

EPIDEMIOLOGICAL STUDY OF CLEFT PALATE IN THE STATE OF BAHIA, BRAZIL

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ABSTRACT | The non-syndromic cleft palate (NSCP) is a common congenital defect in humans. This work has aimed to perform a descriptive epidemiological study of patients with NSCP in the State of Bahia, Brazil. A questionnaire was applied to patients and/or parents at three reference centres for treatment of craniofacial anomalies. Of the 135 patients with NSCP, 60% were female and 40% male. Blacks and mulattos were predominant. The most common systemic disorder was otologic findings. The average age of the surgery was 5 years and 2 months with a percentage of 74.8% operated. With regard to the mothers, 16.3 % consumed alcoholic beverages and 12.6 % smoked. The most cited vitamin supplementation was folic acid. Contact with chemicals involved 20.7 % of the fathers and 14.9 % of the mothers. The most frequent mother's age gestational ranged between 15 and 25 years old. The results showed that the frequency of children with NSCP in the State of Bahia is related to the location of the reference centres. Younger mothers gave birth to cleft palate children even despite using vitamin supplementation. Although no surgical procedure has been performed at an ideal age, the majority of the children with cleft palate were submitted to surgical repair.

Key-words: Cleft palate; orofacial cleft; epidemiology.

INTRODUCTION

Orofacial clefts are the most common congenital anomalies of the face, with worldwide data showing that these conditions affect 1 in 700 live births¹. In Brazil, the mean prevalence of orofacial clefts is 0.36 per 1,000 live births².

Despite being a common congenital defect, the etiopathogeny of this anomaly remains uncertain. This is due to the association of both genetic and environmental factors, which reflects the complexity and diversity of the molecular events involved during embryogenesis¹.

There are many classifications for orofacial clefts, but the one most used in Brazil is based on the incisive foramen and is divided into four groups as follows: incisive pre-foramen clefts or cleft lips (CL), incisive post-foramen clefts or cleft palates (CP), incisive trans-foramen clefts or cleft lip/palates (CLP), and rare facial clefts, which involve facial structures other than lip and/or palate.

Historically, the aetiology of CLP and CP is considered distinct. Today, these two types of fissures are genetically and embryologically different entities¹.

Pathogenesis begins in the sixth week of intra-uterine life and is totally completed in the 12th week. The period from the sixth week to the beginning of the ninth week of pregnancy is considered crucial for the development of palate. This process is mediated by multiple signalling molecules and interactions between epithelial/mesenchymal cells and extracellular matrix. The development of palate occurs in two stages: primary palate and secondary palate³.

The interruption of the secondary palate formation because of genetic and/or environmental changes, without association with other anomalies, will culminate in isolated non-syndromic cleft palate (NSCP). Approximately 50 percent of the cases of CPs involve NSCP, whereas the remaining half involves syndromic malformations¹.

Cleft palate can affect the palate partially, resulting in the so-called incomplete cleft palate, or completely, resulting in complete cleft palate in which hard and soft palates are simultaneously involved.

Patients with NSCP are more likely to have aesthetical, functional and emotional problems, which in turn produce negative psychological effects on the individual's quality of life. Therefore, these individuals need specialised and multidisciplinary approach with surgical or non-surgical treatment, passing by several areas of medicine, dentistry, speech therapy, and psychology.

In Brazil, there are few epidemiological studies in literature investigating the NSCP and in State of Bahia, there is still no study with this aim in mind.

This work has aimed to perform a descriptive epidemiological study by focusing on environmental and socio-demographic risk factors of non-syndromic individuals with isolated cleft palate at three reference centres for treatment of craniofacial anomalies in the State of Bahia.

MATERIAL AND METHODS

The analyses in the present study were performed according to the research ethics norms for human beings, as established by the local research ethics committee through protocol number 378.066 (CAAE 48777315.0.0000.0047).

This is a descriptive cross-sectional study in which individuals with orofacial clefts or/and their parents were interviewed at three reference centres for treatment of craniofacial anomalies in the State of Bahia, namely, Santo Antônio Hospital, Martagão Gesteira Hospital, both located in the Salvador city, and Esaú Matos Hospital, located in the Vitória da Conquista city.

The questionnaire considered socio-demographic data of the patients, such as gender, age, date and place of birth, self-reported skin colour, dwelling area, and family income. Information on the individual's family was also collected, with focus on factors possibly associated with the aetiology of cleft palates, such as smoking habits, alcohol consumption, drug abuse, and use of vitamin supplement before and during pregnancy. In addition to the maternal gestational age, one can consider episodes of abortion or stillbirth, parents' profession, parents'

contact with chemical products, recurrence of cleft palate cases within the family, and familial consanguinity.

