Etiology of Facial Clefts: Prospective Evaluation of 428 Patients

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This article presents the results of prospective evaluation of 428 patients with facial clefts or velopharyngeal insufficiency who were evaluated through the Cleft Palate Program at Children's Hospital, San Diego. Children were examined for patterns of major and minor malformations, and an attempt was made to identify the etiology of the overall pattern of altered structure. Results indicate that 14 percent of 259 patients with cleft lip ± cleft palate, 55 percent of 139 patients with cleft palate, 75 percent of 24 patients with velopharyngeal insufficiency, and 83 percent of 6 patients with atypical clefts had a multiple malformation syndrome. The frequency with which syndromic clefting occurs is higher than previously recognized. Recognition of underlying etiology is important with respect to prognosis and recurrence risk counseling of families and patients. In addition, the underlying diagnosis may significantly impact outcome of medical and surgical treatment of the cleft disorder.

KEY WORDS: *multiple malformation syndrome, cleft lip ± cleft palate, cleft palate, velopharyngeal insufficiency, Stickler syndrome.*

Despite the fact that there are well over 150 recognized disorders in which cleft lip, cleft palate, or both may represent one feature (Cohen, 1978), it is widely believed that the majority of affected individuals are otherwise structurally normal (Fraser, 1970). Numerous epidemiologic studies have documented the nature and frequency of associated defects in children with facial clefts using retrospective chart reviews and birth certificate surveys (Bear, 1976; Emanuel et al, 1973; Fraser and Calnan, 1961; Knox and Braithwaite, 1963, Meskin and Pruzansky, 1969; Welch and Hunter, 1980). Although both methods have consistently demonstrated that a proportion of individuals with cleft lip and palate and a greater proportion of individuals with cleft palate have other anomalies, few attempts have been made to utilize this information to advance understanding of the etiology and developmental pathogenesis of facial clefting (Kadasi, 1980).

Reported in this study is a prospective evaluation of 428 consecutive patients presenting for treatment of facial clefting or velopharyngeal insufficiency to the Cleft Palate Program, Children's Hospital, San Diego. The purposes of this report are to document the frequency with which cleft lip with or without cleft palate, cleft palate alone, and velopharyngeal insufficiency present as one feature of a multiple malformation syndrome and to emphasize the importance of making a specific overall diagnosis when counseling a family with respect to prognosis and the risk of recurrence. Furthermore, recognition that some similarly appearing facial clefts have differing etiologies suggests differences in developmental pathogenesis that might well have significant impact regarding surgical and other treatment modalities.

METHODS

Every child presenting to the Cleft Palate Program at Children's Hospital and Health Center, San Diego during the years 1980 through 1985 was prospectively evaluated by a single ex-

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This paper was presented at the 5th International Congress on Cleft Palate and Related Craniofacial Anomalies, September, 1985 in Monte Carlo.

aminer. Since the diagnosis of a multiple malformation syndrome is almost always based on the presence of a pattern of minor anomalies, careful search was made for both major and minor malformations. An attempt was made to identify an etiology of the overall pattern of anomalies where one existed. Pedigree information was obtained at the first visit and supportive laboratory testing was used where deemed clinically appropriate.

If a recognized pattern of malformation could not be identified, an individual was felt to have a multiple malformation syndrome if, in addition to the cleft, there were two or more major malformations or three or more minor malformations not explained on a familial basis.

Based upon the overall assessment, an individual was felt to have either a single primary defect in development or a multiple malformation syndrome. In the few instances where uncertainty existed, the case was classified as a single primary defect.

Patients were grouped into four categories based upon the anatomic presentation of the cleft: (1) cleft lip with or without cleft palate; (2) cleft palate alone; (3) velopharyngeal insufficiency without obvious, abnormal intraoral structure; and (4) atypical facial clefts (midline, oblique, lateral). Initially, an attempt was made to separate Robin-type palatal clefts from more typical v-shaped clefts. Because many children were evaluated years after initial repair, this proved impossible. Both types of clefts were categorized as cleft palate alone.

RESULTS

Four hundred and twenty-eight consecutive patients were evaluated. The distribution of patients by presentation of the cleft problem are set forth in Table 1.

The number and percentage of each group with multiple malformation syndromes versus single primary defects in development are set forth in Table 2.

Five of the six children (83.3 percent) with atypical facial clefts had major malformations of the central nervous system. These included three children with midline clefts of the lip and palate associated with holoprosencephaly, one child with a unilateral cleft lip and palate extending into the lacrimal ducts associated with a small anterior encephalocele, and one child with bilateral clefts extending into the lacrimal ducts associated with bilateral colobomatous microphthalmia, ocular hypertelorism, cryptorchidism, and micropenis. One child with bilateral oblique facial clefts was otherwise normal.

