A Malformation Profile of Facial Cleft Patients and Their Siblings

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In order to gain further understanding of the pathologic processes leading to the development of facial clefts, a number of investigators have studied the frequency and type of anomalies that accompany these clefts. Greene and associates (*5*), in a survey of birth records from 17 states, found that 16.5% of the study population of facial clefts had an associated malformation noted on the birth certificate. This percentage is in accord with that noted in other investigations (*5*). That study also demonstrated that the frequency of occurrence of additional malformations is not uniformly distributed among the major cleft types. The greatest percentage of additional anomalies was noted in individuals with isolated cleft palate. Lesser frequencies of additional malformations were noted in cleft lip in combination with cleft palate and isolated cleft lip individuals, in that order. Similar studies by other investigators have demonstrated the same findings regardless of the population studied or the method used to obtain the information (*2, 4, 6, 7*).

In addition to this type of study, Drillien and associates (*1*) and Niswander and associates (*8*) studied the prevalence of malformation in relatives of facial cleft individuals. Relatives in these studies included grandparents, parents, aunts, uncles, cousins, and siblings. In these analyses, both investigative groups noted a higher number of total malformations in relatives of individuals with cleft lip in combination with cleft palate than was observed in relatives of individuals with cleft lip alone or isolated cleft palate.

The present study was designed to elicit additional information regarding the previously reported findings as well as to note if a characteristic profile of malformations in facial cleft patients and their siblings could be demonstrated.

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Methods and Materials

Facial cleft cases for study were derived from the records of the University of Illinois Cleft Palate Clinic. The specific information regarding malformations was obtained from two sources: 1) birth certificates of probands, controls, and their siblings, and 2) a mail questionnaire filled out by parents of the probands and controls. The questionnaire return rate for probands and siblings was 94%; and for controls and siblings, 86%. From this return, complete information was received regarding 372 facial cleft individuals and 1,246 of their siblings. An approximately equal number of controls were available for comparison.

Results

Table 1 documents the prevalence of additional malformations noted in the facial cleft probands. It can be noted that 12.9% of the total group exhibited additional malformations. The isolated cleft palate group demonstrated the greatest number of additional malformations and was followed, in decreasing order, by cleft lip in combination with cleft palate, and isolated cleft lip cases. The gross findings coincide with similar observations noted in previous studies. Of considerable interest was the analysis of percent of additional malformations according to sex of proband. Here, independent of cleft type, the female has more additional malformations than her male counterpart (17.3% vs. 9.4%).

Table 2 presents data regarding distribution of cleft type according to prevalence of additional malformations in subjects and prevalence of malformations in siblings of the subjects. The results indicate that individuals with isolated cleft palate not only had the highest percent of additional malformations but they also had the highest percent of malformed siblings. The parallelism was noted for each successive facial cleft group.

TABLE 1. Number and percentage of additional malformations in patients demonstrating a facial cleft.

sex of proband	*cleft lip*		*cleft lip in combination with cleft palate*		*cleft palate*		*total*	
	total number	*malf. %*	*total number*	*malf. %*	*total number*	*malf. %*	*total number*	*malf. %*
male	24	1 (4.2%)	124	10 (8.1%)	63	9 (14.3%)	211	20 (9.4%)
female	12	1 (8.3%)	60	9 (15.0%)	89	18 (20.2%)	161	28 (17.3%)
total	36	2 (5.6%)	184	19 (10.3%)	152	27 (17.8%)	372	48 (12.9%)

TABLE 2. Rank-order of percent of additional malformations in facial cleft patients, index controls, and malformations in corresponding siblings.

rank	*percent additional malformations in facial cleft patients*	*percent of malformed siblings*
1 (highest)	isolated cleft palate	isolated cleft palate
2	cleft lip with cleft palate	cleft lip with cleft palate
3	isolated cleft lip	isolated cleft lip
4 (lowest)	control	control

TABLE 3. Prevalence of malformations in siblings, according to proband cleft type.

probands	*N*	*siblings*		
		type of malformation		
		facial clefts	*other*	*total*
isolated cleft palate	448	CL = 0 CL/P = 0 CP = 19 4.2%	16 3.6%	35 7.8%
cleft lip alone in or combination with cleft palate	598	CL = 5 CL/P = 6 CP = 1 2%	19 3.2%	31 5.2%

As shown in Table 3, further analysis of the malformation profile of facial cleft siblings reveals that the total malformation rate for siblings of individuals with a facial cleft is greater in those siblings whose affected family member had an isolated cleft palate (7.8%) than in the siblings of an affected family member demonstrating cleft lip alone or in combination with cleft palate (5.2%). This difference is essentially due to an increased number of facial clefts in the siblings of the isolated cleft palate probands (4.2% vs. 2%) rather than due to types of malformations other than facial clefts where the rates for both groups are approximately the same (3.6% and 3.2%, respectively).

