abortion history (OR = 3.698), high or low parental age at time of childbirth, poor maternal education level (primary school) (OR = 2.258), maternal common cold during pregnancy (OR = 1.464), and drug use during pregnancy (OR = 3.364) were significant risk factors for NSCLP.
Conclusion: The findings are beneficial for researchers to understand the etiology of NSCLP and to lay a solid foundation for the prevention of NSCLP in eastern Guangdong through educational programs to teach parents about the benefits of folic acid supplementation, adequate parental age at childbirth (25–29 years), higher parental education level (high school or higher), and the dangers of common cold and drug use during the first trimester of pregnancy, positive family history and maternal abortion history.
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1. Introduction

Cleft lip (*cheiloschisis*) and/or cleft palate (*palatoschisis*) are common congenital defects worldwide, which can be divided into two groups: syndromic cleft lip and/or palate (CLP) and nonsyndromic CLP (NSCLP) based on specific clinical symptoms and different mechanisms underlying the defect. Syndromic CLP is associated with monogenic diseases or chromosomal disorders, as well as environmental influences. There are more than 200 different conditions, including CLP, that are characterized by a specific malformation pattern combined with other associated anomalies [1], such as van der Woude syndrome (*IRF6*) [2], Kallmann syndrome (*FGFR1*) [3] and X-linked clefting and ankyloglossia (*TBX22*) [4]. In contrast, NSCLP is a multifactorial disease in which the mechanisms remain largely unknown, even if most researchers assume that the interaction between different environmental risk factors and virulent genes give rise to the disease. NSCLP is able to be classified as nonsyndromic cleft lip with or without palate (CL/P) and nonsyndrormic cleft palate only (CPO); these two diseases have their own genetic background and environmental risk factors [5,6]. In addition, more recent epidemiological and genetic data suggests that CL/P should be further subdivided into cleft lip (CL) and cleft lip and palate (CL + P) [7].

Owing to ethnic or geographic variation, the global incidence of CLP is about 1/700, with Asia (China and Japan) and India have the highest prevalence with incidences reaching 1/500 [8]. Although this condition does not cause mortality in developed countries, it can profoundly affect the patients' quality of life. For instance, affected patients require multidisciplinary care from childhood to adulthood to ameliorate effects on speech, feeding, hearing, aesthetics and self-esteem, which can prove difficult for many

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patients. To some extent, CLP patients are largely ignored in society [9,10]. The solution for these problems is for researchers to disclose the etiology of this disease and to design protocols based on minimizing environmental risk factors; hence, increasing the prevention of NSCLP.

To date, most epidemiological studies of NSCLP derive from studies conducted in western countries. To reduce the incidence of NSCLP in developing countries researchers need to identify environmental factors that increase the risk of NSCLP, and then implement efficient measures to prevent disease occurrence. The incidence of CLP in Guangdong province has been reported as 1:793 of the population [11]. Eastern Guangdong mainly consists of two populations—Teochew and Hakka, who have excellent traditional cultures and long histories. While the dialects spoken by these two populations are different, their lifestyles are very similar. This area is recognized as high risk for NSCLP in Guangdong province. Hence, for the descendent ethnic continuity, it is important to examine the environmental risk factors prevalent for these populations to better understand NSCLP in this region.

At present, it is widely believed that birth characteristics such as, low or high parental childbearing age, birth season, and blood type influence the risk of NSCLP. Furthermore, several environmental factors present during the first trimester of pregnancy have also been proven to heavily influence the risk of NSCLP and these include: tobacco, alcohol and drug use, radiation exposure, and viral infection [12–18]. On the other hand, studies have shown that folic acid, vitamin, and zinc supplementation in the first trimester of pregnancy can prevent NSCLP [19–22]. Our previous assessed the environmental risk factors for NSCLP in Guangdong province [23]; however, because populations in different areas may be exposed to different environmental risk factors, this paper targeted children affected with NSCLP in eastern Guangdong, and assessed their risk by surveying parents with a structural questionnaire. The results of this study will facilitate the implementation of targeted measures to prevent this disease in eastern Guangdong.

