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Original Article

Role of Environmental Factors in the Etiology of Non-syndromic Cleft Lip Palate

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Abstract

Aim: To assess the role of environmental factors such as smoking, alcohol, prescription of drugs or illness of mother and also socioeconomic status attribute to nonsyndromic cleft lip/palate (NSCL/P) and also to evaluate if vitamin supplements play a protective role against NSCL/P.

Materials and Methods: Data were collected using self-formulated questionnaire from a total of 250 mothers of which, 125 were mothers of children with NSCL/P who were undergoing treatment in various CL/P centers in and around Mangalore constituted the study group and 125 mothers of normal healthy children who were the outpatients with trauma or inpatients with bone fractures or under some other treatment in the hospital in and around Mangalore.

Results: There was a positive association between socioeconomic status and NSCL/P occurrence (odds ratio [OR]: 7.76, *P* = 0.000, confidence interval [CI]: 95%). Positive correlation was also seen for maternal exposure to passive smoking (OR: 1.97; CI: 95%, *P* = 0.008). In contrast no statistically significant results were found for history of occupational exposure (*P* = 0.122) maternal alcohol consumption (*P* = 0.498), active smoking (*P* = 0.498), maternal illnesses and drugs taken during pregnancy. It was also seen that vitamin supplementation played a protective role against NSCL/P (OR: 0.19, CI: 95%, *P* = 0.003).

Conclusion: NSCL/P is of multifactorial origin with both environmental risk factors and genetic predisposition concurrently playing a key role in the causation of the same. It can be concluded from our study that absence of maternal nutritional supplementation, maternal passive smoking and mothers of lower socioeconomic strata conferred greater susceptibility to the occurrence of NSCL/P in their offsprings.

Key words: Cleft lip/palate, Environmental factors, Nonsyndromic cleft lip/palate

INTRODUCTION

Craniofacial anomalies in particular cleft lip/palate (CL/P), are the major congenital defects, ranking with a worldwide preponderance of 1 in 700 births per year.[1] CL/P varies considerably in occurrence with wide variability across geographic origin, racial and ethnic groups as well as environmental exposures and socioeconomic status (SES). In general, Asian and American-Indian populations have the highest reported birth prevalence rates, often as high as 1/500, European-derived populations have intermediate prevalence rates at about 1/1000 and African-derived populations have the lowest prevalence rates at about 1/2500. Asian and American Indians having the highest rate and Africans the lowest.[2] They are immediately recognized disruptions of normal facial structures. Although not a major cause of mortality in developed countries, CL/P does cause considerable morbidity to affected children which goes beyond the obvious disfigurement of face and extends to repeated infections, social stigma, and mental impairment that affect the speech, hearing, and teeth formation.[3] These children are teased about their cleft-related features such as speech, teeth, and lip appearance, and lose self-confidence. Research has shown that attractive children are seen by others as brighter, as having more positive social behavior and receive more positive treatment than their less attractive cleft counterparts. These children suffer with emotional "burn out" in adolescence.[4]

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Numerous studies have construed that the etiology of nonsyndromic CL/P (NSCL/P) may be multifactorial in origin with both genetic and environmental causative factors. Environmental factors which are of greater preponderance mentioned in various studies are associated with lower SES,[5] maternal exposures to environmental factors like prescription of drugs which, include pseudoephedrine aspirin, ibuprofen, amphetamine, cocaine or ecstasy and cigarettes smoking;[6] alcohol,[7] and nutritional deficiency particularly folic acid[8] and certain illnesses of mother like ulcerative colitis,[9] and epilepsy,[10] during critical early period of pregnancy. There is a variation in infant mortality and access to care between and within countries, because of which some clefts remain unrepaired into adulthood. Hence for prevention, two things must be done: (1) Identify the etiology to take appropriate preventive measures; and (2) plan for quality of care. Worldwide research is required in developing and developed countries targeting common risk factors, which will not only analyze biological and social determinants of health but also determine other chronic health problems.

Therefore, the purpose of this study was to evaluate the environmental risk factors associated with the occurrence of NSCL with or without palate from various CL/P centers in Karnataka.

MATERIALS AND METHODS

Data were collected using self-formulated questionnaire (Figure 1) from a total of 250 mothers of which, 125 were mothers of children with CL/P who were undergoing treatment in various CL/P centers in and around Mangalore and 125 mothers of healthy children who were outpatients with trauma or inpatients with bone fractures or under some other treatment in the hospital in and around Mangalore. Children with no other malformations diagnosed by specialists confirming their nonsyndromic status were included in the study. Mothers of children with any other anomaly such as neural tube defects, monozygotic twins, various syndromes, and mothers not willing to answer the questionnaire were excluded from the study.

