INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

www.ijabpt.com ISSN : 0976-4550

Volume-6, Issue-2, April-June-2015 Coden IJABFP-CAS-USA

Received: 08th Mar-2015 *Revised: 29th Mar-2015* *Accepted: 29th Mar-2015*

Research article

PARENTAL PESTICIDAL EXPOSURE AND RISK OF CLEFTS IN THE CRANIOFACIAL REGION: A CASE-CONTROL STUDY IN SOUTH INDIA

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ABSTRACT

Objective: The multifactorial etiology of cleft can be due to environmental factors or genetic factors or combination of both. Many studies were conducted to detect the epidemiology of the clefts and the genetic factors causing clefts. There is no or very less studies conducted in India to identify the risk of pesticidal exposure in occurrence of nonsyndromic clefts. The present study is to investigate the risk of parental pesticidal exposure in causing clefts in the craniofacial region. **Methods:** The case-control study included 179 cases of cleft in the craniofacial region and 200 healthy controls matched for age and gender. The data were collected in the proforma from the study group in the departments of plastic surgery, Obstetrics and Gynaecology, and Paediatrics of Vydehi Institute of Medical Sciences and Research Centre. **Result:** Majority (55.3%) of the parents from the cleft group were exposed to pesticides but only 4.5% parents of the control group were exposed which is statistically significant (p=0.001). Compared to other cleft group, more parents of cleft lip palate exposed to pesticides was also significant (p=0.041).The cleft cases which were exposed to pesticides (86%) were from the rural area and the controls which were not exposed (79%) were from the urban area and is statistically significant (p<0.001). **Conclusion:** Parental pesticidal exposure is a risk factor for clefts in the craniofacial region. Among all the clefts, the risk is increased for the cleft lip palate.

Key words: cleft lip palate, craniofacial region, risk factor, pesticidal exposure

INTRODUCTION

The clefts in the craniofacial region is the most disfiguring among the craniofacial anomalies. The birth prevalence of clefts in Indian sub-continent is approximately between 27,000 and 33,000 clefts per year. The most common cleft in the craniofacial region is the cleft Lip and Palate. According to the multicentric study conducted in different regions of India, the cleft lip with or without cleft palate is 9.3per 10000 and cleft palate alone (isolated cleft palate) is 1.7 per 10000 (Mossey P. et.al, 2009). Another study showed that the incidence of CLP in India was found to be 1.09 in every 1000 live births and CLP is predominant in India (Reddy S.G et.al, 2010).The cleft lip can occur alone or associated with cleft palate. Approximately 50% of cleft lip cases also have cleft in the palate (Stainer P et.al2004, Dixon M J et.al 2011).

The prevalence of clefts varies by race, geographic origin, socioeconomic status and sex (Vanderas AP 1987, Murray JC et.al, 1997). The incidence of cleft lip and cleft lip palate is higher than cleft palate (Lidral et.al, 2008). The highest prevalence of cleft lip palate is 1 per 500 seen in North American Indians and Asians. Among the Caucasians it is 1 per 1500 and lowest prevalence is 1 in 2500 seen in African derived populations. The Japanese have the highest prevalence among Asian countries (Murthy J et.al, 2009). The clefts of the lip and palate affect about 1 per 700 births worldwide (Murray JC et. al, 2012). The etiology of cleft is multifactorial. It includes both environmental and genetic factors. The maternal environment can affect the foetal development (Saikrishna et.al, 2011). It includes maternal diet, maternal medication, stress and teratogenic and other occupational exposure (Rahimov F et.al 2012, Nguyen RH et.al, 2007). The exposure to pesticides such as dioxin (Garcia AM et. al, 1999) and nutritional deficiency reports the role in causing the CL/P. The formation of soft and hard tissues of face is occurring in the first 60 days of post conception by a sequence of events. Any disruption of the events during this period result in clefts in this region (Sperber GH et.al 2002, Murray JC et.al 2012).The present study is to investigate the risk of parental pesticidal exposure in causing clefts in the craniofacial region.

MATERIAL AND METHODS

This is a retrospective case-control study over a five year period which includes 179 cleft cases and 200 healthy controls matched for gender, age and locality. The clefts in the craniofacial region were categorized into craniofacial cleft, facial cleft, cleft lip palate, cleft lip (cheiloschisis) and cleft palate (palatoschisis). The distribution of clefts in 179 cases were 8 cranial clefts,7 facial clefts, 22cleft lip,120 cleft lip palate and 22 isolated cleft palate cases. All non syndromic congenital cleft cases of craniofacial region of any age group irrespective to operated or not operated were included. Approval from instituitional ethical committee was obtained. The data from the study group were collected in the proforma from the departments of plastic surgery, Obstetrics and Gynaecology, and Paediatrics departments by conducting the interview with the parents of study group. The data regarding the location of the residence, exposure to pesticides and other radiation, occupation of the parents and their socioeconomic status were collected. The cases were clinically examined to identify the cleft and its severity. Informed written consent was taken from the cases and from their parents in case of minor.

