



MEMORANDUM

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

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From: Dana C. Crawford, EIS Officer, Birth Defects and Pediatric Genetics Branch (proposed, BDPGB), Division of Birth Defects, Child Development, and Disability and Health (proposed, DBDCDDH), National Center for Environmental Health (NCEH).

Subject: Epi-Aid Trip Report: Possible Cluster of Orofacial Clefts (EPI-2001-08)

To: Director, Division of Training, EPO

Through: Coleen Boyle, Director, DBDCDDH, NCEH

Copies: Cynthia Moore, Richard Olney, Larry Edmonds, Bonnie Bashor, William Moore, Deborah Pauli, Jill Brown, Dave Erickson

INTRODUCTION

Orofacial clefts are usually classified as either cleft lip \pm palate (CLP) or cleft palate only (CPO). CLP derives from the embryologic primary palate and involves the lip and alveolar ridge anterior to the incisive foramen (1). In CLP, cleft lip can occur alone or involve the lip and the palate. Accompanying cleft palate can involve the entire secondary palate. In contrast, CPO derives from the secondary palate and involves incomplete fusion of the palatal shelves. CLP and CPO may be incomplete or complete, unilateral or bilateral, with the left more commonly affected than the right (1;2). Complete clefts of the palate include both the primary and secondary palate and are usually associated with a cleft lip. Complete bilateral clefts of the palate are almost always associated with bilateral cleft lip. Submucous clefts include defects of the hard and soft palate with a mucosal web bridging the segments and have three characteristic signs: notching of the posterior border of the hard palate, muscular diastasis of the soft palate with mucosal integrity, and a bifid uvula (1).

CLP and CPO are common birth defects, affecting approximately 1-2 per 1,000 and 0.7 per 1,000 live births, respectively (3;4). Of the cases of orofacial clefts, typically 33% involve cleft palate alone, 46% involve cleft lip and palate, and 21% involve cleft lip alone (1). CLP and CPO are thought to be etiologically distinct and rarely occur in the same family. However, it is not uncommon to observe either CLP or CPO occurring within families, suggesting a genetic component. In the United States, the rate of CLP tends to be higher among Caucasians than among African-Americans, while rates of CPO are more consistent across racial or ethnic groups (3). Compared with CLP, additional anomalies are more common among cases of CPO. CLP occurs more commonly in males than females, and the reverse is true for CPO. As many as 40% of infants with clefts have additional defects (5).

Some cases of orofacial clefts are attributable to chromosomal abnormalities or a

malformation syndrome, many of which are single gene disorders. One such disorder is the 22q11 deletion syndrome. In one series of 181 patients with 22q11 deletions, 27% had velopharyngeal incompetence (VPI), 16% had submucosal cleft palate, 11% had overt cleft palate, 5% had bifid uvula, and 2% had CLP (6). However, the majority of cases do not have a pattern of simple Mendelian genesis; therefore, the origin is thought to be an interaction between genetic susceptibility and the environment (7;8). Intrauterine exposure to anti-epileptic drugs or isotretinoin is known to increase the risk for orofacial clefts, while maternal cigarette smoking, stress, obesity, diabetes, and exposure to organic solvents have sometimes been associated with an increased risk for cleft formation (9-13). First trimester multivitamin use has been linked to a decreased risk for clefts (14).

BACKGROUND

In June 2000, the Tennessee Department of Health (TDH) was alerted by a local early intervention center of a possible cluster of orofacial clefts in Dickson County, Tennessee beginning in 1997. Through case finding at local birth and pediatric hospitals, the TDH identified 18 cases of orofacial clefts born to Dickson County residents for the 1997-October 2000 period. A cluster investigation was performed by the TDH and the CDC to identify the risks factors contributing to the increased rate of orofacial clefts in Dickson County, TN.

METHODS

Case Definition

A case was defined as an infant with CLP or CPO (ICD-9-CM codes 749.00-749.25) born between January 1997 and October 2000, to a mother whose residence was Dickson County at the time of birth. The diagnosis of CLP or CPO was determined by a medical professional, usually at birth or at time of surgical repair.