2. Methods

2.1. Study subjects

Our cleft lip and palate treatment center is located in eastern Guangdong, and cooperates with the Li Ka Shing foundation to provide free comprehensive care for CLP patients. Our center treats patients representing all socioeconomic backgrounds from eastern Guangdong, as well as other provinces. Informed consent was obtained from the parents of the NSCLP cases and control subjects prior to enrollment in the study. This study was approved by the ethics committee of The Second Affiliated Hospital of Shantou University Medical College.

2.2. Case-control selection

We selected NSCLP subjects diagnosed by a plastic surgery team and divided them into three groups: CL, CL + P and CPO. A 1:1 retrospective case-control study was performed.

2.2.1. Case-control selection

The affected children who accepted comprehensive care in our center were recruited as cases from April 2010 to April 2013. An equivalent number of control subjects were recruited from pediatrics during the same period so that the age difference between cases and controls was at most 1 month. To reduce recall bias of parents which increases with time, we selected children that were less than 5 years of age for the study. Subjects exhibiting the following conditions were excluded from the study: (1) syndromes or other congenital malformations; (2) children whose parents' recollections were so obscure that information was unreliable; (3) children with adoptive parents.

2.3. Data collection

We conducted face-to-face interviews with both parents using a structural questionnaire. Parents were asked general information about the children (the child's gender, birth date, blood type, family history). Parents were also questioned about their own sociodemographic characteristics, including: age, education, consanguinity, and maternal abortion history. The survey included questions relating to environmental factors such as tobacco, alcohol and drug use, folic acid intake, and common cold during the child subjects' gestation period.

Blood type was categorized as A, B, AB or O. The birth season was derived from the birth certificate with seasons represented by specific birth month: spring (March, April, May), summer (June, July, August), autumn (September, October, November) and winter (December, January, February). Childbearing age was recorded as $\leq$19 years, 20–24 years, 25–29 years, 30–34 years and $\geq$35 years. Education level of parents was categorized as: illiterate, primary school, middle school, high school, technical school, and junior college or higher. If mothers indicated that they had used drugs in the first trimester of pregnancy, they were asked to give more details about the drug name, dosage, and length of time used. Folic acid supplementation was similarly defined. The other variables were defined as "yes" or "no" dichotomized variables.

2.4. Statistical analysis

Statistical analyses were performed using the Statistical Product and Service Solutions 19.0 (SPSS 19.0 Inc, Chicago, IL, USA). First, chi-square tests were conducted to examine single factors. Then multiple logistic regression analyses with a stepwise regression procedure were conducted by entering ($\alpha = 0.10$) or excluding ($\alpha = 0.15$) all the significant environmental factors ($P < 0.05$) from the univariate analysis. Odds ratios (OR) were reported along with 95% confident intervals (CI). An OR with 95% CI that excluded CI = 1 was judged to be statistically significant.

3. Results

3.1. Descriptive analysis

A total of 958 patients (479 cases and 479 controls) were recruited for the study in accordance with the standards of case-control selection. Subjects with CL + P were the most common ($N = 268$), followed by CL ($N = 123$) and CPO ($N = 88$; Table 1). The mean age of subjects was 16.33 months for cases and 16.26 months for controls (Table 1).

3.2. Gender

Sexual distribution among the case and control groups is shown in Table 1. Chi-squared tests indicated that for CL + P, the number of

Table 1
Number of case-controls by sex and mean age.

	Male	Female	Total	Mean age (month)
Cases	269	210	479	16.33
CL + P	**174**	**94**	**268**	
CL	62	61	123	
CPO	33	55	88	
Controls	318	161	479	16.26

The bold values show the significant association between environmental risk factors and NSCLP.

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