RESULTS

This study was conducted to assess the role of environmental factors in the causation of NSCL/P. This study was based on the data collected from 125 mothers of NSCL/P and 125 mothers of normal children, and it is a case-control study consisting of questionnaires answered by 250 mothers. We assessed the SES of case and controls using Kuppuswamy's

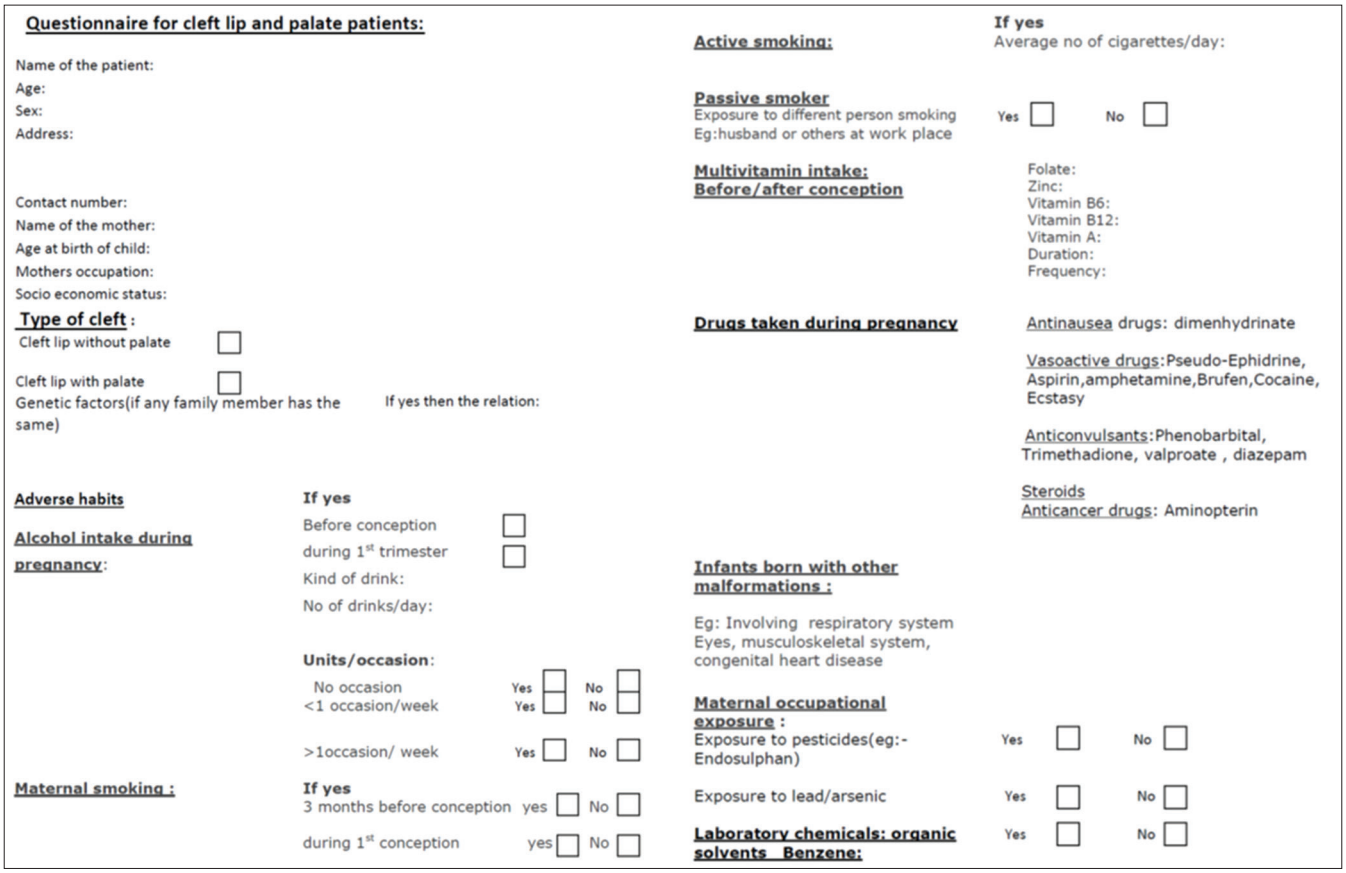

Figure 1: Questionnaire

scale taking into consideration education, income and occupation which showed that 2.4% of cases and 8.8% of controls were coming under upper middle class, 38.4% of cases and 63.2% of controls under middle/lower middle class, 57.6% cases that is the maximum number of cases and 27.2% of controls were under upper part of lower class, and 1.6% of cases and 0.8% of controls were coming under the lower class. The results for this were statistically significant ($P = 0.000$) showing that there is a strong tendency for lower SES group toward CL/P. Giving and odds ratio (OR) of 7.76 (2.03-29.65) at 95% confidence interval (CI) (Table 1).