A further division of the components of this rate according to the sex of the sibling is presented in Table 4. This table indicates that male siblings of either male or female isolated cleft palate probands have the highest total malformation rate; the same male siblings also have the highest cleft rate. Male siblings of either male or female cleft lip or cleft lip in combination with cleft palate probands have the next

TABLE 4. Prevalence of malformations in siblings, according to sex of sibling and proband cleft type.

probands	*male siblings*				*female siblings*			
	N	*facial clefts*	*other*	*total*	*N*	*facial clefts*	*other*	*total*
isolated cleft palate male and female	205	CL = 0 CL/P = 0 CP = 14 6.8%	7 3.4%	21 10.2%	243	CL = 0 CL/P = 0 CP = 5 2.1%	9 3.7%	14 5.8%
cleft lip/cleft palate male and female	406	CL = 3 CL/P = 6 CP = 1 2.2%	18 4.4%	28 6.9%	192	CL = 2 CL/P = 0 CP = 0 1%	1 .5%	3 1.6%

highest total malformation rate and the same male siblings have the next highest cleft rate.

The final analysis of these rates noted in Table 5 indicates that it is the male sibling of the male isolated cleft palate proband who is most often affected with a facial cleft and the male sibling of a female isolated cleft palate proband who has the highest rate of malformations other than facial clefts.

Discussion

The finding regarding a relationship between sex of proband and percentage of additional malformations is in accord with a recent literature report from Germany (*9*). That study investigated the additional malformation rate in an equal number of randomly selected malformed males and females. Of the males, 113 had isolated anomalies and 30 had combined anomalies; of the females studied, 69 had isolated anomalies and 74 had combined anomalies. This difference was highly significant. From the results of the present investigation and those of the German study, there appears to be a pronounced difference between prevalence of single and multiple malformations and the sex of the affected individual; that is, that the female is able to survive with more malformations than her male counterpart.

The results obtained from comparison of the ranking of percent additional malformations on probands and percent malformed siblings appears to indicate that the isolated cleft palate proband and sibling has a greater propensity for malformations than either of the other two cleft type probands and their siblings. The difference in percent malformed is great enough to state that since isolated cleft palate has been previously shown to have a different inheritance pattern from cleft lip alone or in combination with cleft palate, the constitution of the patients with iso-

TABLE 5. Prevalence of malformations in male and female siblings according to sex of sibling, sex or proband, and proband cleft type.

probands	*male siblings*				*female siblings*			
	N	*facial clefts*	*other*	*total*	*N*	*facial clefts*	*other*	*total*
isolated cleft palate								
male	108	CL = 0 CL/P = 0 CP = 9	2	11	122	CL = 0 CL/P = 0 CP = 1	6	7
		8.3%	1.9%	10.2%		.8%	4.9%	5.7%
female	97	CL = 0 CL/P = 0 CP = 5	5	10	121	CL = 0 CL/P = 0 CP = 4	3	7
		5.1%	5.1%	10.3%		3.3%	2.5%	5.8%
cleft lip/cleft palate								
male	196	CL = 1 CL/P = 6 CP = 1	9	17	112	CL = 1 CL/P = 0 CP = 0	1	2
		4.1%	4.6%	8.7%		.9%	.9%	1.8%
female	210	CL = 2 CL/P = 0 CP = 0	9	11	80	CL = 1 CL/P = 0 CP = 0	0	1
		1%	4.3%	5.2%		1.3%	0%	1.3%

lated cleft palate and their siblings may be more easily influenced to produce malformations than is the constitution of the other facial cleft patients and their siblings.

It appears from the detailed sibling analysis that the total malformation rate for siblings of probands with a facial cleft is greater in those siblings whose affected family member has an isolated cleft palate. It is also evident that male siblings of male probands, regardless of cleft type, have a greater risk of demonstrating a cleft than any other sibling-proband combination. We have tested a number of hypotheses utilizing our data to explain this phenomenon and have not been able to conclusively identify the factor or factors responsible. Results of the malformation profile presented in this paper must be tempered by the fact that the information regarding malformations was obtained by either a retrospective search of birth records or reliance on parental observations. This type of information would affect the calculation of absolute risk rates. However, since the source of malformation data in this study was identical for all groups, reliable inter-group and intra-group analyses could be carried out.

The results of these relative comparisons indicate the desirability of

examining in detail component portions of an occurrence. The philosophy for this statement is amply summarized in the following quotation.

> Large scale statistics at present do little more than indicate the total impact of cumulative teratogenic factors. They obscure the characteristic variability of patterns and incidences of specific defects which might be revealed by smaller and more detailed investigations. Upon the quality of these rests the prospect that individually or by summations, they will point to etiologic factors in maldevelopment (*3*).

It is our hope that this detailed sibling analysis may have added additional information toward further research and understanding of the pathologic processes leading to the development of facial clefts.

Summary and Conclusions

The malformation profile of siblings of 372 facial cleft probands and 1,246 siblings demonstrated the following. a) Regardless of cleft types, females with a facial cleft are more likely to have an additional malformation than their male counterparts. This corresponds to findings demonstrated for other types of major malformations. b) There is a striking parallelism between the frequency of additional malformations in probands and the frequency of observation of malformations in their siblings. This parallelism is noted for probands and siblings in each major cleft category. c) Male siblings of either male or female isolated cleft palate probands have the highest total malformation and cleft rate; and the male siblings of either male or female cleft lip or cleft lip in combination with cleft palate probands have the next highest total malformation and cleft rate. d) Male siblings of the male isolated cleft palate proband are most often affected with a facial cleft and the male siblings of a female isolated cleft palate proband have the highest rate of malformations other than facial clefts.

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