With regard to the patient's health, type of cleft palate, presence of syndrome and systemic changes were recorded. It was also considered whether the patient was operated for repair of the cleft as well as the age at which the surgery was performed. The medical records of the patients were also reviewed in order to collect data on the multidisciplinary team of each reference centre.

Before applying the questionnaire, all the patients and/or parents were informed about the study and then they were asked to sign an informed consent form explaining their participation in the research.

After the interviews, the participants were divided into four groups depending on the classification of the cleft palate as CL, CP, CLP or rare clefts. In the present research, the syndromic patients were

excluded (NSCP) and only the group of individuals with CP was studied.

RESULTS

A total of 680 individuals with orofacial cleft were interviewed. Of these, 366 (53.82%) had CLP, 158 (23.23%) had CL, 155 (22.8%) had CP and 1 (0.15%) had rare facial cleft.

Of the 155 individuals with CL, 20 (12.9%) had syndromes and thus were excluded from the group, resulting in a final sample of 135 subjects with NSCP. Of these, 81 (60%) were female and 54 (40%) were male.

The mean age was 11 years and 3 months old, ranging from 1 month to 62 years old, with standard deviation of 10 years and 7 months. With regard to the self-reported skin colour, it was observed that blacks and mulattos accounted for the majority of the subjects (Table 1).

Table 1. Socio-demographic data of individuals with NSCP.

Variable	n	%
Gender		
Male	54	40
Female	81	60
Total	135	100
Skin colour		
White	28	20.8
Mulatto	32	23.7
Black	48	35.6
Indian	6	4.4
Asian	7	5.2
Other	5	3.7
No information	9	6.6
Total	135	100
Reference Treatment Centre		
Santo Antonio Hospital	113	83.7
Esau Matos Hospital	12	8.9
Martagao Gesteira Hospital	10	7.4
Total	135	100

Table 1. Socio-demographic data of individuals with NSCP. (continuation)

Variable	n	%
Dwelling zone		
Urban	98	72.6
Rural	37	27.4
Total	135	100
Family income		
Up to a minimum salary	65	48.1
Up to three minimum salaries	47	34.8
Up to five minimum salaries	8	5.9
More than five minimum salaries	7	5.2
No information	8	5.9
Total	135	100

With regard to the dwelling zone, it was found that 98 (72.6%) lived in urban areas and 37 (27.4%) in rural area. It was also observed that the family income was predominantly (48.1%) up to a minimum salary, as seen in Table 1.

Individuals with NSCP were frequently born in the three mesoregions of the State of Bahia, namely,

metropolitan mesoregion of Salvador, central-southern mesoregion of the state, and central-northern mesoregion of the state, as shown in Figure 1. No information on place of birth was obtained for 2.4% of the subjects. The cities presenting the highest frequency of orofacial clefts were Salvador (37.8%), Vitoria da Conquista (5.2%), Feira de Santana (3.7%) and Santo Antonio de Jesus (3.7%).

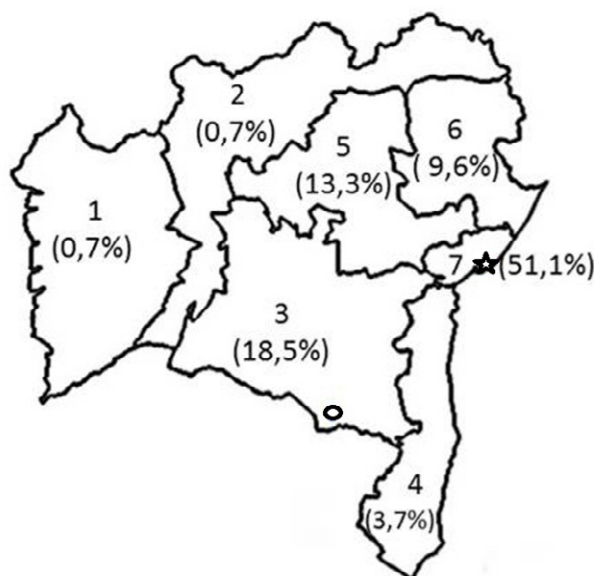


Figure 1. Frequency of individuals with NSCP by mesoregions of the State of Bahia.

Legend: 1- Far-western region, 2- San Francisco Vale region, 3- Central-southern region, 4- Southern region, 5- Central-northern region 6- Northern region, 7- Greater Salvador. The star mark shows location of Salvador city and circle mark indicates the location of Vitoria da Conquista city, where the reference centres for treatment of craniofacial anomalies are sited.