Family history taken showed that 30.4% of the cases had a positive history in comparison to the controls who showed a negative history for the same. The difference is statistically significant ($P = 0.000$) showing that despite the negative family history of CL/P in the subjects, the offsprings still contracted the same suggesting the importance of environmental factors and genetic predisposition in the causation of NSCL/P. Alcohol consumption during pregnancy has been shown to cause CL/P.[7,13,7,22] Hence, we assessed alcohol consumption for 3 months of conception and if reported the number, times they drank/month, units they drank/occasion, and the kind of drink were ascertained. However, our study showed 1.6% consumed alcohol in the form of distilled spirits in the study group, whereas none of the controls consumed alcohol during the first trimester of pregnancy, therefore the result obtained was not statistically significant ($P = 0.498$).

Among the other causative factors most blamed is maternal smoking during the first trimester of pregnancy.[11,16,20,23] In our study only 1.6% of case mothers smoked which was statistically nonsignificant ($P = 0.498$).

Passive smoking at home or at work place also has been considered as one of the etiologic factors.[22,23] In our study, 59.2% of mothers in the study group were exposed to passive smoking as compared to 42.4% of control mothers and the results for this were statistically significant ($P = 0.008$) giving an OR of 1.97 (95% CI) these results confirm the role of tobacco in the etiology of NSCL/P (Table 2).

The previous studies proved that are drugs taken for various illnesses during embryogenesis are teratogenic,[12,14,24] however, in our study none of the cases gave a history of consuming any teratogenic drugs mentioned in questionnaire during the first trimester of pregnancy and also neither did the controls group gave any history of teratogenic drugs taken. The results showed no relation between drugs consumed during pregnancy and occurrence of NSCL/P.

None of the study population nor control group reported of any illnesses like epilepsy, ulcerative colitis, morning sickness or any other uneventful diseases during the first trimester of pregnancy so our study could not assess the relationship between the incidence of NSCL/P and the history of illness during pregnancy. In our exposure of mother to hazardous chemicals was assessed and we found 3.2% of mothers were exposed to various chemicals during the first trimester however the result was not statistically significant ($P = 0.122$), and it ruled out the role of exposure to chemicals in pregnancy as a causative factor for NSCL/P. Both case and control children were confirmed of syndromes, and our collected data through questionnaire showed the absence of any other malformations. Many previous studies have proved protective role of multivitamin on NSCL/P occurrence[5,7,13,15,26,27] and to know the role of vitamins in protection against NSCL/P in our population, we interviewed the case and control mothers about consumption of multivitamin and folic acid in particular and it showed that 85.6% of 125 mothers of cases as compared to 96.8% of control mothers had taken multivitamin supplements. 14.4% of the cases did not take any supplements as compared to 3.2% of controls (OR = 0.19, 95% CI: 0.06-0.59) and this was statistically significant ($P = 0.003$) showing more risk toward the ones who had not consumed the supplement. Hence, results of our study showed the statistically significant relation between the occurrence of NSCL/P with the SES of the mothers and passive exposure of mother to tobacco smoking. Furthermore, it proves a statistically significant protective role of vitamin supplements against NSCL/P when taken during the 1st trimester as shown in control group (OR: 0.19).