Additional Case-Finding

In addition to the cases already identified by the local early intervention center, the TDH requested that the local hospitals search discharge data for ICD-9-CM codes 749.00-749.25 and birth certificate records for the period of January 1997-October 2000.

Case Review

The type and severity of clefting was determined by abstracting data from the infants' birth and surgical records and the mothers' obstetric records.

Case Mother Interviews

Case mothers were interviewed in-person using a computer-assisted interview (CAI) to identify any shared risk factors. The CAI used for the interviews was designed for the National Birth Defects Prevention Study to ascertain a broad spectrum of exposures potentially related to the occurrence of birth defects. This CAI includes

questions related to the mother's health, pregnancy history, reproductive history, lifestyle, occupational exposures, and multivitamin use. These questions are designed to examine the factors hypothesized to play a role in the etiology of birth defects. The CAI also includes a few questions regarding the infant's biological father. In addition to the CAI, a family history questionnaire was sent to the mothers prior to the interview appointment. The questionnaire was designed by the Universities of Iowa and Arkansas as part of the National Birth Defects Prevention Study to obtain information about family history of orofacial clefts and was slightly modified for this investigation.

PRELIMINARY RESULTS

Confirmation of cluster

All 18 case mothers were verified as residents of Dickson County at the time of birth. Currently, the state of Tennessee does not have a statewide birth defects monitoring system. Because of the lack of such a system in Dickson County, several different approaches were taken to establish the rates for orofacial clefting for the county and the state before 1997. First, data from the 1991-1993 Department of Energy (DOE) funded birth defects registry in the state of Tennessee were used to establish statewide baseline rates (Table 1). This registry was a pilot project that used a combined active and passive surveillance approach to ascertain cases occurring in state, born to state residents (15). During the 1991-1993 period, a total of 169 CLP and 66 CPO cases were identified, yielding rates of 0.76 and 0.30 per 1,000 live births, respectively. Compared with state rates, Dickson County rates for CPO were higher (0.60 vs 0.30) while rates for CLP were lower (0.60 vs 0.76) (Table 1). The DOE funded birth defects registry recorded one case of CLP and one case of CPO among Dickson County's 1,601 live births between 1991 and 1993. However, because this registry relied on both active and passive reporting of birth defects, complete ascertainment of orofacial clefts during the specific period may not have been achieved.

To further determine the rates of orofacial clefts for Tennessee and its specific counties, data from 1989-1996 vital statistics were examined (Table 1). Beginning in 1989, a new version of the Certificate of Live Birth was introduced to the state of Tennessee that included specific check boxes for the occurrence of 21 different congenital anomalies, including 'cleft lip/palate.' From these data, the rate for orofacial clefts for the state of Tennessee between 1989-1996 was 0.97 per 1,000. The cleft rate for Dickson County for the same period of time was 1.6 per 1,000. While the rate for orofacial clefts in the state remained relatively constant throughout the 1989-1996 period, the rates for Dickson County varied considerably, with a high of 5.42 per 1,000 recorded in 1989 and a low of zero births with clefts in 1993, 1995, and 1996. This variability is somewhat expected given the relatively low number of live births per year in Dickson County.

Table 1. Establishing baseline rates of CLP and CPO

	Source	Overall Cleft rate per 1,000	CLP rate per 1,000	CPO rate per 1,000
1991-1993 ¹	Dickson County	1.25	0.625	0.625
1989-1996 ²	Tennessee	0.97	-	-
1989-1996 ²	Dickson County	1.60	-	-
1989-1996 ³	MACDP	1.48	0.93	0.55
1989-1996 ⁴	NBDPN	1.51	0.89	0.62

¹Department of Energy funded birth defects registry

²Vital statistics data

³Metropolitan Atlanta Congenital Defects Program

⁴National Birth Defects Prevention Network; period of surveillance varied among the states.