According to the sub-phenotypes of cleft palate, classified as either complete or incomplete, it was observed that 70 individuals presented complete cleft palate (51.9% of the cases) and 65 presented incomplete cleft palate (48.1% of the cases). Systemic changes were found in 34.1% of the sample, whereas 62.9% presented no systemic impairment and 3% had no information about or did not respond to this item. Among the systemic disorder, the otological ones were the most prevalent, accounting for 54.34% of the cases.

A high percentage of individuals with NSCP (74.8%) had already been submitted to surgery

for repairing the anomaly, and those who had not were 25.2 percent. Of those who had surgical treatment, the mean age was 5 years and two months, ranging from 1 month of life to 58 years old (SD = 9 years old).

With regard to the habits of the mothers of cleft palate children before and during their pregnancy, 16.3% reported consumption of alcoholic beverages, 12.6% smoked and 3 percent used illicit drugs (Table 2). The use of vitamin supplement was reported by 59.2% of the mothers, with folic acid being the most cited (31.25%).

Table 2. Habits of the mothers of individuals with NSCP.

Variable	n	%
Consumption of alcoholic beverages		
Yes	22	16.3
No	105	77.8
No information	8	5.9
Total	135	100
Smoking		
Yes	17	12.6
No	111	82.2
No information	7	5.2
Total	135	100
Use of illicit drugs		
Yes	4	3
No	120	88.9
No information	11	8.1
Total	135	100

As for the mothers' occupation, housewife was the most cited (23%), followed by grower and free-lancer, both with 16.3%. The contact with chemical products was reported by 14.9% of the mothers (Table 3). According to the fathers' occupation,

the majority reported to be free-lancers (20%), followed by grower and retired, both with 16.3%. The contact with chemicals was reported by 20.7% of the fathers (Table 3).

Table 3. Parents' occupation and contact with chemical products.

Variable	n	%
Mother's occupation		
Grower	22	16.3
Housewife	31	23
Student	4	3
Free-lancer	22	16.3
Other	33	24.4
Unemployed	21	15.5
No information	2	1.5
Total	135	100
Mother's contact with chemicals		
Yes	20	14.9
No	96	71.1
No information	19	14
Total	135	100
Father's occupation		
Grower	22	16.3
Free-lancer	27	20
Retired	22	16.3
Other	51	37.8
Unemployed	3	2.2
No information	10	7.4
Total	135	100
Father's contact with chemicals		
Yes	28	20.7
No	85	63
No information	22	16.3
Total	135	100

We found a higher percentage of mother's gestational age between 15 and 35 years old. Episodes of abortion and stillbirths were observed in 27.4 and 5.9 % of the cases, respectively (Table 4).

Table 4. Mother's gestational age, abortion and stillbirth.

Variable	n	%
Gestational age (years)		
15 to 25	55	40.74
26 to 35	54	40
36 to 45	14	10.4
46 to 55	3	2.2
No information	9	6.66
Total	135	100

Table 4. Mother's gestational age, abortion and stillbirth. (continuation)

Variable	n	%
Abortion		
Yes	37	27.4
No	95	70.4
No information	3	2.2
Total	135	100
Stillbirth		
Yes	8	5.9
No	124	91.9
No information	3	2.2
Total	135	100

Only ten mothers (7.4%) had consanguineous relationships, with family history of cleft palate representing 28.1% of the sample (38 cases).

DISCUSSION

Different phenotypes of non-syndromic orofacial clefts exhibit distinct distributions between the several regions and across the worldwide population¹. According to epidemiological studies investigating several population samples, CLPs occur more frequently than other types of clefts, such as CL and CP^{1,4-6}. The results of the present study corroborate the literature by showing that CLPs are more frequent than CL and CP, with both latter clefts having similar frequencies.

According to our sample, NSCP is more common in females. This result was expected. Higher prevalence of NSCP had already been reported elsewhere^{1,4} and according to Sperber⁷, this occurs because the secondary palate closure is completed later in female embryos.

An important variable for studies of orofacial clefts is the ethnic group of the population. The prevalence of this anomaly varies depending on the ethnic background. In part, this is due to the genetic base of the clefts as gene polymorphisms reflect both history and effects of natural selection by which determined populations underwent¹.

There is a higher prevalence of NSCP in countries where Caucasian and Asian populations are predominant¹, whereas lower rates were observed in African populations and their descendants as well as in countries of Middle-East, Latin America and India^{1,4}.