Table 1: Socioeconomic status and cleft lip palate

SES	Group *n* (%)		Total *n* (%)
	Cases	Controls	
Upper middle	3 (2.4)	11 (8.8)	14 (5.6)
Middle/lower middle	48 (38.4)	79 (63.2)	127 (50.8)
Lower/upper lower	72 (57.6)	34 (27.2)	106 (42.4)
Lower	2 (1.6)	1 (0.8)	3 (1.2)
Total	125 (100)	125 (100)	250 (100)

SES: Socioeconomic status

Table 2: Passive smoking and cleft lip palate

Passive smoking	Group *n* (%)		Total *n* (%)
	Cases	Controls	
Yes	74 (59.2)	53 (42.4)	127 (50.8)
No	51 (40.8)	72 (57.6)	123 (49.2)
Total	125 (100)	125 (100)	250 (100)

χ^2 value= 7.058, df=1, p=0.008, significant, OR=1.97. OR: Odds ratio

DISCUSSION

Orofacial defects are the most common developmental deformities seen worldwide and they are undoubtedly

an important oral health issue due to their impact on the quality of life, function and also clinical impacts over many years. Etiology of this defect is said to be complex and incompletely understood, but is generally considered to be determined by genetic and environmental factors.[28] Many researches recently conducted show an interrelationship between environmental risk factors that the mother is exposed to during the critical period of pregnancy among which the crucial ones are found to be: Drinking alcohol,[22] smoking,[11,16,20] diseases of mother,[9,10,18] working in harmful environment,[12,29,30] use of drugs[14,31] during first trimester and deficiency of folic acid,[8,35] because of which clefts have been growing in numbers. Hence, the purpose of this study was to evaluate environmental risk factors associated with the occurrence of this NSCL/P.

In this study, data were collected using self-formulated questionnaire from a total of 250 mothers of which, 125 were mothers of children with the defect who were undergoing treatment in various CL/P centers in and around Mangalore and 125 mothers of healthy children from the hospitals in and around Mangalore.

In our study, both case and control mothers were interviewed for the presence of any other congenital malformations in children and confirmed that none of the cases had any other malformations other than CL/P and the controls were normal and also not associated with any malformations. This was done mainly to rule out any syndrome associated as approximately 70% of all CL/P cases occur as isolated, sporadic birth defects, known as NSCL/P, while the remaining 30% occur as a part of more than 300 different syndromes with the Mendelian inheritance pattern, in which CL/P is only one manifestation as mentioned by Sprintz *et al*.[32]

As SES is said to be associated with risks of neural tube defects, conotruncal defects, and orofacial clefts.[5,33,34] We assessed the SES of the cases and controls using Kuppuswamy's scale taking into consideration the income, occupation and education which showed that upper part of lower SES group, were at an increased risk of CL/P, than the higher socioeconomic groups which are in conformity with the previous studies relating low SES to CL/P occurrence.[5,33,34] Upper part of the lower socioeconomic group could be more prone because people in this group are less educated, have no good occupation and are unable to access and interpret health-related information, they also have more chances of workplace hazards exposure, poor living condition and also malnourishment.

In our study, only 30.4% of mothers of children with CL/P had a family history of cleft whereas other cases and controls did not have a family history of CL/P. This shows that the socioeconomic and/or environmental variables shared by the family members could be one of the causative factors of CL/P other than genetic predisposition and this finding is in accordance to the study conducted by González *et al*.[5]

Among the causative factors most blamed environmental factor of NSCL/P is maternal smoking during the first trimester also is associated with risk of CL/P.[11,16,20,23] Maternal smoking modifies variants of gene related to detoxification of compounds of cigarette smoke.[35] Philipp *et al*.[36] stated that women who smoked during pregnancy had compromised utero-placental blood flow that could result in the poor fetal development and also carbon monoxide affects oxygen transfer to the placenta, and nicotine constricts the uterine wall resulting in hypoxia. However, in our study many of them did not indulge in smoking habit which could be explained because of the Indian culture where most of them do not indulge in smoking habits. Interestingly, however we found, passive smoking is common in 74%, and many of the women were exposed to passive smoking at home or work place giving an OR of 1.97, suggesting an increased risk of passive smoking on orofacial clefts. This result is in accordance with a study by Taghavi *et al*.,[37] and various other studies have been conducted in the last which show the association between passive smoking and CL/P.[23,37-40] However, one limitation in our study was the inability to quantify such exposure.

Alcohol consumption has been associated to the occurrence of CL/P in many of the previous studies.[22] It is suggested that alcohol exerts some of its embryopathic effects by destructively affecting cranial neural crest cell activities.[41,42] However, in our study only 1.6% consumed alcohol in the study group which is not statistically significant. The results of our study are in contrast to existing literature[22] showing no such co-relation ($P = 0.156$). In our study, many of them did not indulge in alcohol consumption which could be explained because of the Indian culture where most of them do not indulge in alcohol consumption.