TABLE 1 Anatomic Classification by Cleft Site

Cleft Group	*N*	*%*
Cleft lip ± cleft palate	259	60.5
Cleft palate alone	139	32.5
Velopharyngeal insufficiency	24	5.6
Atypical facial clefts	6	1.4
Total	428	

TABLE 2 Frequency of Multiple Malformation Syndromes Within Each Cleft Group

Cleft Group	*N*	*%*
Cleft Lip ± Cleft Palate		
Single primary defect	222	85.7
Multiple malformation syndrome	37	14.3
Total	259	
Cleft Palate Alone		
Single primary defect	63	45.3
Multiple malformation syndrome	76	54.7
Total	139	
Velopharyngeal Insufficiency		
Single primary defect	6	25
Multiple malformation syndrome	18	75
Total	24	

Of the 37 patients with cleft lip ± cleft palate and a multiple malformation syndrome, 23 (62 percent) had a recognized pattern. Table 3 lists the specific diagnoses in these patients along with recurrence risk for each.

Of the 76 patients with cleft palate alone and a multiple malformation syndrome, 34 (45 percent) had a recognized pattern. Table 4 sets forth the specific diagnoses in these patients.

Of the 18 patients with velopharyngeal insufficiency and a multiple malformation syndrome, 8 (44 percent) had a recognized pattern. Table 5 presents the specific diagnoses. Although six children in the overall velopharyngeal insufficiency group were felt to be otherwise normal on a structural basis, five of these individuals require special educational assistance for learning disorders, hyperactivity, sensory or oral motor problems, or a combination. The one remaining child had a genetically determined, autosomal dominant family history of similar speech problems.

DISCUSSION

The results of this study demonstrate that a significant portion of children presenting to cleft palate treatment programs have the cleft as one feature of a broader pattern of malformation. Of the total 428 patients seen in our clinic, 29 percent had an underlying disorder.

The percentage of patients with cleft palate

TABLE 3 Cleft Lip ± Cleft Palate: 23 Patients With Recognized Syndromes

Syndromes by Etiology	*Recurrence Risk*
Cytogenetic Etiology (N = 5)	
1 Trisomy 21	1%
1 Monosomy 1q (de novo)	Negligible
1 Monosomy 4p (de novo)	Negligible
1 Monosomy 6q (de novo)	Negligible
1 Ring 18 (de novo)	Negligible
Single Gene Defects (N = 7)	
4 Van der Woude syndrome	
2 familial	50%
2 sporadic	Negligible
1 Aarskog syndrome (carrier mother)	50% males
1 Opitz syndrome (carrier mother)	50% males
1 Coffin-Siris syndrome	25%
Teratogens (N = 8)	
2 Fetal alcohol syndrome	Exposure dependent
2 Fetal primidone syndrome	Exposure dependent
2 Fetal hydantoin + primidone syndrome	Exposure dependent
1 Fetal hydantoin syndrome	Exposure dependent
1 Diabetic embryopathy	Unknown
Unknown Genesis Disorder (N = 3)	
3 CHARGE association	Low

TABLE 4 Cleft Palate Alone: 34 Patients With Recognized Syndromes

Syndromes by Etiology	*Recurrence Risk*
Cytogenetic Etiology (N = 6)	
2 Trisomy 21	1%
1 Monosomy 4p (translocation parent)	33%*
1 Monosomy 11q (de novo)	Negligible
1 Trisomy 17p (translocation parent)	33%*
1 Prader-Willi syndrome (de novo 15q deletion)	Low
Single Gene Disorders (N = 24)	
14 Stickler syndrome	
9 familial	50%
5 sporadic	Negligible
1 Campomelic dysplasia	25%
1 Cleft palate/short stature syndrome (familial)	50%
1 Diastrophic dysplasia	25%
1 Nager syndrome (sporadic)	Negligible
1 Orofacialdigital syndrome (affected mother)	33% (females)
1 Otopalataldigital II syndrome (carrier mother)	50% (males)
1 Smith-Lemli-Opitz syndrome	25%
1 Treacher Collins syndrome (familial)	50%
1 Velocardiofacial syndrome (sporadic)	Negligible
1 Van der Woude syndrome (familial)	50%
Teratogens (N = 5)	
3 Fetal hydantoin syndrome	Exposure dependent
2 Fetal alcohol syndrome	Exposure dependent
Unknown Genesis Disorders (N = 3)	
2 Facioauriculovertebral malformation sequence	low
1 Beckwith syndrome	low

* Recurrence risk counseling for balanced translocation carrier is complex and depends upon the sex of the carrier parent and the nature of the translocation. The risk quoted is a theoretical maximum.