The accuracy of these data and estimated rates as recorded by vital statistics, however, is questionable. Despite the improved coding of the Certificate of Live Birth, clefts continue to be under-reported in birth certificates (16). In fact, for the 1997-1999 period in Dickson County, only 3 cases of orofacial clefts were recorded, giving a rate of 1.64 per 1,000 for this three-year period. In comparison, active case finding for the area ascertained a total of 13 cases of orofacial clefts for this time period, highlighting the under-reporting of such cases in the Certificate of Live Birth (Table 2). A second limitation in vital statistics data is the fact that CLP and CPO are not distinguished; thus, separate rates could not be established for the county of interest.

Because of the limitations of the DOE funded registry and the vital statistics data, expected rates for CLP and CPO instead were estimated using data from the Metropolitan Atlanta Congenital Defects Program (MACDP) and the National Birth Defects Prevention Network (NBDPN) (Table 1). Established in 1967, MACDP is a population-based, active surveillance program that ascertains both CLP and CPO in the five-county area of metropolitan Atlanta, Georgia. The NBDPN is a collaboration among states to share surveillance data for selected congenital anomalies. Currently, 26 states report CLP rates and 25 states report CPO rates. The rates for CLP and CPO estimated by MACDP between 1989-1996 were 0.93 and 0.55 per 1,000, respectively (15). In comparison, the rates estimated by the NBDPN for CLP and CPO were 0.89 and 0.62 per 1,000, respectively. The generalizability of MACDP and NBDPN data to clefting rates in Tennessee is uncertain as the different sources of data may represent different population demographics that impact overall CLP and CPO rates.

Despite the lack of baseline rates for CLP and CPO in the county of interest, a compilation of rates for the 1997-October 2000 period revealed higher than expected rates for both CLP and CPO (Table 2). Based on the MACDP rates for CLP and CPO, the number of births for 1997-1999 in Dickson County, and the anticipated number of births for 2000 in Dickson County, two to three infants with CLP and one infant with CPO during the 1997-October 2000 period were expected. Compared with the MACDP data, the Dickson County

rates during 1997-October 2000 for both CLP and CPO are five-fold greater than expected. Exclusion of infants who had a variant type of clefting (4 infants—see Case Review) from the case group does not decrease the rates into the expected range.

Table 2. Rates of CLP and CPO for Dickson County, TN, 1997-2000

	# Live births	CLP	Rate per 1,000	CPO	Rate per 1,000
1997	589	2	3.4	0	-
1998	589	4	6.8	3	5.0
1999	621	2	3.2	2	3.2
2000*	600	3	5.0	2	3.3
1997-2000*	2399	11	4.6	7	2.9

*The number of live births for 2000 was estimated as the mean number of live births for 1997-1999. Rates assume that no infants with clefts will be born in November-December, 2000.

Case Review and Maternal Interviews

Diagnostic information was abstracted from infants' and mothers' medical records. Among the infants with CLP, 2/11 (18%) had other significant anomalies reported. One infant had low set ears and a moderately-sized PDA closed with an intravascular device. The second infant, who died shortly after birth, had microcephaly, congenital heart defect (enlarged right ventricle and overriding aorta), and a low set left ear without an external canal. Among the infants with CPO, 3/7 (43%) had other anomalies reported. One infant had posteriorly rotated external ears, one had left vertical talus, and one had pre-auricular skin tag with no pit. Two infants (2/18; 11%) were documented with developmental delay. None of the infants had a recorded chromosomal abnormality; however only a few infants (17%) had chromosomal analysis documented. Based on medical record review, none were tested for 22q11 deletion syndrome.

Among the 18 case infants, the type and severity of clefting ranged from mild to severe (Table 3). Overall, the most common form of clefting was bilateral cleft lip and palate (44%), followed by overt cleft palate only (22%). Two of the infants classified as CPO could be confirmed only as possible submucous clefts (bifid uvula with notched hard palate); one additional infant as bifid uvula with VPI. For the one infant with a pseudocleft of the lip (rare cleft variant resembling a surgically corrected cleft lip), involvement of the palate could not be established due to limited diagnostic information available. Due to the nature of the phenotypes, these types of clefts are likely to be underascertained in both Dickson County and most reference surveillance systems, including MACDP and NBDPN.

