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Oral clefts: a retrospective study of prevalence and predisposal factors in the State of Mexico

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Abstract: The purpose of this study was to up-date the records concerning oral clefts (OCs) encountered at the Child Hospital of the Maternal Infantile Institute of the State of México, and to examine the association of predisposing factors. A retrospective study of the medical records of patients generated over a 5-year period was carried out. A total of 835 files were reviewed, representing 504 boys and 331 girls. The studied variables were the type of oral clefts and predisposing factors. Kendal correlations at $P \leq 0.05$ and chi-squared at $P \leq 0.05$ were used to find any associations between variables. The distribution of oral cleft was: cleft lip and palate (CLP) 70%, cleft palate (CP) 21%, cleft lip (CL) 8%, separate cleft lip and cleft palate 1%. The sex ratios were 1.7 for CLP, 1.7 for CL, and 1 for CP. Municipalities with ethnic groups as well as industrial, agricultural and pottery activities showed a high rate of prevalence. Although there was no significant association with birth weight, familial history of clefting, consanguinity, medication usage during pregnancy, or paternal occupational risk, the results suggested that the most severe clefts were proportionally related to these factors. A significant association with maternal and paternal age, abortion rate, and parity was found. Additionally, maternal agricultural activities suggested that pesticide exposure might be a factor. (J. Oral Sci. 50, 123-129, 2008)

Keywords: cleft lip; cleft palate; risk factors; State of Mexico.

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Introduction

Although there have been no reports on the incidence of oral clefts in Mexico over long periods of time because of the lack of a reliable and continuous registration system, several states in Mexico – Campeche, Chiapas, Hidalgo, Oaxaca and Guerrero are considered endemic areas, with ratios ranging from 1:600 to 1:1000 live births. (1,2) The WHO (2005) (3) reported a rate of 17.29 per 10 000 CI (13.29 to 22.31) in Mexico as a whole, the Unique Information Register System of Epidemiologic Vigilance (SUIVE, 2005) for the State of Mexico (4) reported 341 cases in 2004. Most of these patients were treated at the Child Hospital, of the Maternal Infantile Institute of the State of Mexico, (IMIEM), with an average of 189 patients per year. These cases originated from both metropolitan and quite remote rural communities, with an intermediate to very low income level. Consequently, in these instances, when complex, long-term treatment was indicated, it was rarely carried out. Despite the fairly high prevalence of oral clefts in the State of Mexico, no studies have examined the prevalence and risk factors of cases already recorded.

The aim of this study was to determine the proportion of varieties of cleft lip with or without cleft palate, as well as cleft palate and related risk factors, drawn from records of affected children treated at the Child Hospital of the Maternal Infantile Institute of the State of Mexico

over a five-year period.

Materials and Methods

Medical records of 1005 oral cleft patients from the Child Hospital of the Maternal Infantile Institute of the State of México (IMIEM) covering a 5-year period were reviewed. The patients were referred to the hospital from rural and urban clinics, and the information was obtained during the patients' first visit using clinical charts. The mothers were asked about exposure to potential risk factors. However, as the hospital is a public institution with a high number of patients, and the interviews were done by different doctors, it was unclear whether all the mothers had been accurately interviewed or if the information had been recorded in all cases. One hundred seventy files lacking sufficient information were excluded. The oral clefts were classified into four groups: cleft lip (CL); clefts of the lip and palate (CLP); cleft palate (CP); and simultaneously separate cleft lip and cleft palate (CL/CP). The municipalities where the children had been born were grouped according to vicinity based on the municipality's political districts. Descriptive statistics and Kendal correlations at $P \leq 0.05$ and chi-squared at $P \leq 0.05$ were used to find any associations between variables.

Results

The relative frequency of oral clefts by cumulative municipalities was: Toluca 139 cases (16%), Tejupilco 119 cases (13%), Ixtlahuaca 103 cases (12%), Tenancingo 90 cases (10%), Valle de Bravo 82 cases (9%), San Felipe del Progreso 85 cases (9%), Atlacomulco 79 cases (9%), and Metepec 73 cases (8%). Sixty-five cases (8%) belonged to 13 districts with less than 25 cases.

The distribution of the different types of clefts was: CLP 70%, CP 21%, CL 8%, and unconnected clefts of both the lip and secondary palate 1%. Males were affected significantly more frequently ($X^2 = 3.902$; $P = 0.002$), the overall male-female ratio was 1.5, CLP male-female ratio was 1.7, and CL male-female ratio was 1.7; separate clefts of the lip and palate occurred exclusively in boys, with one exception.

Average paternal age was 29.5 years (DS 8.0), ranging from 17 to 64 years, and the average maternal age was 27 years (DS 7.13), ranging from 14 to 55 years. An association was observed between the incidence of clefts and paternal age (X^2 20.470; $P = 0.000$) and maternal age (X^2 14.791; $P = 0.005$). The highest number of cases was recorded for those in their third and fourth decades.