Statistical analysis: The data was analyzed using SPSS version 21. Chi square test and odds ratio were done to find the association. $P<0.05$ is considered as statistically significant.

RESULTS

The result showed that the parents exposed to pesticides were more (55.3%) than the not exposed (Table 1). But this increase in the exposed group in each cleft was not statistically significant (p=0.075).Only in cleft lip group, the parents not exposed to pesticides is more.

As the the frequency of cleft lip palate was more, the cleft lip palate was considered as one group and all other clefts in another group and it showed significant difference in its occurrence. (table 2).

Table-1: Shows the parental pesticidal exposure in different clefts

Parental pesticidal exposure	Cranial and facial clefts	Cleft lip (CL)	Cleft lip palate (CLP)	Cleft palate (CP)	Total
Exposed	12(80%)	08(36.4%)	67(55.8%)	12(54.5%)	99(55.3%)
Not exposed	03(20%)	14(63.6%)	53(44.2%)	10(45.5%)	80(44.7%)
Total	15	22	120	22	179

P value =0.075 which is not significant.

Table-2: Shows the parental pesticidal exposure among CLP and other clefts

Parental pesticidal exposure	Clefts			
	Cleft lip palate	Other clefts	Total	P value = 0.041
Exposed	67(55.8%)	32(54.2%)	99(55.3%)	
Not exposed	53(44.2%)	27(45.8%)	80(44.7%)	
Total	120	59	179	

When comparing the cases with controls, the parents of case group is highly exposed to pesticdes(table3) and this difference is highly significant which shows the risk of parental pesticidal exposure in the occurrence of clefts.

Table-3: Shows parental pesticidal exposure before and during pregnancy

Parental pesticidal exposure	**Cases**	**Controls**	**Total**	P value < 0.001
Exposed	99(55.3%)	9(4.5%)	108(28.5%)	
Not exposed	80(44.7%)	191(95.5%)	271(71.5%)	
Total	179	200	379	

The odds of clefts associated with parental pesticidal exposure was 26.26(95% confidence interval 12.65 -54.53 and this strong association was statistically significant(pvalue<0.05).

Table-4: Shows parental pesticidal exposure and locality of residence

Pesticidal exposure	Area of residence		Total	
	Rural	Urban		
Yes	93(86.1%)	15(13.9%)	108	
No	57(21%)	214(79%)	271	P value <0.001
Total	150(39.6%)	229(60.4%)	379	

The pesticidal exposure was more in rural area (86%) than in the urban area. (Table 4)

DISCUSSION

The study shows parental pesticidal exposure is significantly associated with the occurrence of clefts in the craniofacial region (table3). The parents were not aware of the chemicals present in the pesticides and some of the parents were not able to specify the names of the pesticides which they had used. They only know that they used commonly available pesticides in the local market. So all the details of the pesticides which were selling in the local market were collected (Table5). Because of the lack of information about the specific pesticides they used we could not find out which pesticide was used more. The parents of exposed group (table1) were farmers or involved in agricultural activities and they are residing very close to their work place (cultivating area). 35% mothers of the exposed group were involved in the agricultural activities. The remaining mothers were exposed to pesticides as they were residing in the locality of agricultural land. Cordier et al reported that the maternal exposure to glycol ether, a chemical can increase the occurrence of cleft lip (Cordier S et. al 1997). The chemical name is diethyleneglycol monobutyl ether which is used in paints, varnishes, cosmetics, pump spray and is a multipurpose cleaner. This chemical is seen in industrial and domestic products.

The exposure to chemicals acetone, toluene and xylene which are used in organic solvents also make similar effect of glycol ether in clefts (Holmberg PC et. al 1982, Wysyzynski DF et al 1996). In our study, 5% fathers were painters or dealing the fabric dyeing by profession. They were exposed to these organic solvents. In our study, 55.3% parents were exposed to pesticides in case group, while it is only 4.5% in control group. This exposure and occurrence of cleft was found statistically significant in our study. There are few studies which reported the maternal occupations in the fields of agriculture, hair dressing, leather and shoe manufacturing also increased the occurrence of clefts (Wysyzynski DF et al 1996, Bianchi F et al 1997, Garcia AM et al.1998, Lorente C et al 2000). Wennborg et al. specified that benzene an organic solvent can increase neural crest malformation and so the clefts in the orofacial region (Wennborg et al. 2005). The present study contains more urban population (60.4%) than the population of rural area. But the exposed group is more in rural area (86%).This indicates that in rural area the clefting is more than the urban area(table 4). Some studies reported that exposure to hazardous waste (Croen LA et al.1997) and water chlorination (Hwang BF et al.2003) were not showing any risk for cleft lip and palate.