To assess the protective role of vitamin supplement specially folic acid the history of multivitamin and folic acid supplement was interviewed and we found that 84.0% cases and 96.0% controls had taken the multivitamin supplements in pregnancy (OR: 0.196) suggesting that there might be an increased risk of cleft among the ones who had not taken the supplements which agree with the studies about the protective role of multivitamin supplementation especially folic acid before or after conception.[5,7,13,26,27] The reason for the importance of supplements can be attributed to the fact that the human body needs nutrients and it is crucial to have them in adequate concentration in

mothers body at early stages of pregnancy so that fetus can develop normally. Folic acid, in particular, is recognized as playing an important role in neural tube formation. Folic acid supplementation can decline the risk of neural tube defects which in turn leads to prevention of many potential clefts.[43] However, the mothers could not recollect the exact prescription to differentiate between other vitamins and folic acid which could be due to a lack of education or lack of documentation and this remains a drawback of this study.

Studies have also shown that maternal diseases such as epilepsy,[10] ulcerative colitis,[9] and angina pectoris[6] have been one of the contributing factors for causation of CL/P. Whereas, the lower rate of oral clefts was observed among the offspring of women who had experienced severe "morning sickness" with vomiting.[18] But none of the patients interviewed in our study had any of the above-mentioned illnesses or any other uneventful diseases during the first trimester of pregnancy during pregnancy. This suggests that more detailed studies using hospital records which were not accessible to us might be required and also more detailed documentations in the hospitals is suggested for hospital based studies on preventable diseases like NSCL/P.

Some of the drugs taken for illnesses during pregnancy are also considered as a factor associated with clefts. Czeizel *et al.* stated that the use of an antinausea or vomiting drug was more common among mothers of subjects with cleft palate.[18] Werler *et al.* stated that maternal intake of vasoactive drugs, which include pseudoephedrine, aspirin, ibuprofen, amphetamine, and cocaine or ecstasy have been associated with higher risk for oral clefts.[6] In the case of antiepileptic drugs, there is reasonable evidence that valproate is a significant teratogen during therapeutic use in women; the other older antiepileptic drugs phenobarbitone, phenytoin, carbamazepine probably have some teratogenic potential, but less than valproate. However, there is some question as to whether this increase is due to the medications or the underlying epilepsy. An association between maternal intake of sulfasalazine, naproxen, and glucocorticoids during the first trimester has been suggested to be a factor.[14] Aminopterin (a cancer drug) has also been linked to the development of oral clefts.[44] In our study, none of the mothers interviewed took any of the teratogenic drugs during first trimester pregnancy. This may be because none of the mothers had any illnesses which required the teratogenic drugs or may be of lack of education and documentation. Emphasis on documentation of prescription and diseases needs to be implemented.

Exposure to organic solvents, specifically benzene, was reported as a contributing factor to an increase in neural crest malformations in offspring, including orofacial clefting by some researchers.[12,17,19,21,45] In our study, 3.2% of the mothers reported that they were exposured to occupational hazards and pesticides, (based on their profession and the area of residence that is one mother was working as a beautician-suspected of exposure to organic solvents used like benzene in hair spray and three of the mothers were from endosulfan affected areas) and it was statistically nonsignificant relation between this exposure to hazardous chemicals and occurrence of NSCL/P however there could be a bias in the number of people reporting because of the lack of awareness about exposure to these chemicals at home or at work place. Hence, more specific studies have to be conducted in this aspect with the help of industrial hygienists who assess the presence of chemicals and the probability of exposure.

It is, therefore, shown from our study that absence of maternal nutritional supplementation, maternal passive smoking, and mothers of lower socioeconomic strata had a greater susceptibility to the occurrence of NSCL/P in their offsprings.

However, in contrast to the existing literature, our study did not show any significant correlation of NSCL/P occurrence with maternal exposure to environmental risk factors such as active smoking, alcohol consumption, exposure to teratogenic drugs, and illnesses because of Indian culture where maternal smoking and alcohol consumption is uncommon, lack of proper hospital documentation and improper recollection of prescription drugs by the mothers in the population sample included in this study.

CONCLUSION

Confirmation of the risk factors and proving it can be beneficial in preventing a defect with lifelong implication on the affected child. This can be done by educating the mothers about the ill effects of these avoidable environmental factors, and active participation of all the health-care providers in this preventive protocol is the need of the hour. Documentation on of prescriptions and diseases in pregnancy needs to be highly emphasized to prevent any possible bias in the future so we can find the precise factor responsible for the etiology of NSCL/P. Nationwide social awareness programs should be planned that focuses on the environmental factors responsible for NSCL/P.

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