Brazil underwent a process of colonisation which promoted a highly miscegenated population, since European, African and Native American ethnic groups were involved. Because of its continental proportions, one can observe a great variation in the ethnic composition in the different regions of the country. Therefore, it is a complex task to determine the ethnic stratification of the Brazilian population, mainly when such an analysis is performed based on the self-perception of the individuals⁸.

In the present study, it was found that the majority of the individuals reported themselves as black (35.6%) and mulatto (23.7%). This finding is due to the African contribution to the Bahia's population, although NSCP are more frequently seen in individuals of Caucasian and Asian ancestries. Freitas et al.⁶ performed a study with a population affected by orofacial clefts in the State of Bahia, and by analysing the medical records, the authors also reported a higher predominance of blacks and mulattos. On the other hand, Gardenal et al.⁵ conducted a study in the State of Mato Grosso do Sul based on medical records and they identified a higher predominance of Caucasian individuals with cleft palate, followed by blacks and mulattos. Another study conducted by Cuzzo et al.⁹ in the State of Mato Grosso showed a much higher predominance of white individuals.

These differences are due to the variation in ethnic composition in the different regions of the country.

The association between low socio-economic level and occurrence of orofacial clefts is object of several works, but there is still no consensus in literature. In fact, this is a complex variable as it is associated with other socio-economic aspects, such as lack of prenatal care, difficult access to healthcare services, lack of information, nutritional deficit, episodes of stress and violence, alcohol consumption, smoking, and cultural issues intrinsic to each population¹⁰.

The results of the present study have shown evidence that the majority of our sample come from a low-social status population, since families living on up to a minimum salary was more predominant (48.1%), followed by families with up to three minimum salaries (34.8%). However, these data are not enough to correlate low family income with cleft palate. Our sample was recruited from reference centres for treatment of orofacial anomalies, all linked to the Brazilian healthcare system (SUS). Moreover, because of cultural reasons, populations with higher family income do not use public healthcare services.

In mesoregions where reference centres for treatment of orofacial clefts are sited (Greater Salvador, central-southern region and central-northern region) we have observed higher percentages of cases. This fact suggests that the distribution of cleft palate cases in the State of Bahia is closely related to the proximity of treatment centres rather than to the actual frequency of individuals with NSCP in the cities. A study by Freitas et al.⁶, also conducted in the State of Bahia, found that most of the sample consisted of individuals from Salvador city, a finding also reported in our work.

With regard to the presence of systemic impairment in individuals with NSCP, we have observed a higher prevalence of otological disorders. In fact, this finding is in accordance with the literature. Individuals with orofacial clefts, including CP and CLP, are commonly affected by otitis media and loss of auditory acuity due to Eustachian tube dysfunction as a result of the palate opening¹¹.

Surgical treatment is a need for individuals with orofacial clefts, but having access to surgery for repairing the anomaly is a challenge, mainly in

developing countries¹². Our results showed that 74.8 percent of our sample had already undergone surgical treatment for correction of cleft palate. In the majority of the cases, such a surgical procedure was performed in the own reference centre (data not reported). A study performed by Cubitt et al.¹³ used data from the Smile Train Organisation, which provides free surgical treatment for orofacial clefts across several countries in the world, and found a variation in the percentage of individuals who had access to treatment, particularly depending on the country's income. Specifically in the case of cleft palate repair, low-income countries had only 22 percent of individuals operated, whereas high-income countries had 52 percent.

In our study, the mean age at surgery treatment was 5 years and 2 months old. The ideal age recommended by the American Cleft Palate-Craniofacial Association¹⁴ for this treatment is up to 12 months of life. Cubitt et al.¹³ reported that the mean age for such surgery varies depending on the geographic site as well as on each country's income. For cleft palates, individuals from countries of Europe and Central Asia had a mean age of 3 years old when they sought treatment, whereas those from Sub-Saharan Africa had a mean age of 6.7 years old.

Because of their multifactorial origin, cleft palates are associated with both genetic and environmental factors. The association of environmental factors with risk of orofacial clefts has been investigated by several studies. However, despite the efforts, there are conflicting results regarding this association. Among the variables studied, one can highlight smoking^{15,16}, alcohol ingestion^{15,17}, maternal vitamin deficiency, particularly folic acid¹⁵, mother's age^{16,18}, parental consanguinity⁹, and use of chemical products¹⁸ by the parents.