Table 3. Type and severity of clefting

	Number	Frequency
CLP total	11	61%
Pseudo	1	6%
Unilateral	2	11%
Bilateral	8	44%
CPO total	7	39%
Overt	4	22%
Possibly submucous only	2	11%
Bifid uvula, VPI	1	6%

Interviews were completed for 15 of the 18 case mothers. Two case mothers were unavailable for interviewing and one case mother consented to be interviewed but was unavailable for the scheduled appointment. Repeated attempts to re-schedule the interview have been unsuccessful.

Most case mothers were 20-29 years of age at the time of conception, Caucasian, and had completed high school (Table 4). Examination of the epidemiologic factors associated with clefting revealed that 87% (13/15) did not take multivitamins one to three months prior to conception, and 13% (2/15) did not take prenatal vitamins. The reported multivitamin use among case-mothers (13%) is lower than that reported by a national survey of women of childbearing age (44.3%)(17). For questions related to smoking, 27% (4/15) of case-mothers reported smoking cigarettes throughout the entire first trimester of pregnancy. Furthermore, 47% (7/15) of case-mothers reported smoking anytime during the first trimester of pregnancy. Case-mothers reported more smoking during pregnancy (47%) compared with a national survey of women of childbearing age that included pregnant women (12%)(18). In addition to these two factors, two case mothers (13%) had prepregnancy body mass indices (BMI) >30 and had pregnancies complicated by diet controlled gestational diabetes. None of the mothers reported consuming alcoholic beverages or taking medications known to increase the risk for clefting during the first trimester of pregnancy. Approximately half of the case mothers reported administrative duties as their occupation during pregnancy (Table 4), and none reported work-related exposures that are suspected to increase the risk for clefting (19;20).

Analyses of the family history survey revealed that 20% of case mothers reported either a family history of clefting (n=1) or a family history of tooth agenesis (n=2), which is a trait associated with clefting (21). Two case mothers reported some form of heart defects (a mitral valve prolapse and a ventricular septal defect). Among case fathers, family histories of an unspecified heart defect and a case of unspecified mental retardation was reported. Interestingly, two seemingly unrelated case-mothers reported a family history of a rare, hereditary motor-sensory neuropathy that is not known to be associated with clefting. The corresponding case-infants also had different cleft

phenotypes, making it unlikely that this neuromuscular disorder is associated with clefting in these families.

The case infant characteristics are also described in Table 4. The birth weight ranged from 1219 to 4196 g, with a mean of 2996 g. 22% of case infants were considered low birth weight compared with the national rate of ~7% (22); however, only one infant was considered small for gestational age. 33% of case infants were delivered preterm, which is higher than the national rate of ~11% (22). While the percentage of preterm births among the case infant population is higher compared with a national population, it may be that this increase is representative of a population of infants with orofacial clefts (23). The male to female ratio for CLP was 2.6:1, which is consistent with the sex ratio observed among the general population for CLP. For CPO, the observed male to female ratio was 1.3:1, which deviates slightly from the excess of female cases typically observed for CPO.

During the course of the interviews, many parents expressed concerns about reports in the local newspaper that trichloroethylene (TCE)-contaminated drinking water or toluene released into the air may be the cause of this clefts cluster. The Environmental Protection Agency (EPA) assisted the state by following up with these concerns. The scope of this investigation cannot determine whether or not the drinking water for the case mothers was contaminated with TCE during the first trimester of their pregnancies. However, the questionnaire was designed to characterize both water source and water use. The majority of case mothers used the water provided by Dickson County for drinking and cooking at home (87%). One case mother reported filtering this water for drinking and cooking. Another case mother who draws water from a private well reported using a filter for the shower.

Many case-parents also expressed concerns about a local city dump or landfill and its effect on birth defect rates. Again, the scope of this investigation cannot determine the contents of the landfill nor how they relate to the cluster of orofacial clefts in Dickson County. During the course of the investigation, however, we were able to collect data on case-mothers' residences during their pregnancies. Two case mothers reported living less than two miles from the landfill during their pregnancies (1 and 1.1 miles). Two other case-mothers reported living 3.1 and 3.8 miles from the landfill. All other mothers reported living greater than four miles from the landfill during their pregnancies.