The average parity was 3 (SD: 2.54), the minimum being one, and the maximum 16. Of the mothers with a parity of between one and 4, 40% were in their second decade. Among the babies, 32% were first born, 21% were the product of a second gestation, 13% the third, 10% the fourth, and 6% the fifth and sixth respectively; 10% were product of a seventh or higher number of gestations. A history of abortion was reported by 118 mothers: minimum one and maximum four, with an average of 1.44 (SD: 0.69). One abortion was reported by 51% of the mothers, two by 32%, and three and four by 17% (Kendall's tau-b 0.235 $P = 0.006$). The number of abortions and parity showed a significant correlation of 0.241 $P = 0.001$.

Birth weight was registered in only 485 cases, with an average of 3.088 (SD: 0.47), a minimum of 1,600 g, and a maximum of 4,000 g; 17% of the babies weighed 2,500 g or less.

Two cases exhibited Treacher Collins syndrome, four cases 18 trisomy syndrome, one case 21 trisomy syndrome, and five cases 13 trisomy syndrome. Associated congenital defects were observed in 4.5% of the patients: four had microcephaly, two had holoprosencephaly, 23 had polydactyly/syndactyly, and 7 had cardiovascular anomalies. Consanguinity was present in 22 cases (2%).

About 15% of the mothers had used medication during the first trimester of pregnancy: antibiotics (38%), vitamins (26%), contraceptives and hormones (11%), antiemetics, analgesics and antihypertensive medicine (6%), respectively, with no specified type, in addition to one patient (0.7%) who received anti-rabies vaccine. Alcohol consumption was reported in 40.02% of the cases and smoking in 26%, although it was unspecified whether the mother or the father had been the consumer. Paternal occupation was reported to have been mainly agricultural activities (44.7%) in addition to a variety of other occupations (40.2%) including plumber, mechanic, construction, commerce, and unspecified hourly employment. The mother's occupation was typically housework (95.56%), office (2%) and hourly employment (0.2), but 35% reported being engaged in agricultural activities during sowing and harvest time.

Paternal education level was registered in only 830 cases; elementary education alone was recorded in 51%, secondary school in 30%, high school in 6.2%, and higher education in 3%. Some parents had had an inconclusive education, and 9% were illiterate. The mothers' education level was registered in only 896 cases: elementary education in 52%, secondary school in 22%, high school in 7%, and higher education in 3%; education was inconclusive in some, and 16% were illiterate.

Discussion

There has been no reliable information about the incidence of oral clefts in Mexico due to the lack of a well

established and continuous national registration system. According to the WHO (3), the Mexican Registry and Epidemiological Surveillance of External Congenital Malformations (RYVEMCE) reported a rate of 17.29 × 10,000 for a total of 34,128 births during 2002-2003, the number of births registered in the country during this period being 2,655,894. The RYVEMCE program was started in 1978, and reports are obtained from 21 hospitals in 11 cities, in Mexico. Mexico State Registry and Epidemiological Surveillance (SUIVE, 2005) (4) reported 341 cases of oral clefts during the 2004-2005 period, from an unspecified number of public hospitals. The number of babies born with oral clefts in private clinics and hospitals, as well as the number born at home, remains unknown. Although the SUIVE program was started in 2004, registration of these anomalies became mandatory only recently.

The distribution of oral clefts by gender, as well as by type (unilateral/ bilateral), extension (complete/incomplete), and side (left/right), was similar to that in previous national (1,2) and international reports (5-8).

The risk of oral clefts has been reported to show racial/ethnic differences due to genetic factors that are believed to account for some of these anomalies (9,10). Although the ethnicity of the patients was not registered, some municipalities with a high number of cases do indeed have indigenous populations such as Nahúatl, Otomí, Matlazinca and Mazahua. It is likely that the population of Mexico could have genetic susceptibility due to its complex mixture, in addition to environmental factors (11).

Sixteen per cent of the surveyed mothers were less than 20 years old, 54% were in their thirties and 30% were in their forties. Although it has been reported that younger and older mothers have an increased risk of giving birth to babies with oral clefts (12), the present results show that mothers in their third decade are twice as likely to bear infants with oral clefts, probably due to environmental, behavioral, and nutritional factors (13). The high altitude of the Toluca Valley (average 2683 m), in a genetically predisposed population, could also explain these features (14).