Today, it is known that genetic factors have influence on environmental variables. In the case of smoking, two gene markers (i.e. SCL2A and WDR1) have been associated to the risk of NSCP in mothers exposed to tobacco¹⁹. As for the ingestion of alcoholic beverages, the aetiology of cleft palate can be related to the capacity of the mother and/or foetus to metabolise alcohol depending on variations in the gene ADH1C²⁰. Also, in the use of vitamin supplement with folic acid, the cleft may be

related to polymorphic variants of genes controlling metabolism, absorption and transport of folic acid, as it happens with polymorphisms in genes MTHFR and MTHFD1²¹.

Our study has not sought to establish a relationship of cause and effect with environmental factors, but rather to characterise our population sample by means of percentage regarding these factors, which have been widely studied in literature. The few existing studies only sought to assess the NSCP or establish types of clefts.

Maternal smoking before and during the gestational period was observed in 12.6% of our sample. A percentage similar to ours was also reported by Yang et al.¹⁸, who found 14.5 percent in a study with a North-American population sample. However, Grewal et al.²² observed in a North-American sample 26.8 % of the mothers smoked, whereas De Roo et al.¹⁷ found 37 % in a study conducted in Norway. On the other hand, studies performed in China showed percentages much smaller than that found in our research, with Zhang et al.¹⁶ reporting that only 2.5% of the mothers smoked. Jia et al.¹⁵ found a percentage even smaller, that is, only 1.7%.

According to alcoholic beverages, our results showed that 16.3% of the mothers had consumed them. A high percentage was observed in the North-American population, with 54.8% of the mothers before pregnancy and 23% during the gestational period. In fact, by adding the two percentages above, we can see that 77.8% of the North-American mothers consumed alcoholic drinks²². In the Norwegian study, De Roo et al.¹⁷ also found a high percentage, despite being less than the half of the sample, that is, 39%. On the other hand in a Chinese study¹⁵, only 4.54% of the mothers consumed alcoholic beverages. These different results can be explained by the correlation between maternal habits and cultural factors, since these are intrinsic to each population.

In our study, we have shown evidence that among the mothers who used vitamin supplement, folic acid was present in 31.25% of the cases. A similar percentage was reported by De Roo et al.¹⁷, with 39% of the Norwegian population sample. In the Chinese sample, Jia et al.¹⁵ reported a percentage of 22.72 %. On the other hand, the study by Grewal et al.²² found that more than the half of the mothers

(57.8%) used folic acid as supplement in the North-American sample.

The percentage of parental consanguineous relationship was 7.4% only, in this work. This percentage was much lower than that found in a study conducted in Saudi Arabia, that is, 59%²³. This very high percentage is probably related to the culture of that country, where consanguineous marriages are usual, differently from the Brazilian culture. According to Sabbagh et al.²⁴, the prevalence of clefts in Saudi Arabia is high and similar to the worldwide prevalence.

Parental contact with chemical products, such as agrotoxics, was observed in 14.9 percent of the mothers and 20.7 percent of the fathers in our study. The study by Yang et al.¹⁸ with a North-American sample investigated the maternal contact with several types of chemicals. The authors showed evidence that only a minority of mothers had contact with such substances, as also happened in our work.

In the present study, the majority of the mothers in our sample were young in terms of gestational age, with age groups of 15-25 years (40.74%) and 26-35 years (40%) being more prevalent. The higher prevalence of young mothers was also observed in other studies^{15-18,22}.

The familial recurrence of NSCP is common in the literature and it is closely related to the genetic base of cleft palate, which is not completely clarified yet²⁵. Our results showed that 28.1% of the subjects had a family history of cleft palate. Ravichandran et al.²³ reported a percentage similar to that of our study (22.9%), but Jia et al.¹⁵ found a much lower percentage of 4.5%. The literature indicates that the familial recurrence of cleft palate can be higher if some clinical signs are considered as part of the phenotypic spectrum of the clefts, such as dental anomalies, submucous cleft palate, bifid uvula and failure in the lip orbicular muscle, which are observed only by ultrasound¹.

CONCLUSION

The epidemiological evaluation of NSCPs in the State of Bahia has revealed a higher frequency

of individuals with cleft palate in mesoregions where there are centres for treatment of orofacial anomalies. Although most of the sample had access to surgical repair, the surgery was not performed at ideal age. Exposure to risk environmental factors, such as tobacco and alcohol, before and during pregnancy was observed in mother of individuals with NSCP. Despite the use of vitamin supplement, young mothers gave birth to children with orofacial anomalies.

AUTHOR CONTRIBUTIONS

CV, JS and SR wrote the manuscript. PV, RC and AM contributed to critical and intellectual content.

COMPETING INTERESTS

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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