Numinen et al. stated that the mother's locality of residence and parental occupation are important factors as it can be exposed to pesticides. Thus these two factors are linked to parental pesticidal exposure and further to or ofacial clefts (Numinen T et al 1995). In a meta-analysis of 19 studies to evaluate the risk of orofacial clefts associated with pesticidal exposure showed the odds ratio 1.37 for 95% of confidence interval(CI) (1.04 to 1.81) for maternal exposure and for paternal exposure the odds ratio was 1.16 for 95% of confidence interval (0.94 to 1.44) and it was not significant for location of residence. This meta-analysis suggested that the risk of maternal pesticidal exposure in causing cleft was statistically significant. Our study is in consistent with the result of this meta-analysis (Romitti PA et al 2007). In the present study the parental pesticidal exposure did not show any difference among types of clefts(table1). But the cleft lip palate showed significant association with pesticidal exposure when compared with other clefts (table2).The case-control study of 35cases and 35 controls in Greece identified the paternal occupation like farmer was of increased risk and the occurrence of cleft lip with or without palate to their children was also frequent than the control group (p=0.039) and odds ratio 3 with CI=1.03-8.70. The maternal occupation was not significant but passive exposure to tobacco increased the risk of clefts to their offspring. The paternal occupation of a farmer is more exposed to the chemicals present in the fertilizers and pesticides. This can cause teratogenic effect in spermatogenesis and oogenesis or affect any of the complex events occurring in the development of craniofacial region especially during the first trimester of pregnancy (Mirilas P et al 2011). Thus it causes toxic effects in human reoroductive system (Cordier S et. al 1997).

In a 10-year study in Texas to identify the effects of maternal exposure to (BTEX) benzene, toluene, ethyl benzene, and xylene on oral clefts among offspring could not find any association of pollutants with orofacial clefting (Ramkrishnan A et al.2013).

Brender et al opined residing in close proximity to hazardous waste sites is not a risk factor for oral clefts (Brender JD et al 2006). The studies also reported that the maternal exposure to air pollutants like ozone (Hwang BF et al 2008) and SO_2 (Hansen CA et al 2009) were associated with oral clefts. But three U.S. studies did not find any such association between maternal exposure to air pollutants and oral clefts (Ritz B et al 2002, Gilboa SM et al 20005, Marshall EG et al 2010).The residential proximity to industrial area and exposure to pesticides and house hold insecticides were found as risk factors for orofacial clefts in a Brazilian study (Isabel CG et al 2003).

In the present study, the parents are exposed not only during the period of pregnancy, even years before also. The parental pesticidal exposure was more in CLP cases than the other clefts (p value =0.041). Among the control group only 4.5% were exposed but in cleft group it was 55% which is highly significant (p value = 0.001) and is a risk factor of cleft (Table 3).

Table 5: Pesticides used in agriculture

Name of fertilizer/pesticide	Chemicals present
Reeva-5	Lamda Cyhalothrin 5%
Acemain	Acephate 75% Sodium diacetyl sulphosuccinate Fine silica
Profex super	Profenofos 40% Cypermethrin4%
Sulfaf 80	Sulphur Sodium salt of phenol sulphonic acid Sodium salt of alkyl naphtylene sulphonic acid Aromatic sulphonic acid
Agas	Diafnthiuron 50%
Fiprogreen	Fipronil 5% Naphtylene sulphonate Sodium lingo sulphonate Carboxy methyl cellulose Sodium salt of dinaphthyl methanol sulphonic acid Phenol ethoxylate Alkyl benzyl sulphonate
Bilitox 50	Copper oxychloride 50 Sodium salt of alkyl aryl sulphonate Sodium salt of phenol sulphuric acid condensate
Tridel 351	Deltamethrin 1% Triazophos 35%
Endosulfan	

Parental occupational exposure is a risk factor of clefts (Rahimov F et al 2012). The study from Iran showed 64% of cleft cases from rural regions and their parents were farmers and found pesticidal exposure was the risk factors for clefts (Farhadian N et al2013). In a retrospective study on predisposing factors of oral clefts in Mexico reported the paternal occupation of 44.7% cases had agricultural work and the remaining were involved in mechanic, plumbing, construction work and some were in unspecified work. Most of mothers (96%) were doing house hold work and 35% were involved in agricultural activities (Gonzalez BS et al.2008). The agricultural work and the organic solvents exposure are related to the development of CLP (Leite GIC et al 2002, Leite GIC et al 2003). The mothers were exposed to the agricultural chemicals while they were involved in these activities were related to CLP development (Lorente C et al 2000). The waste from the plastic and electronic manufacturing can cause changes in the environmental factors in the locality of residence which can be associated with the oral cleft development (Dolk H et al 1998).

CONCLUSION

The parental occupation and parental exposure to pesticides are significantly associated in causing clefts. The cleft lip palate has increased risk than other clefts. The proximity of residence close to the pesticidal exposure is also significant. Further study is required to identify whether there is any specific pesticide or pollutant or organic solvent which can increase the risk in the occurrence of clefts in the craniofacial region.

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ISSN : 0976-4550

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