Babies with a birth weight of less than 2,200 g showed severe clefts. It seems that babies with a low birth weight have a higher risk of developing oral clefts (15). Birth weight is largely influenced by gestational age, in addition to tobacco and alcohol consumption (16,17), although this could not be confirmed in the present study as the data in the files was not specific. Maternal tobacco and alcohol use would affect intrauterine growth and birth weight. An additional contributing factor may be maternal nutrition during pregnancy (18), as most of the cases belonged to families with a very low income (National Institute of Statistical and Geographical Information, INEGI). The number of families with more than four offspring was also relatively high. It has been reported that multiparity could play a role in the prevalence of clefts (19). It has been suggested that multiparity and a high maternal age are linked. However, in this study the majority of cases were found in the first child, as opposed to only a few cases in mothers more than 40 years old.

Although information related to diseases during the first trimester was not registered or incomplete, in 15% of the cases the mothers reported using medication that, according to the literature, could be related to clefting (20-25). Antibiotics and many medicaments in México are available without medical prescription, thus increasing the prevalence of self medication and the risk of exposure to harmful substances during pregnancy.

As mentioned previously, paternal occupation was found to be mainly agricultural and jobs associated with possible exposure to solvents that are related to CLP development. (26-27) Maternal occupation was generally housework. A seasonal incidence of oral clefts had been reported (28), and this has been attributed to environmental factors (29). In this study, a variation in the frequency by year was noted, but no seasonal relationship was observed, as this information was not registered in the files. However, seasonality of CLP incidence in relation to sowing, fumigation or harvest periods could be possible, as women often work during these periods. This would suggest exposure to agricultural chemical (30).

The average number of abortions among the studied women was high, and this could have been related to pesticide exposure (31), or toxoplasmosis, as in the study area most of the population raised cows, sheep or pigs. There is also a possible relationship with mycotoxins found in farming grains that are grown in the state. According to Kristensen et al. (32), mycotoxins in grain induce labor at an early stage of pregnancy.

It is also possible that lead contamination is present in the districts of Metepec and Temascalcingo resulting from ceramics manufacture, as these areas are famous for their pottery. Another source may be antiquated or new home water pipelines, welded together with lead; as such plumbing is still common in Mexico (33).

A high number of files reported relatives with non-syndromic oral clefts, also there were relatives with nonclefts and nonsyndromic congenital anomalies, the majority were uncles, aunts and cousins. Both, cleft cases and their affected relatives live in districts with indigenous inhabitants, they relied economically on pottery and

agriculture, in addition they live in industrial areas with hazardous waste from plastic and electronic manufacturing. (34) These environmental factors have been associated with oral clefts development.

The available information of the family cases was no enough to determine the recurrence risk and heritage, although parental consanguinity was reported in five of these family cases.

On the other hand, parental consanguinity was detected in a low percentage. Even so, consanguinity, relatives with oral clefts, as well as, the presence of congenital malformations in relatives could suggest genetic predisposition (35).

Associated noncleft congenital anomalies, as well as syndromic oral clefts seen in this study were similar to those reported previously (36).

As the education level for both parents was generally low, lack of information about nutrition and health care during pregnancy may be an influencing factor. The use of medication without medical prescription is common, in addition to a high prevalence in communities with low incomes, resulting in limited healthcare access (37).

This retrospective study provided preliminary data that allowed us to identify the districts that showed the highest prevalence of CLP. These included municipalities with ethnic populations, industrial and agricultural areas, and pottery activities. A number of family cases were also seen in these communities. It was not possible to identify the smoking and alcohol consumption habits of mothers, seasonality, or exposure to specific medication, chemicals or agrochemicals, from the information registered in the files. The possibility of maternal exposure to pesticides was high, as mothers were often involved in seasonal sowing.

A lack of information in the files during the study period

Table 1 Type and gender distribution of cleft lip with or without cleft palate, and cleft palate

Type of cleft	Male*		Female**		Total	%
Lip	41	63%	24	37%	65	8
Lip and Palate	373	63%	217	37%	590	70
Palate	84	48%	89	52%	173	21
Separated cleft lip and cleft palate	6	85%	1	15%	7	1
Total	504	60%	331	40%	835	100

*CLP and CL X^2 14.17 $P = \leq 0.003$ IMIEM Files

**CP X^2 15.991 $P = \leq 0.014$

A significant difference between males and females was noted, considering cleft lip with or without cleft palate. Cleft palate was observed in 160 cases (19%), while sub-mucous palate was detected in 13 cases (1.5%). The CP male:female ratio was 1:1, but females were affected significantly more often.

Table 2 Laterality and gender distribution of cleft lip, with or without cleft palate

Extension	CL Unilateral right side		CL Unilateral left side		CL Bilateral		CLP Unilateral right side		CLP Unilateral left side		CLP Bilateral*		Total	
Gender	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Complete	-	-	-	-	7	6	97	60	132	89	96	50	332	205
Incomplete	14	6	20	12	-	-	22	7	26	11	-	-	82	36
Total	14	6	20	12	7	6	119	67	158	100	96	50	414	241

*Kendall's tau-b 0.047 $P \leq 0.031$. IMIEM Files

The results show that 75% of clefts were unilateral, and that a higher number (58%) affected the left side, without a significant difference in laterality or gender. Complete CLP was observed in 81% of cases and complete CL in 3%, the complete bilateral type occurring mainly in males.