Table 4. Case mother and infant characteristics

Maternal Characteristics	Number	Percent
Age at conception (n=18)		
15-19	2	11
20-24	7	39
25-29	7	39
30-34	1	6
35-39	0	-
40-44	1	6
Race/ethnicity (n=18)		
Caucasian	17	94
African-American	1	6
Education level (n=15)		
9-11 years	1	7
High school or equivalent	7	47
1-3 years college	4	27
4 years college or bachelor's degree	3	20
Occupation (n=15)		
Administration	8	53
Health Care	2	13
Production	1	7
Professional	2	13
Service	1	7
Teacher	1	7
Parity (n=18)		
0	10	56
>1	8	44
Prepregnancy BMI (n=15)		
<25	9	60
25-30	4	27
>30	2	13
Prenatal vitamins (n=15)		
Yes	13	87
No	2	13
Smoked ever (n=17)		
Yes	10	59
No	7	41
Diabetes during pregnancy (n=17)		
Type I or II	0	-
Gestational*	2	12
None diagnosed	15	88

**Some familial form of clefting
(n=15)**

Yes	3	20
No	12	80
Water source (n=15)		
Private well	2	13
City-supplied	13	87

Infant Characteristics	Number	Percent
Preterm (<37 weeks; n=18)		
Yes	6	33
No	12	67
Birth weight (n=18)		
<2500g	4	22
≥2500g	14	78
Sex, CLP (n=11)		
Male	8	73
Female	3	27
Sex, CPO (n=7)		
Male	4	57
Female	3	43

BMI=body mass index (kg per meter²)

*Controlled by diet

DISCUSSION

A cluster is a greater than expected number of cases in a population for a defined geographic area and period of time (24). The cases described within this report during the specific period of 1997-October 2000 meet the definition of a cluster. The majority of these cases can be classified as nonsyndromic. However, previous testing for 22q11 deletion was not identified for any of the infants. Although specific risk factors associated with clefting were identified among the 18 case mothers, it is unlikely that any one factor examined in this investigation could account for the increased rates in the county.

As mentioned previously, baseline rates for Dickson County could not be established with certainty. It is possible that Dickson County's baseline rate for orofacial clefts is elevated compared with statewide or national rates. Interestingly, geographic clusters of orofacial clefts have been reported in the literature (25;26). Also, a recent study spanning 26 years observed that the births of infants with orofacial clefts tended to cluster over time, between which there are gaps of different duration that are independent of seasonal or live birth oscillations (27). Therefore, the increased rates for clefting in Dickson County could be due to an undetermined teratogenic exposure, elevated baseline rates, or statistical fluctuation.

RECOMMENDATIONS

Continued monitoring of the county is recommended to determine if the increased rates of orofacial clefting are due to elevated baseline rates or statistical fluctuation. If the rates are continuously elevated compared with the state and national rates, a more formal case-control study would be needed to quantify the risks associated with the known factors and to test new hypotheses that may yet emerge. At this time, the state of Tennessee does not have a birth defects surveillance program that could serve this community. Local hospitals could fill this surveillance gap by closely monitoring the rates of CLP and CPO determined by discharge diagnoses. The county could also periodically collaborate with Vanderbilt University Medical Center in Nashville as the majority of Dickson County clefts were repaired at Vanderbilt. Finally, the local early intervention center could also continue to monitor the number of children from Dickson County referred for speech difficulties. All potential new cases of clefting must be reviewed medically to determine if they meet the clinical criteria for orofacial clefts. The Birth Defects and Pediatric Genetics Branch at the CDC will be available for assistance in planning surveillance if needed.

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This trip report summarizes the field component of the investigation and is preliminary in nature. It is possible that future correspondence or reports may present results, interpretations, and recommendations that differ from those contained in this document. If further analyses substantially alter any of these findings or recommendations, you will be notified promptly.

Dana C. Crawford, Ph.D., EIS Officer
Birth Defects and Pediatric Genetics Branch
Division of Birth Defects, Child Development, and Disability and Health
National Center for Environmental Health