TABLE 5 Velopharyngeal Insufficiency: 8 Patients with Recognized Disorders

Syndromes by Etiology	*Recurrence Risk*
Cytogenetic Etiology (N = 1)	
1 Monosomy 18q (de novo)	Negligible
Single Gene Disorders (N = 6)	
4 Velocardiofacial syndrome	
3 familial	50%
1 sporadic	Negligible
1 Primary Microcephaly	25%
1 Multiple Epiphyseal Dysplasia (sporadic)	Negligible
Unknown Genesis Syndrome (N = 1)	
1 Facioauriculovertebral malformation sequence	Low

alone and velopharyngeal insufficiency with multiple malformation syndromes is much higher than has previously been recognized. Several factors may account for this discrepancy. Most authors ascertained the presence of associated defects in a retrospective fashion, using the hospital or clinic chart or birth certificate. Those studies depend upon the recording practices and diagnostic skills of the individuals who actually evaluated the patients. Minor malformations are virtually never recorded in hospital charts, and unless the specific syndrome was recognized at the time of evaluation, it is impossible to reconstruct a physical examination from records. As expected, past studies indicate that a higher percentage of associated defects is recorded when the authors are closer to the patient population in providing care (Emanuel et al, 1973; Meskin and Pruzansky, 1969; Welch and Hunter, 1980).

Two more recent studies have also emphasized both the frequency of associated defects and the genetic heterogeneity of facial clefting (Rollnick and Pruzansky, 1981; Shprintzen et al, 1985). Rollnick and Pruzansky retrospectively reviewed 4,180 patients seen at the Center for Craniofacial Anomalies at the University of Illinois. Muliple anomalies were identified in 35 percent of 1,365 patients with cleft lip with or without cleft palate, 54 percent of 806 patients with cleft palate alone, and 55 percent of 341 patients with submucous clefts. Shprintzen et al reviewed 1,000 patients with facial clefting from the Center for Craniofacial Disorders at Montifiore Medical Center. In their study 63.4 percent of the population had associated defects, and an increased percentage of multiple malformation syndromes was recognized.

Concern was raised by the authors of each paper regarding a possible ascertainment bias toward complex patients imposed upon the studies because of the nature of referral patterns of both centers. Since the cleft palate program at Children's Hospital of San Diego was not, during the years 1980–1985, the local center for care of children with complex craniofacial anomalies, this bias does not exist in the present study. Rather, the results of this study support the conclusion of these authors that facial clefting occurs more frequently as a part of a broader pattern of malformation than has been appreciated. Moreover, since the author of the present investigation was meticulous in excluding any child with a cleft seen for dysmorphology consultation who was not referred to and assessed by the team, this study clearly underrepresents the percentage of all facial cleft children with multiple malformation syndromes. Excluded from the study population are stillborn infants and those who do not survive to present to the team for treatment (Kadasi, 1980), a group which consists entirely of infants with multiple malformations, since it is rare for a child with an isolated cleft to die in infancy in the United States.

In addition, it is important to recognize that structural defects are not, for the most part, randomly associated. The presence of other major and minor malformations in association with a facial cleft implies that a single etiologic factor—genetic, chromosomal, or teratogenic—produced the pattern as a whole. In the future, investigators need to attempt to identify patterns of anomalies rather than "associated defects."

Of special importance is the frequency with which the Stickler syndrome is encountered (Opitz et al, 1972; Smith and Stowe, 1961; Liberfarb et al, 1981). This autosomal dominantly inherited condition is characterized by flat facies, epicanthal folds, dolichostenomelia, scoliosis, and arthritic symptoms in older individuals (Herrmann et al, 1975). The most devastating complications of this condition relate to ocular problems and include severe myopia, glaucoma, and retinal detachment. Because the disorder may be extremely difficult to recognize in infancy, the author recommends that all children with cleft palate alone should have an ophthalmologic evaluation in the first year of life. Of the 14 children with Stickler syndrome in the present study, the diagnosis had not been recognized in 12 prior to clinic evaluation.

The importance of identifying those individuals with underlying disorders cannot be overemphasized from the standpoint of patient care. Parents need precise information regarding the prognosis and recurrence risk of the condition in addition to assistance with treatment of the cleft. Such information is dependent upon the overall diagnosis.

In addition, investigators in the area of facial clefting need to consider underlying etiology in assessing such factors as speech development, altered neurodevelopmental function, midface growth, dental development, and the timing and nature of surgical reconstruction. It is suggested that many underlying conditions impact outcome despite the nature and timing of treatment received.

Acknowledgement. The author wishes to express her gratitude to Jan Kvandal for assistance in the preparation of this manuscript and for coordinating the program from which these data were obtained.

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