Table 3 Frequency of family cases according to affected relatives and types of cleft

Affected relatives	Cleft lip	Cleft lip palate	Cleft palate	Separated cleft lip and palate	Total
Parents	-	7	3	-	10
Grandparents	1	9	1	-	11
Paternal uncles and aunts	5	29	6	-	40
Maternal uncles and aunts	7	35	7	-	49
Siblings	-	15	4	1	20
Cousins	5	42	4	2	53
Total	18	137	25	3	183

IMIEM Files

Affected relatives were reported in 183 cases (19%); cousins (29%), maternal aunts and uncles (27%), paternal aunts and uncles (22%), siblings (11%), grandparents (6%), and parents (5%).

Table 4 History of affected relatives and working activities by district with indigenous populations

Main activity by District	Indigenous inhabitants	Affected relatives						Total
		Parents	Grandparents	Paternal uncles	Maternal uncles	Siblings	Cousins	
Agriculture	Yes	3	2	7	1	1	13	27
Floriculture	No	-	2	6	11	2	4	25
Agriculture	No	-	2	6	4	4	8	24
Industry and Agriculture	Yes	2	1	6	4	2	3	18
Agriculture Pottery	No	2	1	-	5	2	7	17
Agriculture	Yes	-	-	6	7	2	1	16
Industry and Agriculture	Yes	1	-	3	3	3	6	16
Agriculture Pottery	No	2	-	2	5	-	3	12
Districts with less than 3 cases	No	-	3	4	9	4	8	28
Total		10	11	40	49	20	53	183

INEGI and IMIEM Files

Even though some patients came from urban communities, the majority were born in rural areas and very poor towns, some with indigenous inhabitants, such as Nahúatl, Otomí, Matlazinca, Mazahua. The majority of these districts have municipalities with agricultural, industrial, pottery and handicraft activities. These facts should be taken into consideration in families with several affected relatives.

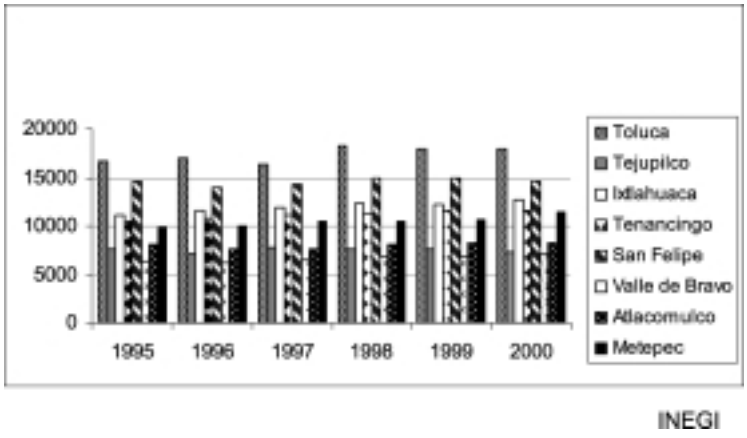

Fig. 1 Number of live births by year and district.
Each district has a variable number of municipalities. Those with a larger number of municipalities logically have a higher birth rate. The two largest districts are Toluca and San Felipe del Progreso.

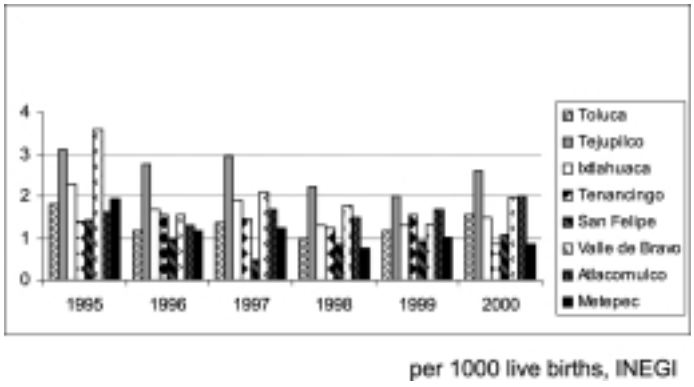

Fig. 2 Distribution of cleft rates by year and district.

was noted, and it is unknown whether this was due to incomplete clinical interview or incomplete registration of the information. A computer registration system has now been created to record the types of cleft and their predisposing factors.

It will be necessary to improve the efficiency of case control studies to clarify the role of predisposing factors detected in this exploratory study.

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